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The fifth edition of the *Handbook of Small Animal Practice* is dedicated to

Scamp (1976-1990)
Corky (1991-2006)
Duma (1991-2007)

During the first 30 years of my career and the preparation of all five editions of the *Handbook of Small Animal Practice*, these three Pembroke Welsh corgis were my constant companions. They spent innumerable hours resting at my feet as I labored to edit the books and also frequently prompted me to take well-timed breaks for walks and other adventures. These intelligent, enthusiastic, and entertaining friends greatly enriched my life and continuously reminded me of how fortunate we are to share the world with animals.

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Ocular Manifestations of Systemic Disease

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Preface

Welcome to the fifth edition of the *Handbook of Small Animal Practice.* For those of you unfamiliar with *HSAP,* you will notice it is written entirely in an outline format. Every effort has been made to keep standardized prose to a minimum. This format provides the busy practitioner with the latest, most applicable information on a subject in a concise and easily retrievable manner.

Whenever applicable, each subject is explored under the headings of *Definition, Causes, Pathophysiology, Clinical Signs, Diagnosis, Differential Diagnosis, Treatment,* and *Monitoring of the Animal.* The book consists of nineteen different sections and four appendices. Many sections are subdivided into chapters based on the anatomic components of that body system. In turn, each chapter is organized in a chronological fashion, beginning with congenital and developmental disorders and followed by degenerative, infectious, inflammatory, idiopathic, parasitic, metabolic/toxic, immune-mediated, vascular, nutritional, neoplastic, and traumatic diseases. This chronology is maintained wherever possible so the reader can predict and find the location of a given subject within a chapter.

Although the goals, aspirations, organization, and format of the fifth edition remain similar to previous editions, the following noteworthy changes were made in this edition:

- The first chapter of the book now addresses preoperative evaluation and anesthetic protocols.
- The Cardiovascular, Neurologic, Digestive, Urinary, Musculoskeletal, Dermatologic, Behavioral Disorders, Nutrition, Toxicology, and Environmental Injuries sections were written primarily by new authors.
- Some large chapters were split into two separate chapters so the authors could be more thorough in addressing their respective subjects.
- The Dermatologic System section was reorganized using a problem-based approach. Readers are encouraged to use the index to help locate certain diseases within this section.
- The Toxicology section was also reorganized to better reflect the most common toxicants now encountered in small animal practice.
- The Drug Appendix was extensively revised and updated.

I am deeply indebted to the section editors who helped on this project and to all the contributors who provided up-to-date, concise information in their respective chapters. A special "thank you" is due Leah Ann Crussell for her work in producing the drug appendix. Compilation of the drug dosages from all 136 chapters is an enormous and tedious task, and Leah Ann did a great job.

I would also like to recognize the talented crew at Elsevier who helped me manage and produce this text, especially Ms. Shelly Stringer, Ms. Stacy Beane, and Mr. Jonathan Taylor. It takes tremendous coordination to complete a project of this size on time and to do it well. The Elsevier team was supportive, responsive, detail-oriented, and great to work with.

Although it might seem a bit crazy to spend almost three decades working on such monolithic projects as the five editions of *HSAP*, the process has been a rewarding experience. Working with so many expert authors on each edition has taught me many things, not the least of which is how lucky our profession is to attract so many dedicated and gifted people.

As always, I hope this edition will continue to be a useful *and* often-used guide for all the veterinarians who strive each day to make ill and injured animals well and whole again.

Rhea V. Morgan, DVM

CHAPTER 1

Preoperative Evaluation and Anesthetic Protocols

Andrea L. Looney

PREOPERATIVE EVALUATION

Identify Proper Signalment

I. Age
   A. Age is not a disease, but often affects many body system functions and reserves.
   B. Cardiac output depends on heart rate in neonatal and pediatric animals; therefore anticholinergic agents are often recommended for premedication (Pascoe and Moon, 2001).
   C. Geriatric animals often have reduced cardiac output and baroreceptor activity, reduced chest compliance, and decreased hepatic and renal function (Carpenter et al., 2005).

II. Reproductive status
   A. In the case of an intact female, has the owner observed any recent estrous cycle? Is pregnancy a possibility?
   B. Many anesthetic drugs have teratogenic or abortigenic effects if administered in early pregnancy (Papich, 1989).

III. Breed
   A. Beware of breed misconceptions and breed-related myths (Wagner et al., 2003; Cuvelliez and Rondenay, 2002).
      1. Many large-breed dogs are not sensitive to certain agents, but are more accurately dosed based on body surface area (vs weight).
      2. Many Persian cats may not metabolize ketamine as readily as other breeds (Shamir et al., 2004).
      3. Idiosyncratic hepatic disease has been reported in Labrador retrievers on carprofen; however, many Labradors and Labrador-mix dogs utilize this drug without hepatic problems (MacPhail et al., 1998).
   B. Anesthetic problems may be more common in certain breeds because of common congenital or hereditary issues.
      1. Standard poodles have a higher incidence of Addison's disease (Famula et al., 2003), and Addisonian crises may be precipitated by certain preanesthetic and anesthetic agents (e.g., acepromazine, medetomidine, isoflurane, sevoflurane).
      2. Brachycephalic dogs and cats are more likely to have respiratory difficulties during induction and recovery.
      3. Afghan hounds have a higher incidence of subclinical pulmonary disease (Neath et al., 2000), which may become clinical during positive pressure ventilation.
      4. Greyhounds may metabolize many drugs, including propofol, less effectively than other breeds, even other sighthounds.
      5. Greyhounds also have more perioperative coagulopathies than other breeds (Feeman, 2005; Robertson et al.; 1992; Cuoto, 2006).

Identify the Chief Complaint

I. Determine if the animal is stable for the intended procedure.
II. The first goal of the anesthetist is to devise an accurate and objective preanesthetic problem list.

TABLE 1-1

Blood Flow, Oxygen Consumption, and Cardiac Output That Organs Receive in a Resting Individual

ORGAN	BLOOD FLOW (mL/100g/min)	OXYGEN CONSUMPTION (mL/100g/min)	CARDIAC OUTPUT (%)
Liver	57	2	28
Kidneys	420	6	23
Brain	54	3.3	14
Heart	84	9.7	5
Muscle	2.7	0.2	16
Skin	13	0.3	8

A. Blood flow, cardiac output, and oxygen consumption determine which organ systems need to be addressed first on the problem list (Table 1-1).
   1. Based on the high blood flows and oxygen consumptions of both the kidneys and the heart, it is predictable that these organs would suffer most with even a mild to modest decrease in cardiac output, such as occurs with heavy sedation, general anesthesia, or both.
   2. Because the kidney also receives a high percentage of cardiac output, it is likely to have the most severe perfusion consequences of any organ system from reduced cardiac output.
   3. Hence, stabilize animals with renal or cardiac disease before heavy sedation and anesthesia, or postpone anesthesia until adequate function of both systems is ascertained.

B. Stabilize animals with renal and heart disease through appropriate medical therapy before deep sedation and general anesthesia.
   1. Renal disease: pressor therapy with fluid therapy
   2. Heart disease: pressor therapy and fluid restriction

C. Renal failure and heart failure are contraindications to general anesthesia.

D. Renal insufficiency and heart disease are not contraindications, but caution is indicated.
   1. Function of these organs must be optimal before initiation of general anesthesia.
   2. Warn owners of the increased chance of decompensation.
   3. Use drugs that aim to maintain cardiac output and improve perfusion and oxygenation (dopamine, ketamine infusions).
   4. Monitor blood pressure and treat abnormalities aggressively.

Review Medical History

I. Establishing a thorough checklist that is reviewed by the clinician for each animal is a key to success.

II. Medical clearance for anesthesia is defined as evaluation of the animal's current health against the history of prior illness and treatment, both of which help to predict reserve and outcome.

III. Recent travel to different geographical areas may predispose to certain diseases (vector transmitted, fungal disease) that worsen gastrointestinal (GI) (dogs) and respiratory diseases (many species).

IV. Determine and record history of vaccination, infectious diseases, parasite control, and heartworm status.
   A. Avoid nonspecific ("up-to-date") terminology to avoid medical errors.
   B. Establish the following:
      1. Is the animal protected within the hospital?
      2. Are other animals at risk from this pet entering the hospital?
      3. Are hospital staff members at risk from zoonotic diseases?
   C. Recommendations for reduced frequency and individualization of vaccinations may necessitate measurement of titers and flexible regulations concerning vaccination status before a procedure (Moore and Glickman, 2004).
   D. Heartworm disease is not a contraindication to anesthesia, but cardiac and pulmonary changes affect oxygenation and perfusion of other organ systems (see Table 1-1).

V. Elucidate any previous illnesses, procedures, surgeries, or anesthetic events.
   A. Prior masticatory myositis may preclude routine orotracheal intubation.
   B. Prior lumbosacral trauma may impact routine epidural placement.
   C. Repeated endotracheal intubation in smaller animals, especially cats, can predispose to tracheitis, tracheal rupture, or stenosis (Mitchell et al., 2000).
   D. Platelet aggregation abnormalities or thrombocytopenias may be aggravated by acepromazine, which can inhibit platelet adhesion and function (Barr et al., 1992).

VI. Record known or suspected allergies or adverse reactions to medications, foods, or nutritional supplements.
   A. Propofol contains egg phosphatide and soybean oil, and some formulations also contain sulfite stabilizers.
      1. Multiple reports of human anaphylactoid reactions have occurred with the use of propofol (Nishiyama and Hanaoka, 2001; Marik, 2004).
      2. Although no reports of anaphylaxis exist in animals, avoid use of propofol in animals with known (intradermal or serologic) allergies to eggs, soybeans, or sulfites.
   B. Morphine and meperidine readily cause histamine release, so dogs and cats with histamine-related fleabite dermatitis, endoparasitism, and allergic lung disease may experience severe hypotension and tachyphylaxis with these drugs.

Pursue Other Pertinent Questions

I. Environment and temperament
   A. Nordic breeds and working dogs (especially intact males) used for outdoor activity may experience hyperthermia with routine heat supplementation used during general anesthesia.
   B. Stressed animals are often difficult to sedate or anesthetize with any agent because of extreme neurohormonal fluctuation. The inability of acepromazine to work effectively in very anxious animals (also known as *epinephrine reversal of acepromazine*) epitomizes this phenomenon (Benson et al., 2000).

II. Current and recent medications
   A. Insecticides or insecticide-laden collars, powders, and sprays often contain anticholinesterases (organophosphates, carbamates), and some (amitraz) may potentiate the effects of anesthetics (Mealey and Matthews, 1999).
   B. Determine concurrent administration of over-the-counter medications, especially aspirin, antihistamines, or acetaminophen.

1. Washout periods are usually required for animals on aspirin therapy to avoid microvasculature platelet-related bleeding and to allow use of perioperative injectable nonsteroidal antiinflammatory drugs (NSAIDs) and corticosteroids (Lascelles et al., 2005).
2. Antihistamines have anticholinergic effects that may preclude the use of atropine or glycopyrrolate.

C. Glucosamine and chondroitin are synthetic heparinoids that may contribute to coagulopathies in animals undergoing anesthesia or surgical procedures (Goodman and Trepanier, 2005).
D. Topical flea and tick medications applied by an owner may inadvertently be carried through the epidermis with perioperative subcutaneous or IM injections and may cause deep, irritant chemical dermatopathies (Ackermann, 2005).
E. Herbal or homeopathic supplements may interact with perioperative medications.
   1. Ginkgo, garlic, ginger, and ginseng inhibit platelet aggregation (Glintborg et al., 2005).
   2. Herbs that contain salicylate, such as meadowsweet and willow, may also exacerbate the adverse effects of aspirin and other NSAIDs (Rubin, 2005).
F. Behavioral modification drugs, such as monoamine oxidase inhibitors, specific seratonin reuptake inhibitors, and tricyclic antidepressants, have caused pyrexia, hyperthermia, and even fatalities in humans treated with certain premedicants (morphine, ketamine) and general anesthetics (Mealey and Matthews, 1999).
G. Topical atropine commonly used in treating ophthalmic diseases can be absorbed systemically thereby precluding use of further anticholinergics and contributing to increased myocardial work and oxygen consumption.
H. Oral carbonic anhydrase inhibitors predispose to metabolic acidosis.
I. Prednisone use has certain effects.
   1. Catabolic state induced by chronic use is likely to weaken myocardial and respiratory musculature.
   2. Immunosuppression and weakened vasculature can predispose to skin infections near sites of venipuncture and regional nerve blocks.
J. Anticonvulsant usage must be determined.
   1. Phenobarbital is a potent enzyme inducer and may lead to rapid metabolism of other barbiturates.
   2. Liver enlargement caused by anticonvulsants may add to respiratory difficulties from compression of the diaphragm.
K. Many antibiotics given perioperatively reduce blood pressure intraoperatively (ampicillin, penicillin, cefazolin).
L. Some antibiotics (neomycin, vancomycin, amikacin) may act as neuromuscular blockers owing to acetylcholine inhibition.
M. Concurrent cardiac medications require attention.
   1. Angiotensin-converting enzyme inhibitors may predispose to hypotension.
   2. Beta blockers may reduce cardiac output and add to intraoperative or perioperative bronchospasm.

III. Recent illnesses

TABLE 1-2

Normal Physiologic Values for Conscious Small Animals Breathing Room Air

PHYSIOLOGIC PARAMETER	CANINE VALUES	FELINE VALUES
Temperature (° F)		
	99.5-102.5	100-102.5
Pulse Rate (beats per minute)		
Small (toy) breeds	120-160	120-200
Medium breeds	80-140	
Giant (large) breeds	60-100	100-150
Respiratory rate (breaths per minute)		
	10-35	10-50
Blood pressure (mm Hg)		
Systolic	120-150	150-170
Diastolic	70-90	90-120
Mean	100-120	110-140
Pulse oximetry (%)		
	93-95	93-95

Modified from Muir WW III, Hubbell JAE, Skarda RT: Handbook of Veterinary Anesthesia. Mosby, St. Louis, 2000.

A. Animals suffering from recent illness may be at increased anesthetic risk.
B. If possible, delay procedures until dehydration, fever, altered acid-base status, and abnormal electrolytes are corrected.

Perform a Thorough Physical Examination

I. Obtain weight and vital signs (Table 1-2) as soon as the animal enters the hospital to avoid stress-induced changes.
II. Body condition score is also noted (Figure 1-1).
   A. Obesity can cause multiple problems.
      1. Fat stores act as a depot of nonmetabolizing tissue that tends to release anesthetic agents back into the circulation slowly throughout the intraoperative or perianesthetic periods.
      2. Obese animals have decreased ventilatory capacity.
      3. Increased cardiac stroke work results in ventricular insufficiency and decreased myocardial perfusion.
      4. Drug dosages are calculated based on ideal body weight (Grimm, 2002).
   B. Excessive thinness may indicate underlying subclinical diseases, such as renal failure, heart disease, or chronic parasitism.
   C. Animals with little body fat are prone to hypothermia and heating pad injuries and may be unusually sensitive to highly fat-soluble drugs.
III. Pain and anxiety scoring can be performed with use of a relatively simple subjective scale and, ideally, is an average of the owner's and an impartial observer's (technician's) subjective rating (Figure 1-2).

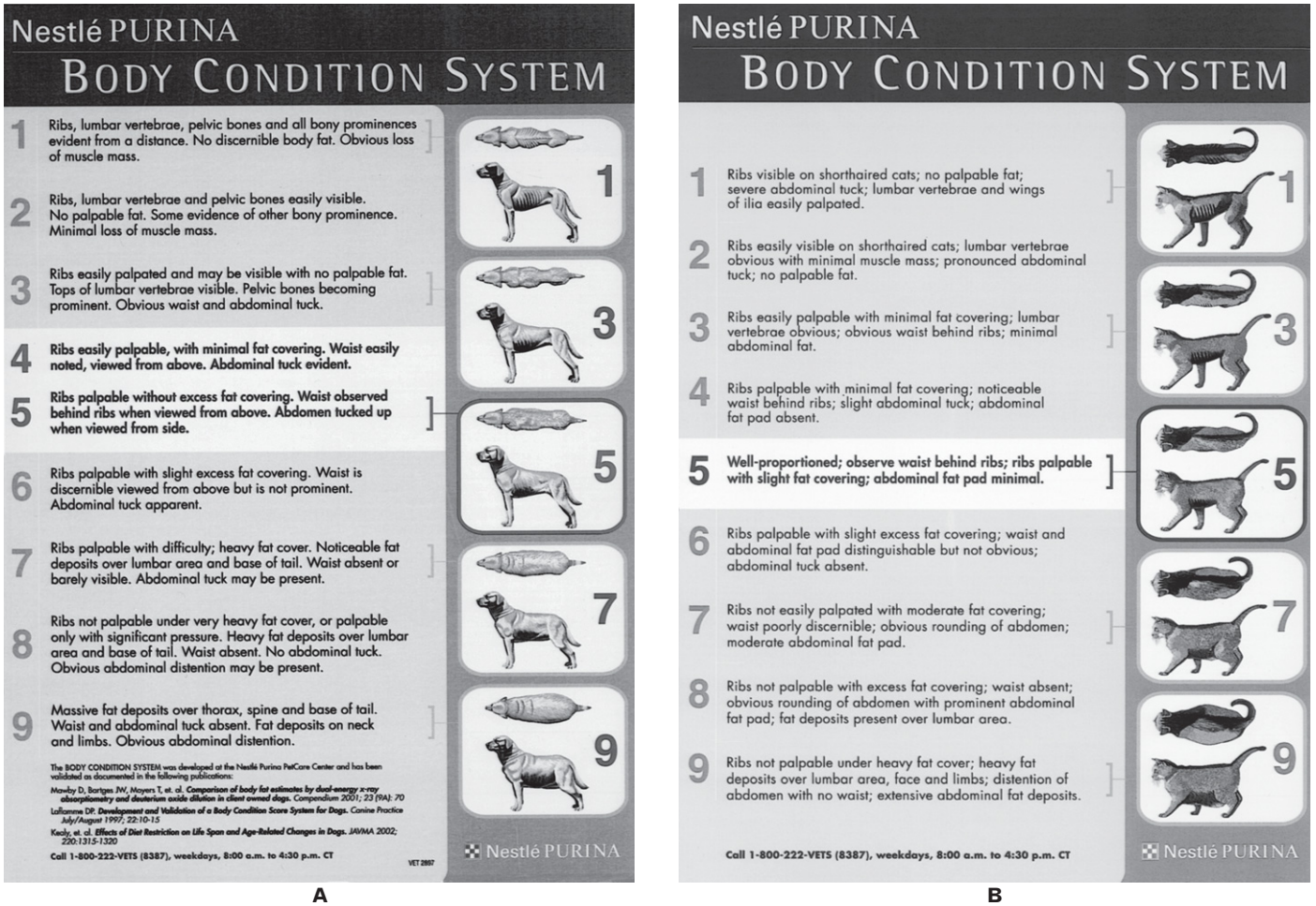

FIGURE 1-1 **A,** Body condition scoring system used in the dog. **B,** Body condition scoring system used in the cat. *From Laflamme DP, Kealy RD, Schmidt DA: Estimation of body fat by body condition score. J Vet Intern Med 8:154, 1994; with permission.*

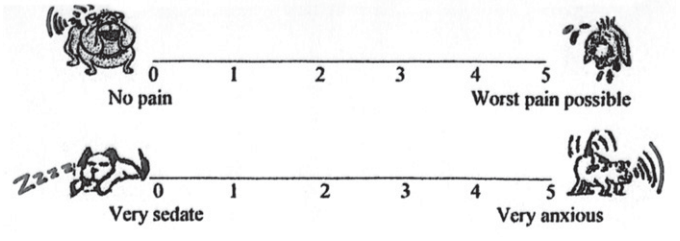

FIGURE 1-2 Simple pain and anxiety scales used in small animal medicine and surgery. The owner is asked to identify a point on each line. An impartial observer (technician or veterinarian) is also asked to identify a point on each line. Scores are then averaged and the final pain and anxiety scores are noted in the pet's record. *Courtesy P. Wantuch, with permission.*

IV. Preoperative blood pressure and pulse oximeter readings are obtained when warranted (e.g., presence of cardiac, renal, pulmonary diseases).
V. Ideally the preanesthetic examination includes determination of hydration status and examination of the oral cavity and pharynx.
VI. Examination of range of motion of the temporomandibular joint and documentation of cephalic conformation are useful in brachycephalic breeds or animals with neoplastic or inflammatory myositis.
VII. Auscultation of heart and lungs, palpation of pulses in several areas, abdominal palpation for the presence of fluid or a space-occupying mass, and assessment of neurologic and musculoskeletal systems are performed.

Classify Anesthetic Risk

I. The most widely accepted classification system for anesthesia risk is the American Society of Anesthesiologists (ASA) categorization (Hosgood and School, 2002; McKelvey and Hollingshead, 2000) (Table 1-3).
II. Inform owners of any increased risk and add an "E" status for emergency anesthesia.

Obtain Minimum Data Base

I. No universal guidelines for preanesthetic diagnostic tests exist.
II. In all but elective surgeries on young (<1 to 1.5 years), healthy animals, perform quick assessment tests (QATs).
III. Ideally, packed cell volume (PCV), albumin, total white blood cell (WBC) count, creatinine, serum alanine transferase, and urine specific gravity are measured to help

TABLE 1-3

Classification of Physical Status and Anesthesia Risk

CATEGORY—ASSOCIATED RISK	PHYSICAL CONDITION	CASE EXAMPLES
Class I—minimal risk	Normal, healthy animal No underlying disease	Ovariohysterectomy Castration Declawing Sedation for radiography, ear examination, nail trim
Class II—mild risk	Animal with slight to mild systemic disturbance Animal that is able to compensate without intervention	Neonatal or geriatric animals Mild obesity Skin mass removal Uncomplicated hernias Cystotomy Abscesses or minor wound debridement
Class III—moderate risk	Animal with moderate systemic disturbance Animal unable to compensate and showing clinical signs	Anemia Dehydration Low-grade fever Mild heart or pulmonary disease Renal insufficiency Controlled endocrinopathy
Class IV—high risk	Animal significantly and systemically ill with major organ compromise or failure	Severe dehydration Shock High fever Uremia Moderate heart or pulmonary disease Renal failure Trauma Uncontrolled endocrinopathy
Class V—grave risk	Animal moribund or comatose	Animal not expected to survive >24 hours, with or without surgery Advanced cases of multiple organ failure Major trauma Terminal neoplasia Shock Terminal endocrine disease

Modified from McKelvey D, Hollingshead KW: Small Animal Anesthesia and Analgesia. 2nd Ed. Mosby, St. Louis, 2000.

prioritize choice of drugs, monitoring, IV fluid types, and volumes.

A. Animals with albumin <2.0 mg/dL often require colloidal infusions perioperatively and use of low protein-binding, reversible preanesthetic and anesthetic agents, such as midazolam, fentanyl, thiopental, and etomidate.
B. Animals with low specific gravity and mildly elevated creatinine may require measures to preserve blood pressure.
   1. Benzodiazepines might replace acepromazine as premedication.
   2. Periods of hypotension are aggressively treated with fluid volume expansion (5 to 10 mL/kg crystalloid IV infusion over 5 to 10 minutes) and vasopressor therapy (dopamine 3 to 5 µg/kg/min IV).
   3. Animals with low PCVs (<20% to 24%, depending on acute or chronic state) may be transfused before removal or biopsy of a vascular organ, such as the spleen or kidney.
   4. Hyperkalemic (>6.0 to 6.5 mEq/L) animals require treatment before induction of general anesthesia to avoid cardiac disturbances (see Chapter 48).

IV. Additional testing (coagulation profile, electrolyte determination, blood gases, lactate levels, electrocardiography, and thoracic or abdominal radiographs) is performed based on body system abnormalities identified on physical examination.

SELECTION OF ANESTHETIC PROTOCOLS

Safe and Effective Sedation/Anesthesia

I. Stabilize the animal according to the triaged problem list before administering anesthesia.

II. The goal of anesthesia is to maintain, if not improve, oxygenation, perfusion, and waste removal of all tissues during a procedure.
III. The basic protocol followed for anesthesia of most animals is outlined below:
  A. Premedication is delivered either IM or IV, and consists of the following:
    1. A sedative or anxiolytic drug, such as a phenothiazine or benzodiazepine
    2. An analgesic drug, usually an opioid, alpha-2, agent, or both
    3. An anticholinergic drug, such as glycopyrrolate, if needed
      a. Glycopyrrolate is used in ophthalmic procedures, animals with GI disease, central nervous system (CNS) space-occupying lesions, and cervical or laryngeal diseases.
      b. Glycopyrrolate is not used in animals with cardiac disease, hyperthyroidism, pancreatic disease, overt nervousness or anxiety, or shock.
      c. Atropine is no longer used for routine premedication owing to its ability to induce potent tachycardias, potentiation of CNS disorders, and because of its profound potential for ileus.
  B. An induction agent is usually delivered IV.
    1. The induction agents may be delivered with premedications in protocols for elective surgery (e.g., ketamine, butorphanol, and medetomidine combined and delivered together IM).
    2. Common choices of induction agents include ketamine, ketamine/benzodiazepine combinations, thiopental, opioid/benzodiazepine combinations, propofol, and etomidate.
  C. A maintenance agent, usually isoflurane or sevoflurane, is typically delivered in oxygen or oxygen-nitrous oxide mixtures via agent-specific vaporizers.
  D. Local or regional nerve blockade is usually administered after induction.
  E. Nonsteroidal antiinflammatory agents are administered preoperatively, intraoperatively, or postoperatively.
  F. Infusions of certain agents (morphine, fentanyl, lidocaine, or ketamine) can be given pre-, intra-, or postoperatively to reduce administration of more potent induction and inhalant agents, aid in anxiolysis, promote muscle relaxation, and provide analgesia.
  G. Suggested doses of agents are listed in Table 1-4.

Drug Options for Problem Cases

I. Animals with pulmonary or thoracic diseases
  A. Intrathoracic effusion and/or accumulation of air are removed before inhalant administration.
  B. Arterial blood gases help to determine severity of respiratory dysfunction.
  C. Preoxygenation is essential to reduce hypoxemia of induction agent administration.
  D. Sedation usually improves oxygenation, but may worsen hypercarbia.
  E. Low-dose anticholinergics and ketamine are useful for bronchodilation.
  F. Pure mu agonists, such as hydromorphone and fentanyl, may cause marked respiratory depression.
    1. Their use is warranted for prevention and treatment of pain.
    2. Monitoring via capnography and pulse oximetry is recommended.
    3. Mechanical ventilation may be necessary with end-tidal carbon dioxide >50 mm Hg.
  G. Ventilation with high frequencies and low tidal volumes is useful in the presence of intrathoracic or large pulmonary mass lesions.
  H. Local or regional nerve blockade (intercostal, intrapleural, or epidural analgesia) is *highly recommended* to provide excellent comfort and avoid systemic opioid side effects.
II. Animals with upper respiratory disorders
  A. Minimize stress to improve oxygenation and decrease anxiety of dyspnea.
    1. Acepromazine relieves stress and improves blood flow.
    2. The combination of low-dose medetomidine coupled with mild opioids (butorphanol or buprenorphine) relieves anxiety, provides analgesia, is antitussive, and is reversible.
  B. Anticholinergics are usually necessary to combat increased vagal tone, but avoid high doses and repeat dosing.
    1. Bronchodilation potentially increases negative inspiratory pressure further.
    2. Increased viscosity of secretions worsens main airway obstruction.
  C. Preoxygenation is important but can be of limited help if obstruction (laryngeal paralysis, nasopharyngeal polyp) is severe.
    1. Masks must not be used in cases of upper airway obstruction unless the animal tolerates them.
    2. Masks worsen stress, hypoxia, and hypercapnia.
    3. Flow-by oxygenation is suggested instead.
      a. The end of rebreathing circuits held to an animal's nares or mouth.
      b. Oxygen line directly from an oxygen flowmeter is held similarly.
      c. Oxygen line is directed into an Elizabethan collar "chamber."
      d. Oxygen can be delivered via an oxygen cage.
  D. Assorted tracheal tubes (smaller than expected), suction apparatus, and tracheostomy kits are made readily available *before* induction.
  E. Ketamine and benzodiazepine combinations, as well as carefully titrated propofol, are suitable induction agents.
  F. In most cases, postoperative extubation is delayed as long as possible for animals with nasal disease.
  G. Ironically, many animals with pharyngeal or laryngeal inflammatory disease oxygenate better if extubated earlier, as long as attention is paid to their potential for aspiration.
III. Animals with cardiovascular instability

TABLE 1-4

Preanesthetic and Anesthetic Agents with Suggested Dose Ranges

DRUGS	CANINE DOSE	FELINE DOSE
Preanesthetic Agents		
Anticholinergics		
Glycopyrrolate	0.003-0.01 mg/kg SC, IM, IV	0.003-0.007 mg/kg SC, IM, IV
Sedatives and Tranquilizers		
Acepromazine	0.01-0.03 mg/kg SC, IM, IV	0.01-0.03 mg/kg SC, IM, IV
Diazepam	0.1-0.5 mg/kg IV	0.1-0.5 mg/kg IV
Midazolam	0.1-0.5 mg/kg SC, IM, IV	0.1-0.5 mg/kg SC, IM, IV
Sedative Analgesics		
Medetomidine	0.001-0.010 mg/kg SC, IM, IV	0.005-0.030 mg/kg SC, IM, IV
Dexmedetomidine	0.001-0.005 mg/kg SC, IM, IV	0.002-0.015 mg/kg SC, IM, IV
Opioid Analgesics		
Butorphanol	0.1-0.2 mg/kg SC, IM, IV	0.1-0.2 mg/kg SC, IM, IV
Buprenorphine	0.01-0.02 mg/kg SC, IM, IV	0.02 mg/kg mucosally, SC, IM, IV
Morphine	0.3-0.7 mg/kg SC, IM	0.2-0.5 mg/kg SC, IM
Hydromorphone	0.1-0.15 mg/kg SC, IM, IV	0.1 mg/kg SC, IM, IV
Oxymorphone	0.1-0.2 mg/kg SC, IM, IV	0.1 mg/kg SC, IM, IV
Fentanyl	0.003-0.005 mg/kg SC, IM, IV	0.003-0.005 mg/kg SC, IM, IV
Remifentanil	0.001-0.003 mg/kg IV	0.001-0.003 mg/kg/IV
Nonsteroidal Antiinflammatory Drugs (parenteral only)		
Meloxicam	0.2 mg/kg SC, IM, IV	0.2-0.3 mg/kg SC, IM, IV
Carprofen	2.2-4 mg/kg SC, slow IV	2.2 mg/kg SC
Ketoprofen	1-2 mg/kg SC, IM, IV*	1 mg/kg SC, IM, IV*
Single and Combination Induction Agents		
Thiopental	6-10 mg/kg IV to effect†	6-10 mg/kg IV to effect†
Propofol	3-6 mg/kg IV to effect†	3-6 mg/kg IV to effect†
Ketamine and diazepam or ketamine and midazolam	3-5 mg/kg ketamine with 0.3-0.5 mg/kg diazepam or midazolam IV‡	3 mg/kg ketamine with 0.3-0.5 mg/kg diazepam or midazolam IV‡
Fentanyl and etomidate	0.003-0.005 mg/kg fentanyl with 1 mg/kg etomidate IV§	0.005 mg/kg fentanyl with 1 mg/kg etomidate IV§
Midazolam and fentanyl	0.3 mg/kg midazolam with 0.02 mg/kg fentanyl IV§	0.3 mg/kg midazolam with 0.01 mg/kg fentanyl IV§
Midazolam or diazepam and oxymorphone or hydromorphone	0.3 mg/kg midazolam or diazepam with 0.1 mg/kg oxymorphone or hydromorphone IV§	0.3 mg/kg midazolam or diazepam with 0.1 mg/kg oxymorphone or hydromorphone IV§
Ketamine, medetomidine, and butorphanol	3 mg/kg ketamine, 0.005 mg/kg medetomidine, and 0.2 mg/kg butorphanol IM‖	5 mg/kg ketamine, 0.025 mg/kg medetomidine, and 0.2 mg/kg butorphanol IM‖

SC, Subcutaneous; *IM,* intramuscular; *IV,* intravenous.

*Hemorrhage has been seen with preoperative and intraoperative use of ketoprofen. If used perioperatively, administer it postoperatively and ensure adequate coagulation ability before administration.

†"To effect" implies administration of agents until adequate laryngeal relaxation and central nervous system depression are seen.

‡Drugs listed are mixed together before administration.

§Drugs listed are given in succession, with the second drug often given to effect.

‖Used for elective surgical procedures. In the dog, additional IV induction agents may be required to achieve adequate plane of anesthesia for intubation.

Continued

TABLE 1-4

Preanesthetic and Anesthetic Agents with Suggested Dose Ranges—*cont'd*

DRUGS	CANINE DOSE	FELINE DOSE
Local and Regional Blockade		
Perilesional or perineural infiltration with lidocaine	2-5 mg/kg SC	2-3 mg/kg SC
Perilesional or perineural infiltration with bupivacaine	0.5-2 mg/kg SC	0.2-0.5 mg/kg SC
Epidural	0.1 mg/kg morphine with 0.3 mg/kg bupivacaine or 0.1 mL/kg saline	0.05 mg/kg morphine with 0.1 mg/kg bupivacaine or 0.1 mL/kg saline
Continuous Rate Infusions		
Lidocaine	0.05 mg/kg/min IV	0.005 mg/kg/min IV
Ketamine	0.01-0.02 mg/kg/min IV	0.01 mg/kg/min IV
Morphine	0.002 mg/kg/min IV	0.002 mg/kg/min IV
Fentanyl	0.3-0.7 μg/kg/min IV	0.3 μg/kg/min IV
Remifentanil	0.1-0.3 μg/kg/min IV	0.1 μg/kg/min IV

A. Stabilization of fluid balance before induction of anesthesia is critical.
   1. Pulmonary, pleural, or abdominal fluid accumulations are drained (at least partially) with appropriate diuretics or centesis before any agent administration or procedures.
   2. Normovolemia to hypovolemia with adequate blood pressure (mean Doppler pressure of >60 to 70 mm Hg) is required.

B. Preoxygenation is essential.
   1. It avoids desaturation and hypoxemia that occurs with preanesthesia and induction agent use.
   2. It readily relieves anxiety and angina, especially in cats.
   3. Oxygen is a potent pulmonary and cardiac vasodilator that improves cardiac function.

C. Choice of premedication is carefully considered.
   1. Opioids and benzodiazepines are drugs of choice for premedication.
   2. Morphine is very beneficial for anxiolysis, anginal pain, and redistribution of vascular volume from the pulmonary circulation through peripheral vasodilation.
   3. Anticholinergics and acepromazine are avoided.
   4. When decreased myocardial perfusion is present (cardiomyopathies in cats), alpha-2 agents may be indicated (Lamont et al., 2001; Lamont et al., 2002).
   5. Alpha-2 agents are not used in dogs with valvular disease or any animal with a life-threatening bradyarrhythmia or dilated cardiomyopathy.

D. Induction agents are given to effect.
   1. Cats
      a. Ketamine and ketamine/benzodiazepine combinations are avoided.
      b. Appropriate options are fentanyl, fentanyl and midazolam, propofol in small doses, and etomidate.
   2. Dogs
      a. Ketamine with diazepam or midazolam combinations are useful for increasing cardiac output in mild to moderate cardiac deficient states (valvular disease or mild dilated cardiomyopathy).
      b. Other appropriate induction options are opioid/benzodiazepine and fentanyl/etomidate combinations.

E. Isoflurane is the preferred maintenance inhalant agent to improve myocardial blood flow.

F. Local and regional nerve blockade, such as epidural opioid administration, is useful to provide excellent analgesia and avoid respiratory depression associated with systemic opioid use.

G. Pericardial disease requires unique intervention before induction of anesthesia.
   1. Effusions are removed before induction with use of ultrasonography or electrocardiographic guidance.
   2. Maintenance of preload is essential, so fluids are given to maintain cardiac output (mean Doppler blood pressure >70 mm Hg) and to increase central venous pressure (5 to 10 cm H_2O) when it is low in this subset of cardiac patients.

IV. Animals with renal disease

A. Animals with acute renal failure *should not be sedated or anesthetized* until adequate hydration, volume, acid base and electrolyte status, as well as blood pressures are attained.

B. Animals with renal insufficiency *must be well hydrated* before sedation and anesthesia.

C. Minimal premedication is suggested with use of drugs that are least likely to diminish cardiac output (e.g., benzodiazepines, opioids).
   1. Hydromorphone or oxymorphone is the preferred opioid; metabolites of morphine may accumulate with renal disease.

2. Acepromazine may be beneficial to allow afferent vasodilatation and increased renal blood flow (Bostrom et al., 2003).

D. Most induction and inhalant agents reduce glomerular filtration rate through decreases in renal blood flow; therefore, maintenance of blood pressure becomes paramount to success.

E. Induction agent choices are limited.
1. Avoid highly protein-bound drugs, such as barbiturates, or drugs excreted primarily by the kidney (e.g., ketamine).
2. Opioid/benzodiazepine combinations and propofol are suggested induction agents.

F. Isotonic crystalloid solution is administered at a fairly high rate (10 to 15 mL/kg/hr IV) to promote diuresis, with the rate reduced over time if adequate blood pressure and urine output are maintained; if preexisting hypoalbuminemia is present, judicions use of both colloids and crystalloids is recommended.

G. Isoflurane and sevoflurane are used as inhalant agents.

H. A byproduct of sevoflurane's interaction with the carbon dioxide absorbent, Compound A, has been found to cause renal impairment in laboratory animals, but this phenomenon has not been documented in domestic species anesthetized with sevoflurane.

I. Colloids (hetastarch 2 to 4 mL/kg/hr IV) or vasoactive agents (dopamine 3 to 5 μg/kg/min IV) can be added to increase blood pressure or urine output.

V. Animals with neurologic disease

A. Limited evidence exists that acepromazine reduces the seizure threshold (Wagner et al., 2003; Blaze, 2005; Brock 1994).

B. Although some anesthetic agents (ketamine, methohexital, etomidate) appear to increase the potential for seizures, use of acepromazine is not likely to do so (McKelvey and Hollingshead, 2000; Tobias et al., 2006).

C. Anticholinergics are used sparingly; glycopyrrolate is preferred over atropine because of its modest effect at increasing heart rate and purported inability to cross an intact blood-brain barrier and aggravate delirium.

D. Avoid anesthetics known to increase intracranial pressure, such as ketamine, tiletamine, and halothane.

E. Direct effects of opioids on cerebral blood flow and intracranial pressure are negligible, so they are useful agents.

F. Benzodiazepines and ultra–short-acting barbiturates in low doses are useful, owing to their effect on maintaining intracranial pressure and reducing neuronal activity.

G. Thiopental, propofol, benzodiazepine, and fentanyl combinations are all useful induction agents that act to slow neuronal activity and decrease intracranial pressure.

H. Sevoflurane is the preferred inhalant for maintenance of cerebral perfusion pressure.

I. Controlled hyperventilation with monitoring by capnography counteracts the effects of inhaled agents (central vasodilatation) on intracranial pressure.

J. Fluid administration is restricted to maintaining euvolemia, normal to hyperosmolarity, and adequate arterial blood pressures.
1. Fluids are regularly restricted to 2 to 5 mL/kg/hr IV.
2. Mannitol (0.5 to 1 g/kg IV slowly over 20 minutes) is given when increased intracranial pressure or tentorial herniation is suspected (ventral eye rotation, papillary dilation, optic disc edema, bradycardia, bradypnea, apneustic breathing patterns).
3. Fluid therapy is stopped during mannitol administration.
4. Furosemide can be administered at 1 to 2 mg/kg IV for enhanced diuresis after mannitol therapy.

VI. Animals with liver disease

A. Premedications and induction agents that are highly protein bound to gamma aminobutyric acid (GABA) receptors (benzodiazepines and barbiturates) are avoided in animals with overt or suspected hepatic encephalopathy.

B. Opioids are useful, but hepatic clearance is usually impaired.
1. Lower doses and less frequent administration are often required.
2. Epidural administration is the preferred route for opioid analgesia.
3. Remifentanil is an ultrapotent, short-acting opioid metabolized by plasma esterases; in animals with severe liver dysfunction, it represents a suitable induction agent and analgesic infusion agent.

C. Hypotension is often severe in animals with end-stage chronic disease or hepatic encephalopathy, and is often resistant to treatment with vasoactive or vasopressor agents.

D. Because of the potential for severe hypotension, impaired coagulation, and hypoalbumenimia, avoid acepromazine.

E. Alpha-2 agonists may be useful as premedicants because their sedative and cardiovascular effects are short-lived, and effects of these agents are reversible.

F. Induction agent choice is very limited.
1. Thiopental is metabolized actively by the liver, so prolonged recovery is expected if liver impairment is significant.
2. Propofol is the agent of choice, owing to its short half-life and limited hepatic uptake.

G. Sevoflurane is metabolized by the liver slightly more than isoflurane, but both are acceptable choices for animals with liver disease.

H. Avoid lactate-containing fluids; Normosol-R, Plasmalyte, or saline are the preferred crystalloid solutions.

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CHAPTER 2

Collection and Interpretation of Laboratory Data

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This chapter presents the techniques and procedures for collecting samples for certain laboratory tests (Tables 2-1 to 2-4). Normal values and interpretative guidelines are included. (For normal physiologic values, see Appendix I.)

ANION AND OSMOLAL GAPS

Anion Gap

Definition

I. By the law of electroneutrality, the concentration of circulating anions equals that of circulating cations.
II. Cations and anions are classified as measured or unmeasured.
  A. Measured
    1. Anions: Cl^-, HCO_3^-
    2. Cations: Na^+, K^+
  B. Unmeasured
    1. Anions (UA): albumin, α- and β-globulins, PO_4^{3-}, SO_4^{2-}, organic acids, certain toxins and drugs
    2. Cations (UC): gamma globulins, Ca^{2+}, Mg^{2+}, certain drugs
  C. In electroneutrality:

$$Na^+ + K^+ + UC = Cl^- + HCO_3^- + UA$$

III. Anion gap is the difference between measured cation and anion concentrations.
  A. Denotes an alteration in some unmeasured component of the equation
  B. Anion gap = $(Na^+ + K^+) - (Cl^- + HCO_3^-)$
    1. Normal: 12 mEq/L; range: 8 to 16 mEq/L
    2. May be increased by either a decrease in UC or an increase in UA
    3. Is decreased by either an increase in UC or a decrease in UA
    4. Potassium sometimes deleted from equation because of its low, constant concentration

Causes

I. Causes of increased anion gap
  A. Increase in UA
  B. Increase in serum lactate, ketoacids, and uremia
  C. Certain medications: carbenicillin, penicillin
  D. Dehydration: concentrated normal anions
  E. Alkalemia
  F. Decrease in UC concentrations: Ca^{2+}, Mg^{2+}
  G. Increase in serum albumin
  H. Toxins: ethylene glycol, methanol, salicylate, paraldehyde
II. Causes of decreased anion gap
  A. Increase in normal cations, especially Ca^{2+}, Mg^{2+}, and globulins
  B. Retention of abnormal cations (e.g., multiple myeloma)
  C. Loss of UA: hypoalbuminemia

Clinical Significance

I. Increases index of suspicion that unexpected (or unmeasured) cations or anions are present in serum
II. Allows further definition and classification of metabolic acidotic states
  A. Metabolic acidosis with normal or decreased anion gap is usually caused by renal or intestinal loss of bicarbonate (hyperchloremic acidosis).
  B. Metabolic acidosis associated with an increased anion gap may have various causes.
    1. Diabetic ketoacidosis
    2. Lactic acidosis
    3. Ethylene glycol or paraldehyde intoxication
    4. Acute renal failure

Osmolal Gap

Definition

I. Osmolal gap is the difference between measured serum osmolality and calculated osmolality.
II. Serum osmolality can be measured with an osmometer.
  A. The major osmotically active solutes are Na^+, K^+, glucose, and urea (measured as blood urea nitrogen [BUN]).
  B. Normal osmolality is 285 to 300 mOsm/kg.
III. Calculated serum osmolality is derived from the following equation:

$$2(Na^+ + K^+) + \frac{\text{Glucose}}{18} + \frac{\text{BUN}}{3}$$

IV. A difference of >10 mOsm between the measured and calculated values is significant.

Causes

I. If the calculated value exceeds the measured value, a mathematical or laboratory error exists.
II. If the measured value is normal but the calculated value is low, a decrease in serum water is the usual cause.

TABLE 2-1

Endocrine Assays

TEST	PROTOCOL	SAMPLE REQUIRED	NORMAL VALUES	INTERPRETATION OF ABNORMAL VALUES
Basal T_3, T_4		Serum	*Dog:* T_3 = 80-200 ng/dL = 0.8-2 ng/mL = 1.2-3.1 nmol/L T_4 = 1.3-4 µg/dL = 13-40 ng/mL = 20-52 nmol/L *Cat:* T_3 = 60-150 ng/dL = 0.6-1.5 ng/mL = 0.6-1.9 nmol/L T_4 = 1-4.5 µg/dL = 10-45 ng/mL = 15-58 nmol/L	Suggestive of hypothyroidism: *Dog:* T_3< 30 ng/dL T_4 < 1 µg/dL Hyperthyroidism: *Cat:* T_3 > 200 ng/dL T_4 > 5 µg/dL *Dog:* T_3 > 290 ng/dL T_4 > 4 µg/dL
Free T_4 (FT_4) by dialysis		Serum	*Dog:* 16-30 pmol/L *Cat:* 15-48 pmol/L	*Dog:* FT_4 < 16 pmol/L suggestive of hypothyroidism, but may accompany other diseases *Cat:* FT_4 > 48 pmol/L indicative of hyperthyroidism
TSH response test	*Dog:* 0.1 IU TSH/kg IV *(Thytropar);* TSH inconsistently available	Measure serum T_4 at 0 and 4 or 6 hr after TSH	Post-TSH $T_4 \geq 2 \times$ basal T_4 or >35 nmol/L	Post-TSH $T_4 < 2 \times$ basal T_4 or < 35 nmol/L diagnostic of hypothyroidism
Canine endogenous TSH		Serum	*Dog:* 2-30 µU/L 2.7-7.9 ng/mL	Primary hypothyroidism: T_4 decreased, TSH increased (20-30 ng/mL) Canine assay validated for cats
TRH stimulation test	*Dog:* 0.2 mg TRH IV *Cat:* 0.1 mg TRH IV	Measure serum T_4 at 0 and 4 hr after TRH	*Dog:* Post-T_4 > 2 µg/dL or > basal T_4 + 0.5 µg/dL *Cat:* Post-T_4 increased by > 60%	Hypothyroidism (dog): Post-T_4 < 0.5 µg/dL Hyperthyroidism (cat): Post-T_4 increased by < 50% Equivocal findings (cat): Post-T_4 elevation of 50%-60%
T_3 suppression test	*Cat:* 25 µg T_3 PO TID × 7 doses	Measure T_4, T_3 before and 2-4 hr after last dose of T_3	$T_4 \leq$ 15 ng/mL ≤ 20 nmol/L	Hyperthyroid cats: T_4 does not suppress High T_3: confirms administration of T_3
ACTH response test	A. Synthetic ACTH *(Cortrosyn)* *Dog:* 0.5 U/kg IV, IM (max = 20 U) *Cat:* 0.125-0.25 mg IV, IM B. *Dog or cat:* ACTH gel 2.2 U/kg IM	A. Measure serum cortisol at 0 and 1 hr after ACTH in dogs or at 0, 30, and 60 min in cats B. Measure serum cortisol at 0 and 2 hr after ACTH in dogs and at 0, 1, and 2 hr in cats	≤ 50% of pretreatment values *Dog:* Pre-ACTH = 1.1-5 µg/dL, 25-38 nmol/L Post-ACTH = 6.2-16.8 µg/dL, 200-500 nmol/L *Cat:* Pre-ACTH = 0.33-2.6 µg/dL, 15-72 nmol/L Post-ACTH = 4.8-7.6 µg/dL, 130-210 nmol/L	Hyperadrenocorticism: Pre-ACTH = 4-10.8 µg/dL Post-ACTH = 11.7-50 µg/dL Primary hypoadrenocorticism: Pre- and post-ACTH = ≤1 µg/dL, ≤30 nmol/L

T_3, Triiodothyronine; *T_4,* thyroxine; *TSH,* thyroid-stimulating hormone; *TRH,* thyroid-releasing hormone; *ACTH,* adrenocorticotropic hormone; *max,* maximum.

ACTH assay	Draw sample into chilled syringe and insert into chilled EDTA tube; transfer sample to plastic tube and cool for 20 min in ice water; centrifuge sample for short time, retrieve plasma into another plastic tube, and Trasylol; freeze sample immediately and transport on dry ice		*Dog:* 20-80 pg/mL (avg. 45) 2-8.8 pmol/L *Cat:* 20-61 pg/mL 1-20 pmol/L	Pituitary-dependent hyperadrenocorticism: ACTH ≥40-500 pg/mL >88 pmol/L Functional adrenal tumor: ACTH ≤20 pg/mL ≤4.4 pmol/L
Low-dose dexamethasone suppression test	0.01 mg/kg dexamethasone sodium phosphate IV	Measure serum cortisol at 0, 4, and 8 hr after dexamethasone	*Dog:* Pre = 1.1-5 µg/dL Post = <1 µg/dL (Normal dogs suppress)	Hyperadrenocorticism: no suppression 4 or 6 hr post: 30% of pituitary-dependent hyperadrenocorticism cases suppress
High-dose dexamethasone suppression test	0.1 mg/kg dexamethasone sodium phosphate IV	Measure serum cortisol at 0, 4, and/or 8 hr after dexamethasone	Pre values reflect hyperadrenocorticism (4-10.8 µg/dL)	8 hr post: >1 µg/dL, >30 nmol/L
Urine cortisol:creatine ratio		Fresh urine sample	Urine cortisol (nmol/L):urine creatinine (mmol/L) ratio ≤35 (dog), <28 (cat)	Ratio > normal is suggestive of hyperadrenocorticism
Insulin assay		Measure serum insulin after 24-hr fast or during episodes of hypoglycemia	6-22 µU/mL	Values < normal preclude diagnosis of insulinoma Values > normal are suggestive of insulinoma
GH assay		Serum; assay currently unavailable	*Dog:* 0-10 ng/mL (usually 2-3 ng/mL) *Cat:* 0-8.5 ng/mL (mean = 1.21 ± 1.0 ng/mL)	Values > 90 ng/mL have been associated with neoplasia causing diencephalic syndrome in the dog and acromegaly in the cat Low values are difficult to asses; stimulation tests should be performed
Clonidine stimulation test	10 µg clonidine kg IV *(Catapresan)*	Measure plasma GH at 0, 15, 30, 45, 60, and 120 min after clonidine; keep samples frozen until assayed; GH assay currently unavailable	Normal dogs show increase in GH between 15 and 45 min with a peak of 25-40 ng/mL	Clonidine is a GH stimulant; pituitary dwarfs demonstrate either no or little response to clonidine
Xylazine stimulation test	100 µg/kg IV *(Rompun)*	Measure plasma GH at 0, 15, 30, 45, 60, and 120 min after xylazine; keep samples frozen until assayed GH assay currently unavailable	Normal dogs show increase in GH between 15 and 45 min with a peak of 25-40 ng/mL	Pituitary dwarfs show no response to xylazine

EDTA, Ethylenediamine tetraacetic acid; *GH,* growth hormone.

Continued

TABLE 2-1

Endocrine Assays—*cont'd*

TEST	PROTOCOL	SAMPLE REQUIRED	NORMAL VALUES	INTERPRETATION OF ABNORMAL VALUES
Somatomedin-C; IGF-1		Serum	*Dog:* 280 ± 23 ng/mL (adults) 345 ± 50 ng/mL (immature dogs) 5-45 nmol/L	Pituitary dwarfs have low value (11 ± 2 ng/mL or <5 nmol/L) Acromegaly in cats: Values of 70-100 nmol/L are nondiagnostic; repeat in 3 mos Values > 100 nmol/L are diagnostic
Gastrin assay		Plasma after 12-hr fast	*Dog:* 45-125 pg/mL *Cat:* 28-135 pg/mL	Plasma gastrin levels are increased with primary gastrointestinal tract disease (e.g., functional gastrinomas) or secondary to other systematic diseases, especially chronic renal failure
Antidiuretic hormone response test	Perform water deprivation test first; give desmopressin acetate 2-4 drops intranasally or conjunctivally or 10-20 µg/kg SC (dogs); if available, aqueous vasopressin may be given at 2-5 UIM (dogs)	Empty bladder and collect urine at 60, 120, 180, and 240 min	Normal: sp. gr. >1.025	Central diabetes insipidus: sp. gr. >1.015 Nephrogenic diabetes insipidus or medullary washout: sp. gr. <1.015
PTH assay		Serum	*Dog:* 2-13 pmol/L, 16-136 pg/mL *Cat:* 0-4 pmol/L, 3.3-22.5 pg/mL	Hypoparathyroidism: PTH is low or undetectable, especially if ionized calcium is low Parathyroid adenoma: PTH as high as 45 pmol/L Secondary hyperparathyroidism (renal failure): PTH grossly elevated
Calcitonin assay		Plasma	*Dog:* ≤25 pg-Eq/mL	Values of plasma calcitonin are difficult to interpret at this time; extreme elevations may be caused by calcitonin-producing thyroid tumors
Erythropoietin		Serum	*Dog:* 5-15 mU/mL *Cat:* 5-22 mU/mL	Low: primary polycythemia, chronic renal failure Normal or high: secondary polycythemia Very elevated: asplastic anemia, certain renal tumors
Ionized calcium		Serum	1.12-1.42 nmol/L	Primary hyperparathyroidism: increased values Malignant hypercalcemia; increased values Renal failure: normal or increased values Hypoparathyroidism: decreased values Feline pancreatitis: decreased values

IGF-1, Insulin-like growth factor-I; *sp. gr.,* specific gravity; *PTH,* parathormone.

TABLE 2-2

Gastrointestinal Studies

TEST	PROTOCOL	SAMPLE REQUIRED	NORMAL VALUES	INTERPRETATION
Bile acid assays	1. Fast animal 12 hr 2. Feed a routine or high-protein meal	Serum samples are colleted after 12-hr fast and 2 hr after a meal	*Dog:* Fasting ≤5 µmol/L Postprandial ≤ 15.5 µmol/L *Cat:* Fasting ≤ 2 µmol/L Postprandial ≤ 10 µmol/L	Elevations indicate dysfunction of normal hepatobiliary physiology, with the degree of elevation providing limited quantitative information
Ammonium tolerance test	Give 100 mg/kg NH_4Cl PO (max dose = 3 g)	1. Draw blood sample into EDTA or heparinized saline before and 30 min after NH_4Cl 2. Cool blood on ice immediately	Fasting ≤ 120-150 µg/dL Post-NH_4Cl ≤ 200-250 µg/dL	Elevation of blood ammonia indicates either hepatic dysfunction or shunting of portal blood away from the liver (i.e., portocaval shunt)
Glucagon tolerance test	1. Fast animal 2 hr 2. Give glucagon 0.03 mg/kg IV	Measure serum glucose at 0, 15, 30, 60, and 90 min after glucagon administration	Serum glucose rises in response to glucagon, with peak at 15 min, and returns to normal by 90 min	Glucose curve remains flat with severe hepatic insufficiency, portocaval shunt, glycogen storage disease, and prolonged anorexia or starvation
BT-PABA test	1. Fast animal 18 hr 2. Give 5 mL 1% BT-PABA/kg PO followed by 25-100 mL water 3. Stomach tubing is preferred 4. Avoid concurrent use of chloramphenicol, sulfonamides, diuretics, and pancreatic extracts for 5 days before test	Heparinized plasma is obtained for measuring plasma PABA at 0, 30, 60, 90, and 120 min	*Dog:* >5-35 µg/mL *Cat:* >7.5 µg/mL (at 90 min)	Indirectly measures chymotrypsin activity Values <1.25 µg/mL are compatible with pancreatic exocrine insufficiency and also reflect small intestinal absorption capabilites Values of 1.25-4 µg/mL are compatible with malabsorption
TLI; canine (cTLI) and feline (fTLI) assays available	Fast animal 6-12 hr	Serum	*Dog:* 5-35 µg/L *Cat:* 17-49 µg/L	Maldigestion (exocrine pancreatic insufficiency): <2 µg/L (dog), <8 µg/L (cat) Malabsorption: >5 µg/L (dog) Pancreatitis: >50 µg/L (dog) >200 µg/L (cat)

BT-PABA, N-benzoyl-L-tyrosyl-p-aminobenzoic acid; *TLI,* trysin-like immunoreactivity.

Continued

TABLE 2-2

Gastrointestinal Studies—*cont'd*

TEST	PROTOCOL	SAMPLE REQUIRED	NORMAL VALUES	INTERPRETATION
PLI	Fast animal 6-12 hr	Serum	*Dog:* 0-200 µg/L *Cat:* 2-6.8 µg/L	Poor diagnostic accuracy for pancreatitis Pancreatitis: >400 µg/L (dog) >12 µg/L (cat)
Fecal alpha 1-protease inhibitor assay	Collect fresh fecal specimens	Feces	*Dog:* 0-32 µg/g	Increased with protein-losing enteropathies
Folate levels	Fast animal 6-12 hr	Serum	*Dog:* 6.7-17.4 µg/L *Cat:* 13-4-38 µg/L	Increased with gastrointestinal bacterial overgrowth, pancreatic exocrine insufficiency, folate supplementation, or hemolyzed blood samples Low with small intestine malabsortion
Cobalamin levels	Fast animal 6-12 hr	Serum	*Dog:* 225-660 ng/L *Cat:* 200-1680 ng/L	Low with cobalamin malabsorption (ileal disease), pancreatic exocrine insufficiency, or small intestinal bacterial overgrowth Increased with parenteral supplementation

PLI, Pancreatic lipase immunoreactivity.

TABLE 2–3

Renal Function Tests

TEST	PROTOCOL	SAMPLE REQUIRED	NORMAL VALUES	INTERPRETATION
PSP excretion in urine	A. 1. Empty bladder via catheterization 2. Give 6 mg PSP IV B. Give 1 mg PSP/kg IV	A. Catheterize bladder 20 min later and collect all urine B. Collect 4 mL heparinized plasma before and 60 min after PSP administration	A. Normal: >30% excretion of PSP B. Normal: 80 µg/dL Suspicious: 80-120 µg/dL Abnormal: ≥120 µg/dL	A. Assesses renal blood flow B. Assess renal tubular function; abnormal retention occurs with renal insufficiency
SS clearance	Give 0.2 mL of 10% solution/kg IV after a 12-hr fast	Obtain heparinized blood at 30, 60, and 90 min	Results are expressed as the time needed to clear 50% of dye from the blood ($t_{1/2}$) Normal $t_{1/2}$ = 32-84 min.	SS retention in plasma above normal reflects diminished GFR SS clearance is usually reduced before the development of either azotemia or urine concentration defects
Endogenous creatinine clearance	1. Acclimate animal to metabolism cage 2. Catheterize and empty bladder 3. Allow access to free-choice water 4. Collect all urine for 24 hr; empty bladder again at end of test 5. Avoid contamination of urine with feces 6. Store urine in closed, refrigerated container until test is concluded 7. Record total volume of urine	1. Submit serum sample obtained midway through test for creatinine assay (SC) 2. Submit urine sample from the pooled collection for creatinine measurement (UC) 3. Use equation to calculate clearance: $\text{GFR} = \frac{\text{UC (mg/dL)} \times \text{urine volume (mL)}}{\text{SC (mg/dL)} \times 1440 \text{ min} \times \text{weight (kg)}}$	Normal, dogs: 2-5 mL/min/kg Normal, cats: 1.6-4 mL/min/kg	Decreased GFR occurs with decreased renal blood flow (prerenal), obstruction of urine outflow (postrenal), and renal parenchymal disease Decreased GFR in an otherwise normal dog indicates renal insufficiency
Urine protein quantitation	Follow protocol outlined for endogenous creatinine clearance Most common assay is trichloroacetic acid–ponceau S method	1. Submit pooled urine sample 2. Protein excretion/24 hr = urine protein (mg/dL) × urine volume (dL) 3. Protein excretion/kg = total protein (mg)/weight (kg)	1. Protein/kg/day ≤30 mg/kg/day 2. Total protein: 333 ± 309 mg/day	Significant proteinuria occurs with glomerular disease Other causes include Bence Jones proteinuria, myoglobinuria, and severe urinary tract trauma
UP/C ratio	Random sample	*Dog:* urine	Normal ≤1.0	Significant proteinuria: UP/C >1.0 Results are affected by both pyuria and gross blood contamination

PSP, Phenolsulfonphthalein; *SS,* sodium sulfanilate; *GFR,* glomerular filtration rate; *UP/C,* urine protein:creatinine.

TABLE 2-4

Interpretation of Selected Serologic Tests

DISEASE	TEST	INTERPRETATION
Brucellosis	A. RSAT	A. Good screening test False positives occur, so perform further seologic assay to confirm the diagnosis; a modification of the test (ME-RSAT) using a less mucoid (M-) variant of *Brucella canis* has fewer false positives; it becomes positive within 3-4 wk, but false negatives can occur up to 8 wk
	B. Tube agglutination tests 1. TAT	B. Most common confirmatory test 1. Becomes positive by 3-6 wk Titer results: 1:50 = early or recovering infection 1:50-1:100 = suspicious ≥1:200 = active infection Occurrence of false positives similar to RSAT
	2. ME-TAT	2. Fewer false positives Becomes positive 1-2 wk after TAT or 5-8 wk post-infection ≥1:200 = active infection
	C. AGID	C. Becomes positive in 8-12 wk Very specific; used to confirm diagnosis, especially in chronic cases Both somatic and cytoplasmic (CPAg-AGID) tests available, but somatic rarely used Results reported as positive, suspicious, or negative Repeat in 4-6 wk if first results are suspicious May remain positive for 1 yr
	D. ELISA	D. Very specific, but less sensitive than TAT tests Becomes positive by 4 wk
	E. IFA	E. Sensitivity is uncertain, so some infected dogs may be missed
Leptospirosis	A. MAT	A. Titers <1:400 may be postvaccinal Titers >1:800 usually indicate infection Paired samples 2-4 wk apart are tested; a fourfold increase in titer is diagnostic Tests for serovar groups, not individual serovars
	B. ELISA	B. IgM titer: develops after 1 wk IgG titer: develops in 2-3 wk Vaccinates: high IgG titer with low or negative IgM titer
Feline infectious peritonitis (FIP)	A. IFA, ELISA	A. Titer >1: 1600 (most laboratories) or fourfold increase over 2-4 wk is compatible with a positive diagnosis Titer > 1: 240 is inconclusive NOTE: This titer cross-reacts with other feline coronaviruses, so is not specific for FIP
	B. PCR assay	B. May help confirm presence of coronavirus in seronegative cats, but false negatives can occur and is not specific for FIP
Canine parvovirus	A. Hemagglutination inhibition, ELISA	A. Positive diagnosis: Single high IgM titer Fourfold rise in IgG titer over 2-4 wk; also considered protective
	B. Fecal ELISA or hemagglutination	B. Sensitive and specific test Shedding of virus is brief and usually not detected by day 10-12 of infection (day 5-7 of clinical illness) Vaccination produces false positives 5-12 days after administration

RSAT, Rapid slide agglutination test; *TAT,* tube agglutination test; *ME-TAT,* 2-mercaptoethane TAT; *AGID,* agar-gel immunodiffusion; *ELISA,* enzyme-linked immunosorbent assay; *IFA,* indirect immunofluorescence antibody; *MAT,* microscopic agglutination test; *IgM,* immunoglobulin M; *IgG,* immuoglobulin G; *PCR,* polymerase chain reaction; *FIP,* feline infectious peritonitis.

TABLE 2-4

Interpretation of Selected Serologic Tests—*cont'd*

DISEASE	TEST	INTERPRETATION
Ehrlichiosis *(Ehrlichia canis)*	A. IFA	A. Becomes positive in 7-28 days Titer >1:80 is considered positive in endemic areas Any measurable titer (>1:10) is significant in dogs in nonendemic areas Submit a second sample 2-3 wk later if suspicious case is negative on first sample Titers persist for 6-9 mo after infection Cross-reactivity occurs with *Neorickettsia* spp., *Helminthoeca* spp., and other ehrlichial agents
	B. Western immunoblotting assay	B. Detects antibodies 2-8 days after exposure Can distinguish *E. canis* from *E. ewingii*
	C. PCR assay	C. Positive within 4-10 days In the future, it may be able to distinguish active infection from titers that persist following successful treatment of disease
Rocky Mountain spotted fever	A. Indirect immunofluorescence test (Micro-IF) or ELISA for IgG	A. Submit acute and convalescent titers 2-3 wk apart Titer ≤1:64 = normal Titer ≥1:1024 in East, ≥1:25 in West = infected Fourfold increase in titers is diagnostic False negatives occur early in disease Titers may stay elevated (1:128) for 5-10 mo
	B. Micro-IF or ELISA for IgM	B. Decreases within 4-8 wk Single high titer indicates active infection
	C. Latex agglutination	C. Sensitivity lower than Micro-IF tests Single high titer (≥132) is diagnostic
	D. PCR assay	D. Can be run on both whole blood and tissues Nested PCR more sensitive in treated dogs
Borreliosis (Lyme disease)	A. IFA, ELISA	A. Titers are difficult to interpret and may indicate exposure rather than active infection Can cross-react with other bacteria, especially other *Borrelia* spp. and *Leptospira* spp. Symptomatic dogs usually have titers >1:128 Measure IgG and IgM titers simultaneously Fourfold increase in paired samples submitted 2-4 wk apart is supportive IgG titers become positive in 4-6 wk and persist for ≥2 yr IgM titers may persist for several months Titers do not distinguish postvaccinal responses from actual infection
	B. Western immunoblotting assay	B. Can distinguish postvaccinal responses from actual exposure/infection and identify false negatives
	C. ELISA for specific outer surface proteins (Osp)	C. Antibodies to OspA and OspB indicate post-vaccinal response Antibodies to OspC indicate active infection C_6 assay way indicate active infection and help assess response to treatment
Toxoplasmosis	A. IHA	A. Becomes positive in 2 wk; detects IgG Relatively insensitive, not species specific Fourfold rise in titer over 2-3 wk supportive
	B. LAT, MAT	B. Become positive in 2 wk, detects IgG MAT more sensitive Positive results: LAT > 1:64 MAT > 1:100 Fourfold rise in titer over 2-3 wk supportive Test may be applied to aqueous humor or CSF

IHA, Indirect hemagglutination; *LAT,* latex agglutination test; *CSF,* cerebrospinal fluid.

Continued

TABLE 2-4

Interpretation of Selected Serologic Tests—*cont'd*

DISEASE	TEST	INTERPRETATION
	C. IFA for IgM, IgG	C. False positives occur IgM elevated within 1-2 wk and IgG detectable after 2 wk Single high IgM titer (1:64), with negative IgG titer, implies active infection Fourfold increase in titers over 2-5 wk supportive Test may be applied to aqueous humor or CSF
	D. ELISA for IgM, IgG	D. More sensitive than IHA or LAT IgM titer >1.256, with negative IgG titer, implies active infection IgM is detected within 1-2 wk IgG is detectable in approximately 2-4 wk Fourfold increase in titers over 2-3 wk supportive Test may be applied to aqueous humor or CSF
	E. All tests	E. NOTE: Use caution when interpreting results; antibodies can occur in the sera of both healthy and diseased cats; therefore serologic tests alone do not confirm the presence of disease; titers may persist for months to years following infection
Blastomycosis	A. AGID	A. If positive, dog has 91% chance of having active disease but test may be negative in acute stages
	B. ELISA	B. May be more sensitive than AGID in cats Accuracy and sensitivity poorly defined
Cryptococcosis	A. LAT	A. *Cat:* Titer >1:12 indicative of active infection *Dog:* Any positive result indicative of infection False negatives can occur with localized disease False positives possible with contamination of assay; test cross-reacts with *Trichosporon* spp. Titers correlate well with extent and course of disease, and response to therapy May be assayed in serum, urine, CSF
	B. PCR	B. May be performed on tissues May be assayed in serum, urine, CSF
Coccidioidomycosis	A. TP test	A. Becomes positive in 2-6 wk Detects IgM; is a qualitative test and fades quickly (within 4-6 wk)
	B. CF test	B. Detects IgG and appears in 8-10 wk Titer ≤1:4 = negative Titer ≥1:16 = suspicious, chronic, or localized disease Titer ≥1:32 = active disease Rise or drop in titer corresponds well with clinical course, but titers remain elevated for months after treatment or disease arrest
	C. LAT	C. Measures IgM, so detects acute infection Some false positives in dogs
	D. AGID-TP, AGID-CF	D. More sensitive assays AGID-TP detects IgM; AGID-CF detects IgG
	E. ELISA	E. Available for detection of both IgM and IgG Some false positives in dogs; cross-reacts with blastomycosis
Histoplasmosis	A. CF titer B. Skin histoplasmin test	Neither test is considered reliable in dogs and cats for definitive diagnosis
Aspergillosis	A. AGDD	A. False positive rate of 6%; cross-reacts with *Penicillum* spp.
	B. CIE	B. Up to 15% false-positive results
	C. ELISA	C. Less reliable than AGDD or CIE
	D. PCR assay	D. Used experimentally; clinical availability limited NOTE: Some infected dogs never seroconvert; false negative rate is higher when only one antigen tested

TP, Tube precipitin; *CF,* complement fixation; *AGDD,* agar gel double diffusion; *CIE,* counterimmunoelectrophoresis.

III. An unmeasured osmole is suggested when both values are elevated and a significant gap exists.
   A. Mannitol, glycerin
   B. Sorbitol, acetone
   C. Ethylene glycol, alcohol
   D. Myeloma protein, hyperlipidemia
   E. Infused hyperosmotic solutions
   F. Activated charcoal containing propylene glycol and glycerol (Burkitt et al., 2005)

Clinical Significance

I. Directs attention to laboratory errors
II. Detects presence of unmeasured osmoles (e.g., ethylene glycol)
III. Can be used to confirm hyperproteinemia and hyperlipidemia

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CHAPTER 3

Selected Diagnostic and Therapeutic Procedures

Rhea V. Morgan

CENTRAL VENOUS PRESSURE MEASUREMENT

Definition

I. Central venous pressure (CVP) is the measurement of fluid pressure in the anterior vena cava or right atrium.
II. It is a dynamic function of both cardiac output and venous return to the heart.
III. CVP does not correlate with pulmonary venous pressure in left-sided congestive heart failure.

Indications

I. Assessment of intravenous (IV) fluid therapy
II. Monitoring circulation hemodynamics during shock
III. As a diagnostic aid in cases of heart failure and pericardial effusion with tamponade

Restraint

I. The animal may be placed in either sternal or lateral recumbency.
II. Sedation is neither indicated nor desirable.

Technique

I. Insert an indwelling IV catheter into the external jugular vein, bringing the tip of the catheter to rest in the cranial vena cava.
   A. The length of catheter to use can be estimated by measuring the distance from the entrance site in the neck to a point near the 4th rib.
   B. Positioning can be confirmed via a lateral radiograph if an IV catheter with a radiopaque marker is used.
II. Connect the catheter to the male end of a three-way stopcock via extension tubing.
III. Attach a manometer calibrated in centimeters to the stopcock, perpendicular to the catheter line (Box 3-1).
IV. Attach an IV infusion solution to the third portal of the stopcock.
V. Fill the tubing and manometer with heparinized saline or IV solution, ensuring no air bubbles are present.
VI. Hold the manometer so the zero mark is level with the right atrium.
   A. Sternal recumbency: 4th intercostal space, 2 to 3 inches above the sternum
   B. Lateral recumbency: parallel to the sternum near the 4th sternebra
VII. Turn the stopcock so that the infusion set is off and the manometer connection to the catheter is open.
VIII. Allow liquid in the manometer to equilibrate.
IX. Note the pressure at the point where the meniscus stops descending.
X. If the meniscus falls below zero, refill the manometer and lower it so that the zero point is now at the 5-cm mark, with values between 0 and 5 cm denoting negative measurements.
XI. In cats, caudal vena cava CVP measurements can be used as an alternative (Machon et al., 1995).

Sources of Error

I. Incorrect positioning of the manometer
II. Rapid or labored breathing
III. Kinking of catheter or extension tubing
IV. Clots within the catheter
V. Malfunctioning of stopcock
VI. Pleural effusion: falsely elevates CVP in absence of right-sided congestive heart failure (Gookin and Atkins, 1999)

Interpretation

I. CVP is an insensitive test, but the sensitivity can be increased by using minimal lengths of connective tubing and removing all extraneous catheter adapters.
II. The trends that develop with sequential CVP recordings are more significant than isolated or individual measurements.
III. Values above 10 cm H_2O reflect hypervolemia/venous congestion.
IV. CVP measurement can be used to judge the endpoint of diuresis (unacceptably low values) or a large fluid infusion (high values).
V. See Appendix I for normal CVP values.

PERICARDIOCENTESIS

Definition

Pericardiocentesis is the transthoracic insertion of a needle or cannula into the pericardial space for the collection of fluid for diagnostic or therapeutic purposes.

Indications

I. Collection of pericardial fluid for gross, cytologic, and bacterial analysis

Box 3-1

Diagnostic and Therapeutic Instruments

Manometer

Pharmaseal Manometer Tray (Baxter Healthcare Corp., Pharmaseal Division, Glendale, Calif.)

Blood Pressure Monitors

Dinamap monitor Model 8100 (Critikon, Inc., Tampa, Fla.)
Parks (ultrasonic Doppler) flow detector model 811-B (Parks Medical Electronics, Inc., Aloha, Ore.)
Cardell monitors, various models (CAS Medical Systems, Branford, Conn.)
Trax (manufactured by Colin for DRE, Louisville, Ky.)
Memoprint (S+B medVET, Babenhausen, Germany)
Colin 8800c (Colin Medical Instruments, San Antonio, Tex.)

Indwelling Chest Tube

Argyle trocar catheter with Sentinel Eye (Argyle Division of Sherwood Medical, St. Louis, Mo.)

One-way Air Valve

Heimlich Chest Drain Valve (Bard-Parker/Becton, Dickinson Acute Care, Franklin Lakes, N.J.)

Continuous Evacuation Pump

Pleur-Evac (Deknatel, Division of Pfizer, Queens Village, N.Y.)
Closed chest suction (Argyle Division of Sherwood Medical Products, St. Louis, Mo.)

Nasal Oxygen Tubes and Nasal Feeding Tubes

Kaofeed II polyurethane feeding tube (Jorensen Laboratories, Loveland, Colo.)
Sterile single-use feeding tube and urethral catheter (Jorensen Laboratories, Loveland, Colo.)
Argyle nasogastric feeding tube (Argyle Division of Sherwood Medical, St. Louis, Mo.)

Nasal Oxygen Humidification

Hudson Humidifier (USA Hudson Respiratory Care, Research Triangle Park, N.C.)

Tracheostomy Tube

Portex (Portex, Wilmington, Mass.)

Transtracheal Fluid Trap

Lukens specimen container (Sherwood Medical Company/Tyco Kendall Healthcare, Deland, Fla.)

Percutaneous Gastrostomy Tubes

Medicut intravenous cannula (Sherwood Medical Industries, Inc., St. Louis, Mo.)
Bard urologic catheter (Bard Urologic Division of C.R. Bard, Covington, Ga.)
Silicone percutaneous endoscopic gastrostomy kit (Ballard Medical of Kimberly Clark, Roswell, Ga.)
EndoVine low-profile percutaneous endoscopic gastrostomy kit (Boston Scientific, Natick, Mass.)

Gastrostomy Tube Placement Device

Eld Gastrostomy Tube Applicator (Jorgensen Laboratories, Loveland, Colo.)

Bone Marrow Biopsy Needles

Osgood needle (Becton, Dickinson and Co., San Jose, Calif.)
Rosenthal needle (Becton, Dickinson and Co., San Jose, Calif.)
Jamshidi needle (Baxter Healthcare, Pharmaseal Division, Glendale, Calif.)

Bone Biopsy Instrument

Michel trephine (Jorgensen Laboratories, Loveland, Colo.)

II. Removal of pericardial fluid that is restricting diastolic filling of the ventricles during cardiac tamponade
III. Performing radiographic contrast studies, with administration of intrapericardial positive or negative contrast media to enhance radiographic visualization of intrapericardial structures

Restraint

I. Restrain the animal in lateral or sternal recumbency, or in a standing position.
II. Many dogs undergo this procedure with local anesthesia only.
III. If needed, mild chemical sedation (opioids, benzodiazepines) may be used, but must be used cautiously in animals with cardiovascular compromise (see Chapter 1).

Technique

I. A rectangular area of the right lateral thoracic skin is clipped and prepared aseptically from the sternum to the midthorax and from the 2nd to the 8th rib.
II. Thoracic ultrasonography can be used for needle placement.
III. Electrocardiography (ECG) is performed throughout the procedure.
IV. If ultrasound is unavailable, the site for needle insertion is selected based on review of the dorsoventral and lateral thoracic radiographs to assess the location of the pericardial silhouette.
    A. Usually the 4th, 5th, or 6th intercostal space is best.
    B. The right side is preferable for minimizing trauma to the lungs (because of the cardiac notch) and the major coronary arteries (located mostly on the left).
    C. A point one fourth of the distance from the sternebrae to the costochondral junction at the strongest palpable cardiac impulse (usually between the 4th and 6th ribs) is selected.
        1. The ventral location reduces the risk of coronary artery laceration by the needle.
        2. Also avoid the internal thoracic artery, which lies just dorsal to the sternebrae.

D. The skin and subcutaneous and intercostal tissues may be infiltrated with a local anesthetic before needle insertion. Note that the intercostal vessels and nerves course along the caudal edge of the ribs.
E. A variety of equipment can be used.
   1. Over-the-needle catheters (12 to 20 gauge) are used based on the size of the animal.
   2. A 19-gauge through-the-needle catheter is also appropriate.
   3. The needle is passed through the skin, subcutis, and intercostal muscles until it is in the pericardial space.
   4. The catheter is advanced, and the needle is withdrawn from the chest wall.
   5. The stylet is removed, and a three-way stopcock and sterile syringe (12 or 20 mL) are attached.
   6. If the beating heart can be felt against the tip of the catheter, withdraw it for a short distance and monitor the ECG for arrhythmias.
F. Fluid is aspirated.
   1. If no fluid is obtained, the catheter is slowly withdrawn while applying intermittent suction.
   2. As the volume of fluid decreases in the pericardial sac, the catheter may need to be repositioned.
   3. After completion of fluid collection, the catheter is withdrawn.
G. The fluid is transferred to ethylenediamene tetraacetic acid (EDTA) tubes for cytologic study and to transport medium for bacteriologic analysis.

Complications

I. Cardiac arrhythmias may be induced by the needle contacting or penetrating the myocardium.
II. Laceration of a coronary artery can lead to hemorrhage and tamponade.
   A. Collection of bloody fluid that clots soon after collection may indicate coronary artery laceration.
   B. Insertion of the needle in a ventral location (near cardiac apex) or under guidance with fluoroscopy or ultrasonography reduces the likelihood of this complication.

THORACENTESIS

Definition

Thoracentesis is the surgical puncturing of the chest wall for drainage of fluid or air from the pleural cavity.

Indications

I. Alleviation of pneumothorax
II. Obtaining fluid samples for analysis
III. Removal of fluid to relieve dyspnea

Restraint

I. Sternal recumbency is preferred so that gravity causes intrathoracic fluid to be positioned ventrally in the chest and air to be trapped dorsally.
II. Compromised animals are restrained manually.
III. Fractious or anxious animals may be mildly tranquilized.

Technique

I. Shave the hair and aseptically prepare the skin at the site of puncture.
   A. To remove air, aspirate dorsally at the 7th to 9th intercostal spaces.
   B. To retrieve fluid, aspirate ventrally at the 7th or 8th intercostal space, avoiding the apex beat of the heart.
   C. Avoid inserting the needle close to the caudal edge of the ribs because the intercostal vessels and nerves lie in this area.
   D. Also avoid inserting the needle in the area just dorsal to the sternebrae, or the internal thoracic artery may be punctured.
II. Aspirate either air or fluid using appropriate equipment.
   A. Air and most fluids can be retrieved using a 21-gauge butterfly catheter, a three-way stopcock, and a 20- to 60-mL syringe.
   B. In large dogs and in cases with viscous fluids, 14- to 16-gauge IV over-the-needle catheters are used, with extension tubing, a three-way stopcock, and syringe attached after the stylet is removed.
III. Pass the needle through the skin, intercostal muscles, and parietal pleura into the pleural cavity.
IV. If an IV catheter is used, thread the catheter into the chest for several inches and withdraw the needle.
V. Apply negative pressure to the syringe with the three-way stopcock in the open position.

Complications

I. Accidental puncture of the internal thoracic artery, intercostal or coronary vessels, and myocardium
II. Accidental pneumothorax if the three-way stopcock is left open, connections in the aspiration line become loose, or if the visceral pleura is lacerated

CHEST TUBE PLACEMENT

Definition

Chest tube placement refers to insertion of an indwelling chest tube for treatment of pleural cavity disease.

Indications

I. Providing access to the pleural space for repeated, intermittent aspiration of free pleural fluid or air
II. Providing continuous evacuation of air in cases of severe and/or tension pneumothorax
III. Providing a means for installation and subsequent drainage of intrathoracic antibiotics, lavage solutions, and chemotherapeutic agents

Restraint

I. For insertion of the chest tube, the animal is placed in lateral recumbency.
II. Manual restraint is preferred but sedation may be considered.
III. Once the chest tube is inserted and positioned, actual aspiration of the chest may be attempted in any position that facilitates removal of the fluid or air.

Technique

I. The hair is shaved and the skin is aseptically prepared.
II. If time allows, the skin and musculature are infiltrated with a local anesthetic, one to two ribs caudal to the insertion site.
III. The sites chosen for insertion are similar to those for thoracentesis.
   A. Air: dorsal 7th or 8th intercostal spaces
   B. Fluid: ventral 6th to 8th intercostal spaces
   C. One or more tubes inserted unilaterally or bilaterally
IV. A stab incision with a scalpel blade is made through the skin over the infiltrated site.
V. The chest tube with trocar is inserted through the incision and advanced cranially under the skin to the desired site.
VI. With a quick, forceful movement, the tube is pushed through the intercostal muscles and into the thorax (Figure 3-1).
VII. As the trocar is removed, the tube is cross-clamped, and the free end is attached to a three-way stopcock, one-way valve, or continuous evacuation pump (see Box 3-1).
VIII. The clamp is released, the patency of the tube ensured, and a purse-string suture placed in the skin where the tube exits.
   A. The tube is marked at the level where it enters the skin, so that migration of the tube can be detected.
   B. A non–water-soluble ointment is applied at the exit site.
IX. The tube is fixed to the chest by placing stay sutures through a tape butterfly surrounding the free end of the tube, and a light chest wrap is applied to protect the tube from dislodgment.
X. Postprocedural thoracic radiographs are recommended to verify correct placement of the chest tube.

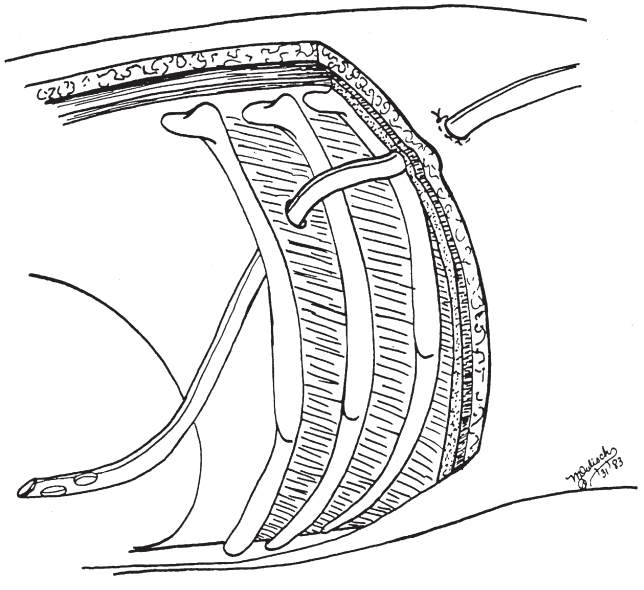

FIGURE 3-1 Technique for inserting an indwelling chest tube. *From Morgan RV: Manual of Small Animal Emergencies. Churchill Livingstone, New York, 1985; with permission.*

Complications

I. Inadvertent laceration of intercostal, internal thoracic, or cardiac vessels (see Thoracentesis for vessel location) is a potential complication.
II. Accidental pneumothorax can occur during removal of the trocar.
III. In the days after insertion of the chest tube, close monitoring is necessary to ensure the following:
   A. The chest tube remains patent, and all moving parts remain free of viscous discharges.
   B. The position of the tube is correct within the chest, and it does not back out.
   C. All connections are tight, with no leakage of air into the chest.
   D. All portals are protected from bacterial contamination.

NASAL OXYGEN ADMINISTRATION

Definition

Nasal cannulation allows the administration of oxygen from a tube placed through the nares into the ventral nasal meatus to increase arterial blood oxygen concentration.

Indications

I. Any cause of hypoxia
   A. Cardiopulmonary disease
   B. Hematologic abnormalities
   C. Metabolic disease
   D. Shock
II. Useful in animals too mobile for an oxygen mask or too large for an oxygen cage
III. May be more effective than some oxygen cages

Restraint and Technique

I. Topical anesthesia is usually all that is required.
   A. With the head extended, 0.1 to 0.5 mL of 2% lidocaine is dripped into the nares.
   B. Lidocaine gel is also applied to the junction of the skin and the nares laterally, allowing several minutes for the region to become anesthetized.
II. A fenestrated polyurethane or soft rubber catheter of appropriate size (usually a 4, 6, or 8 French) is selected.
III. Infant feeding tubes also work well.
IV. The tube is measured from the nares to approximately the level of the fourth premolar tooth and marked.
V. The tube is then passed through the nares into the ventral nasal meatus until the predetermined mark is reached.
VI. It is sutured to the skin lateral to the nares using 3-0 or 2-0 nylon.
   A. It is important to place this first suture as close to the nasal mucosa as possible to ensure good tube stability.
   B. Once the first knot is placed, the suture material is passed several times around the tube in a "bootlace" pattern.
VII. A second suture is placed on the midline of the forehead, fixing the skin to an adhesive tape butterfly placed around the tube.

VIII. Humidified oxygen is delivered to the animal.
  A. Commercially available humidifiers may be used (see Box 3-1).
  B. A homemade humidifier can be made (Fitzpatrick and Crowe, 1985).
    1. An IV extension tube is attached to the nasal oxygen tube (see Box 3-1) and run into the administration port of a half-full bottle of warm saline.
    2. The tube carrying the oxygen source is attached to the vent hole of the bottle, and the oxygen is bubbled through the water.
  C. The oxygen flow rate is set at 50 to 150 mL/min/kg body weight initially and then adjusted as needed.
IX. Mostly commonly, a unilateral tube is placed; bilateral tubes increase the risk of oxygen toxicity with prolonged administration (Dunphy et al., 2000).

Complications

I. If the oxygen flow rate is too high, nasal mucosal erosions ("jet lesions") and nasal irritation may occur.
II. Gastric dilatation can occur if the tube is placed too far caudally toward the pharynx or if the oxygen flow rate is too high.
III. Unhumidified oxygen causes dryness of the respiratory passages.
IV. Traumatic tube placement may result in mild epistaxis.

TRACHEOSTOMY TUBE INSERTION

Definition

A tracheostomy is the surgical creation of an opening into the trachea for insertion of a tracheostomy tube.

Indications

I. Providing a means for delivering air or oxygen past an upper airway obstruction
II. Allowing a means to evacuate secretions from the airway
III. Facilitating passage of air or oxygen to the lungs under positive pressure

Restraint

I. General anesthesia is preferred.
II. In an emergency, physical restraint with or without local anesthesia may be all that is required.

Technique

I. Shave the hair and aseptically prepare the skin from the angular process of the jaw to the thoracic inlet, with the animal in dorsal recumbency.
II. Make a longitudinal incision over the trachea immediately caudal to the larynx or caudal to the obstruction.
III. Separate the two sternohyoid muscles with blunt dissection (Figure 3-2, *A*).
IV. Incise the trachea between the cartilaginous rings. For high obstructions, make the incision between rings 2 and 3 or 3 and 4.
V. Enlarge the incision with a scalpel blade, being careful not to lacerate the endotracheal tube (Figure 3-2, *B*).
VI. A loop of 2-0 silk suture is placed around the ventral aspect of the tracheal ring cranial and caudal to the tracheostoma to facilitate intubation and reintubation.
VII. Withdraw the endotracheal tube and insert a tracheostomy tube (Figure 3-2, *C,* and see Box 3-1).
VIII. If the tracheostomy tube is supplied with an obturator, remove it.
IX. Tie the tracheostomy tube in place with umbilical tape or suture the tube to the skin of the neck.
X. Sterile endotracheal tubes may be used in giant-breed or thick-necked dogs in which ordinary tubes cannot be adequately secured.

Complications

I. Patency of the airway may be compromised during the tracheostomy procedure by blood and secretions, so suction the airway immediately after inserting the tube.
II. The normal warming and humidification of air by the nasal passages is bypassed with a tracheostomy tube.
  A. Thick, dry mucus may accumulate as a result and diminish the tube's patency.
  B. Measures can be taken to prevent accumulation of mucus.
    1. Suction the tube every 2 to 4 hours using aseptic technique.
    2. Liquefy secretions.
      a. Nebulize with saline every 4 to 8 hours.
      b. Instill 1 mL saline into the tracheal tube every 2 to 8 hours.

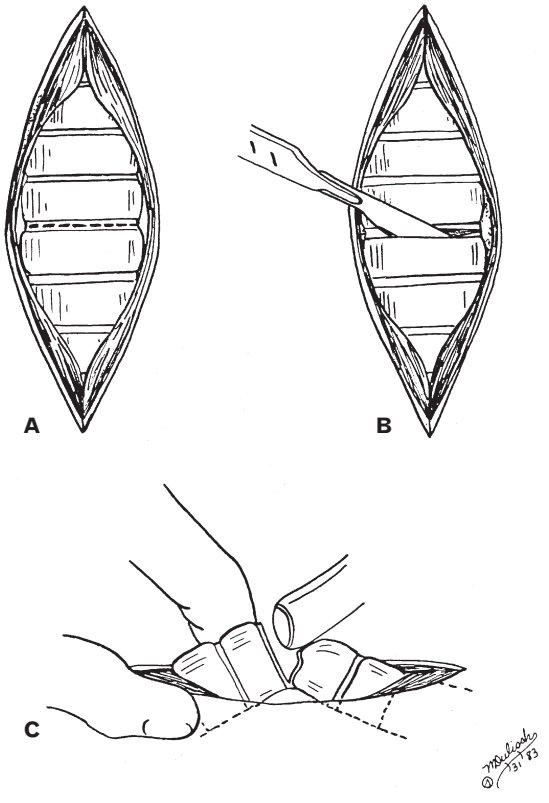

FIGURE 3-2 Technique for insertion of a tracheostomy tube. *From Morgan RV: Manual of Small Animal Emergencies. Churchill Livingstone, New York, 1985; with permission.*

3. Maintain normal body hydration with SC or IV fluids.

III. Overzealous aspiration may cause rupture of the airway and secondary pneumothorax or mediastinum.
IV. Forceful insertion of an overly large tracheostomy tube may result in pressure necrosis of the tracheal mucosa and possible damage to the dorsal tracheal membrane and cartilaginous rings.
V. When the tracheostomy tube is removed, the site is left open to heal by second intention.
   A. The open site is cleaned several times daily.
   B. Surgical closure of the tracheostomy site may result in subcutaneous emphysema or pneumomediastinum.

TRANSTRACHEAL/ENDOTRACHEAL ASPIRATION

Definition

I. Transtracheal aspiration (TTA) is the placement of a cannula from the rostral trachea into the lower respiratory tract for the collection of uncontaminated bronchial secretions.
II. Endotracheal aspiration is the passage of sterile tubing through a sterile endotracheal tube into the lower respiratory tract for the collection of uncontaminated bronchial secretions.

Indications

I. To determine the cause of inflammatory conditions of the respiratory tract
   A. Bacterial infections
   B. Viral infections
   C. Fungal infections
   D. Allergic disease
   E. Parasitic infestation
   F. Neoplastic disease: high number of false negative results
II. As a prognostic aid after smoke inhalation or exposure to fire and toxic fumes

Restraint

I. Dogs
   A. Mild sedation (butorphanol 0.2 to 0.4 mg/kg IV and diazepam 0.2 mg/kg IV) may be indicated, depending on the temperament and physical status of the animal.
   B. Hold the conscious dog in sternal recumbency, with the neck outstretched and the head pointing towards the ceiling.
II. Cats
   A. IV induction of general anesthesia with an ultra–short-acting thiobarbiturate or propofol
   B. Heavy sedation with ketamine 2 to 4 mg/kg IV and diazepam 0.1 to 0.2 mg/kg IV
   C. Sternal or lateral recumbency

Technique

I. Dogs
   A. Aseptically clip and prepare the ventral cervical skin.
   B. Palpate the site for catheter insertion, and either the cricothyroid membrane or the space between any of the first three tracheal rings may be used.
   C. Infuse the skin and subcutaneous tissues with a local anesthetic.
   D. Advance a 16- to 19-gauge IV through-the-needle catheter through the skin and subcutis and into the tracheal lumen at the selected site (Figure 3-3).
   E. Once the needle is within the tracheal lumen, direct the needle distally toward the carina, and the catheter is advanced. A transient cough reflex usually occurs during this step.
   F. Retract the needle from the site.
   G. Attach a sterile syringe containing a multiple-electrolyte solution (1 mL/5 lb body weight).
   H. Aspiration on the syringe yields air if the catheter is placed correctly.
   I. If central suction is available, inject the entire calculated dose of fluid.
      1. Disconnect the syringe from the catheter, and attach a Lukens specimen container (14 French with 20-mL trap and male adapter plug) to the catheter (see Box 3-1).
      2. Apply central suction to the trap, and collect fluid.
      3. When a sufficient specimen has been collected, turn off suction and withdraw the catheter.
   J. If central suction is not available, the fluid is injected at 2-mL increments with intermittent aspiration until fluid, not air, is retrieved.

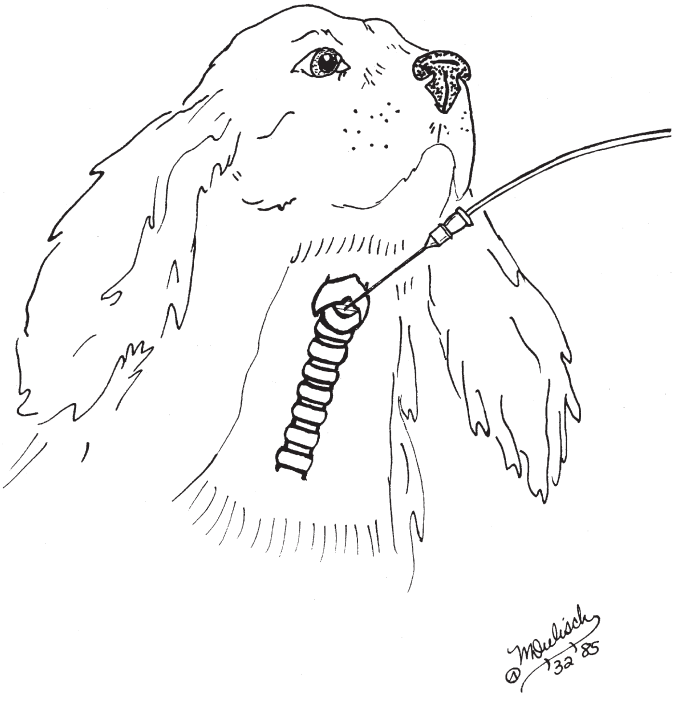

FIGURE 3-3 Transtracheal aspiration is accomplished by inserting an intravenous catheter through the cricothyroid membrane of the larynx into the trachea. The catheter is then advanced into the lower airway.

1. The volume of fluid necessary may vary from 2 to 25 mL.
2. The actual specimen collected is usually 0.5 to 2 mL.

II. Cats
   A. The technique is basically the same as for the dog except that it is performed under sedation through a sterile endotracheal tube.
      1. Carefully place a sterile endotracheal tube in the trachea by intubation.
      2. Advance the catheter through the endotracheal tube; administer and collect fluid in the same manner as described for the dog.
   B. An alternative method is to perform the technique outlined for the dog.

III. Specimen handling
   A. Place a portion of the fluid in transport medium for microbiologic analysis.
   B. Spin the remaining fluid in a centrifuge, and examine the cellular fraction microscopically.

Complications

I. Most complications are mild and transient.
   A. Coughing
   B. Subcutaneous or mediastinal emphysema
   C. Hemoptysis
   D. Subcutaneous hematoma

II. Inadvertent collection of pharyngeal (squamous epithelium present in sample) or upper tracheal secretions may yield inappropriate results.

III. The use of collection fluids containing bacteriostatic agents may cause false-negative culture results.

IV. Although neoplastic cells from bronchial or pulmonary tumors may be identified microscopically in TTA specimens, there is a high incidence of false-negative results with pulmonary tumors.

CEREBROSPINAL FLUID COLLECTION

Definition

A cerebrospinal fluid (CSF) tap is used to collect CSF by percutaneous needle aspiration of the subarachnoid space.

Indications

I. Retrieval of CSF for analysis when organic dysfunction of the central nervous system (CNS) is suggested
   A. Recent history of neurologic symptoms
   B. Neurologic deficits present on examination

II. Insertion of contrast medium into the subarachnoid space to localize spinal cord lesions (see Chapter 4)

Restraint

I. General anesthesia is always indicated for CSF taps in dogs and cats.

II. Proper positioning is critical to accomplish accurate needle placement.
   A. Cisternal tap
      1. Place the animal in lateral recumbency, with the head flexed ventrally to open the atlanto-occipital interspace.
      2. Pull the ears forward to tense the skin.
      3. Elevate the nose slightly so that it is parallel to the surface of the table.
      4. A towel or sandbag may be positioned under the head to maintain the entire spine a consistent distance from the table surface.
   B. Lumbar tap
      1. Place the animal in sternal recumbency, with an assistant pulling the hind legs in a cranial and dorsal direction to open the interarcual space between the caudal lumbar vertebrae.
      2. The entire spine must be kept straight.

Technique

I. Cisternal tap
   A. Clip the hair and aseptically prepare the skin on the dorsal cervical region from 2 cm rostral to the occipital protuberance to the level of the 3rd cervical vertebra.
   B. With one hand, the operator digitally palpates the external occipital protuberance and the rostral wings of the atlas.
      1. The index finger can be used to palpate a depression between these three structures.
      2. This depression marks the site for needle placement (Figure 3-4).
   C. A spinal needle with stylet is slowly inserted through the skin, subcutaneous tissues, and muscles.
      1. Large dogs: 20-gauge, 1- to 3-inch needle
      2. Small dogs and cats: 22-gauge, 1- to 2-inch needle

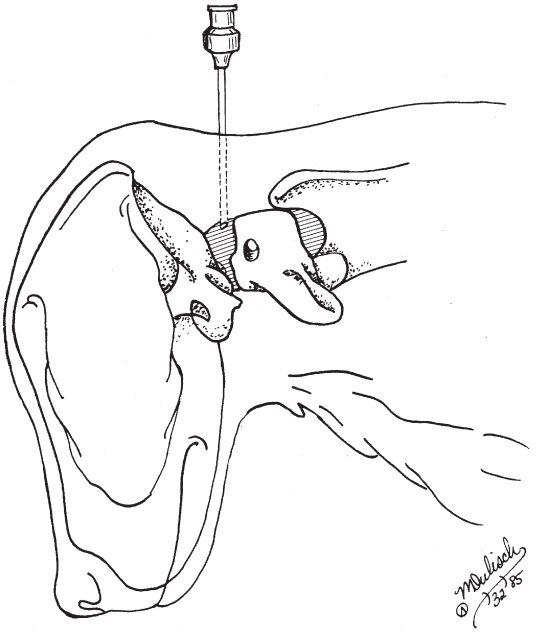

FIGURE 3-4 Cisternal puncture for spinal fluid collection and/or insertion of contrast medium for myelographic study.

D. The combined dura mater and arachnoid membranes are penetrated.
   1. Withdraw the stylet with each incremental advancement of the needle through the membranes to check for the presence of fluid.
   2. Always replace the stylet before advancing the needle.
E. When fluid is observed, attach a spinal manometer with three-way stopcock if measurement of CSF pressure is desired.
F. Allow the CSF to drip directly from the needle into a collection tube.
   1. It is important not to move the needle during pressure measurement and fluid collection.
   2. The quantity of fluid recovered varies.
      a. Large dogs: 1.0 to 3.5 mL
      b. Small dogs, cats: 0.5 to 1.5 mL
   3. Jugular vein compression may increase the flow of CSF.
G. If indicated, contrast material may be administered for myelography (see Chapter 4).
H. The needle is carefully and smoothly withdrawn.
I. Place fluid in a sterile tube for microscopic, chemical, and microbiologic analysis.

II. Lumbar tap
A. Clip the hair and aseptically prepare the skin over the dorsal lumbar spine.
B. Palpate the dorsal spinous processes of the lumbar (L) vertebrae.
C. Optimal sites for the collection of CSF are at the L4-5 or L5-6 interspace (Figure 3-5).
D. Insert a 20- or 22-gauge, 3.5-inch spinal needle immediately cranial to the dorsal spinous process of the vertebra at the caudal aspect of the planned puncture site.
   1. Advance the needle toward the spinal canal until it contacts a dorsal laminar surface.
   2. The needle must be maintained parallel to the dorsal spinous processes.
   3. The needle is "walked" cranially or caudally along the laminar surface until it drops into the interarcual space.
   4. A twitch in the rear legs or tail may indicate proper needle placement (see Figure 3-5).
E. Withdraw the stylet, attach a syringe to the needle, and apply gentle aspiration until fluid is recovered.
   1. The depth of needle insertion may be adjusted slightly during aspiration.
   2. The subarachnoid space is small in the region of the lumbar cord, and only a small quantity of fluid may be recovered (0.5 to 2.5 mL).
F. At this point, contrast medium can be injected if myelographic study is indicated (see Chapter 4).
G. Remove the needle and place fluid into a sterile tube for microscopic, chemical, and microbiologic analysis.

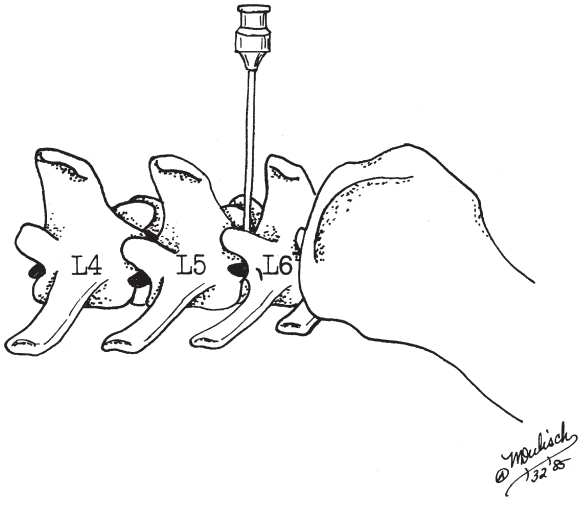

FIGURE 3-5 A lumbar spinal tap is demonstrated at the interarcual space between lumbar vertebrae 5 and 6.

Complications

I. Direct needle trauma to the parenchyma of the brain or spinal cord can occur if careful, controlled advancement of the needle is not performed.
II. Iatrogenic hemorrhage may make interpretation of laboratory results difficult; if contamination with blood occurs, consider the following correction factors:
   A. One white blood cell (WBC) is expected for every 500 red blood cells (RBCs).
   B. One thousand RBCs will increase CSF protein by approximately 1 mg/dL.

NASAL FEEDING TUBE PLACEMENT

Definition

I. A nasal feeding tube is a tube placed from the external nares into the stomach (nasogastric) or distal esophagus (nasoesophageal) for administration of fluids and nutrients or to allow decompression of a dilated or distended stomach.
II. For feeding purposes, if the esophagus is functional, a nasoesophageal tube is inserted; if the esophagus is nonfunctional (e.g., megaesophagus or esophageal stricture), a nasogastric tube is inserted.

Indications

I. Provide short-term (≤10 days) nutritional support to animals unwilling or unable to eat for various reasons
   A. Facial, maxillary, and mandibular fractures
   B. Oral and esophageal disease
   C. Prolonged anorexia from a systemic disorder
II. For temporary decompression of the stomach before or after corrective surgery for gastric dilatation volvulus
III. For evacuation of gastric fluid in cases of ileus

Restraint

I. Usually, local anesthesia is all that is required.
II. Occasionally, mild sedation is useful.
   A. Dog: butorphanol 0.2 to 0.4 mg/kg IV
   B. Cat: diazepam 0.1 to 0.5 mg/kg IV, with or without ketamine 2.0 mg/kg IV

Technique

I. Based on the animal's size, a 3.5 to 8 French polyurethane or polyvinyl chloride tube is selected (see Box 3-1).
II. The distance from the tip of the nares to the last rib (for nasogastric tube) or to the 7th rib (for nasoesophageal tube) is measured and the tube is marked accordingly.
III. Instill 2% lidocaine into the nostril (several drops for cats; 0.5 to 1 mL for dogs), and keep the head slightly elevated for 1 to 2 minutes as the lidocaine takes effect.
IV. The tube, nares, and skin where the sutures are to be applied are lubricated with 2% lidocaine jelly (Figure 3-6).
V. The tube is then advanced through the nostril and into the ventral nasal meatus.
    A. In dogs the tube is inserted dorsomedially for the first centimeter to avoid the alar fold and nasal vestibule, and then advanced ventrally. Alternatively, the external naris is pushed dorsally as the tube is advanced in a caudal-ventral-medial direction (Abood and Buffington, 1991).
    B. In cats the tube may initially be directed ventromedially, because there is no well-developed alar fold.
VI. As the tube enters the pharynx, the animal is encouraged to swallow, allowing for easy passage into the esophagus.
VII. Advance the tube until the premarked spot reaches the tip of the nares.
VIII. Inject a small quantity of air and then saline into the tube to check for correct placement.
    A. Abdominal auscultation indicates air bubbling in the stomach.
    B. The injection should be well tolerated by the animal without struggling or coughing.
    C. A lateral caudal thoracic radiograph is taken if there is any uncertainty as to the final location of the tube.
IX. Secure the tube in place using 3-0 nonabsorbable sutures.
    A. Place the first suture in the skin as close to the lateral margin of the external nares as possible to ensure tube stability.
    B. Once the first ligature is made, pass the suture around the tube several times in a bootlace pattern and then tie the suture in place.
    C. Pass the second suture through an adhesive butterfly tape around the tube and into the skin along the dorsal midline of the head.
X. Attach an IV extension tube to the exposed end of the nasal tube to allow for appropriate connections and free movement of the animal.
XI. An Elizabethan collar is usually required to prevent tube removal by the animal.
XII. The tube may be left open to allow constant decompression of gas, or it may be capped with an IV catheter cap and opened intermittently for infusion of nutrients and intermittent evacuations.
XIII. A variety of canine and feline liquid diets are available for use with this type of feeding tube (Table 3-1) (Wortinger, 2006).
XIV. Flush the tube periodically to maintain lumen patency.

FIGURE 3-6 Correct placement of a nasal feeding tube.

Complications

I. Mild discomfort and rhinitis can occur, although animal compliance is usually good.
II. Nasogastric tubes may predispose to gastroesophageal reflux or produce gastric irritation and vomition, which can be decreased by placing the tube in the distal esophagus.
III. Vomiting or regurgitation from other causes can alter tube location, which can be verified with radiography and/or capnography (Johnson et al., 2000).
IV. If the liquid diet is too thick, the tube may become plugged.
    A. Flushing the tube before and after feedings helps keep it from clogging.
    B. Use of a syringe pump also decreases clogging of the tube.
V. Feeding of cold liquids or too rapid administration may result in vomiting.
VI. Feeding of hot foods may cause damage to the esophageal or gastric mucosa.
VII. If hyperosmolar solutions are used, diarrhea may occur, which can be minimized by diluting the formulation to an osmolarity between 200 and 300 mOsm/kg.

ESOPHAGOSTOMY TUBE PLACEMENT

Definition

I. An esophagostomy tube is placed directly through the skin into the lumen of the rostral esophagus.
II. Vomiting may make it difficult to maintain the tube, but such tubes can be kept in place for weeks to months.

Indications

I. It is indicated in animals that have a functional esophagus, stomach, and intestines.
II. It is designed to provide nutritional support to animals unwilling or unable to eat for various reasons.
    A. Facial or head trauma

TABLE 3-1

Liquid Diets for Use in Tube Feeding

BRAND	MANUFACTURER	INDICATIONS
CliniCare, Renal Care	Abbott CliniCare	Various formulations available; designed to meet protein caloric requirements of dogs and cats but require functional GI integrity
Concentration Instant Diet	Waltham/Pedigree Waltham/Whiskas	Designed to meet protein caloric requirements of dogs and cats but require functional GI integrity
Nutritional Recovery	Iams/Eukanuba	Specifically formulated for critically ill dogs and cats
Formula V Enteral Care	Pet Ag, Inc.	Various formulas of supplemental products available; not designed as a complete diet
Osmolite HN	Ross Nutritional	High in both protein content and quality but difficult to balance both protein and caloric requirements
Peptamen	Nestlé Clinical Nutrition	Complete elemental diet for use in animals with impaired GI function

GI, Gastrointestinal.

B. Oral or esophageal disease or after surgery
C. Anorexia secondary to systemic disease

III. Because esophagostomy tubes are larger than nasoesophageal tubes, different types of gruel may usually be delivered through the tube.

Restraint

I. General anesthesia is usually required.
II. The animal is placed in right lateral recumbency.
III. A mouth gag is used to facilitate placement.

Technique

I. Use a soft latex or rubber catheter (12 to 22 French).
II. Mark the tube so that, when placed, the tip of the catheter will sit in the distal esophagus (approximately at the level of the 7th rib).
III. Advance a long, right-angle hemostat through the cricopharyngeal sphincter.
IV. Force the tip of the hemostat upward to show the position of the incision.
V. Make an incision through the skin, and use blunt dissection to the level of the esophagus.
VI. Open the hemostat slightly, allowing a stab incision to be made through to its tips.
VII. Advance the tip of the hemostat through the wall of the esophagus and out through the skin incision.
VIII. Grasp the end of the feeding tube and pull it into the esophagus and out the mouth until the female end of the tube is left protruding from the neck.
IX. Redirect the distal end of the catheter down the esophagus.
X. Secure the tube with a bootlace suture and place a light bandage.
XI. To remove the tube, cut the sutures and pull the tube, leaving the stoma to heal by second intention.

Complications

I. Proper care when dissecting down to the esophagus will prevent disruption of vessels or nerves.
II. Vomiting may cause displacement of the tube, which may be verified with radiography.
III. Feeding of cold liquids or too-rapid administration may result in vomiting.
IV. Feeding of hot foods may cause damage to the esophageal mucosa.
V. Other complications include premature removal by the animal and secondary infection of the skin at the entrance site.

PERCUTANEOUS TUBE GASTROSTOMY

Definition

This procedure involves the placement of a feeding tube directly through the skin and into the gastric lumen with the use of an endoscope.

Indications

I. Percutaneous endoscopic gastrostomy (PEG) tubes provide long-term (>10 days) nutritional support to animals unwilling or unable to eat for various reasons.
A. Facial and head trauma
B. Oral and esophageal disease or after surgery
C. Anorexia secondary to a systemic disorder (e.g., hepatic lipidosis in cats)
II. The larger diameter of the gastrotomy tube allows for more routine feeding (e.g., a mixture of blended canned food and water).
III. Nutrition is easily administered while the animal is cared for at home.

Restraint

I. General anesthesia with either injectable or inhalation anesthetics is required.
II. The animal is placed in right lateral recumbency, and a mouth gag is used to facilitate the passage of the endoscope.

Technique

I. Clip the hair and aseptically prepare the skin of the left paracostal region.
II. Advance the endoscope through the mouth and esophagus into the gastric lumen; insufflate the stomach with air until the gastric wall is under tension and in contact with the abdominal wall.
III. Select a gastrostomy tube and cannula.
  A. Silicone percutaneous endoscopic gastrostomy kit (see Box 3-1)
  B. A 14 to 20 French mushroom-tipped catheter with a 16-gauge Medicut IV cannula and stylet (see Box 3-1)
IV. Make an appropriate site for tube insertion by endoscopic observation or digital palpation.
V. Advance the cannula (with stylet in place) through the skin, abdominal wall, and gastric wall and into the gastric lumen.
VI. Remove the stylet and place a No. 1 or 2 nonabsorbable suture through the catheter into the stomach.
VII. The suture is grasped in the stomach by a snare from the endoscope; together they are pulled cranially toward the oral cavity.
VIII. The cannula is removed from the abdominal wall and passed tapered end first over the suture exiting the mouth.
IX. Cut the funneled end of the gastrostomy tube to fit inside the catheter, and suture the two together using 3-0 nylon on a straight needle that passes transversely through the catheter sheath and tube.
X. Apply a water-soluble lubricant to the cannula and tube, and pass both through the oral cavity and esophagus and into the stomach, using gentle traction from the transabdominal suture.
XI. Using an endoscope, check for correct positioning (against the left body wall) of the gastrostomy tube.
XII. Using the transabdominal suture exiting the abdomen, pull the cannula and gastrostomy tube through the gastric and abdominal walls (by pushing down on the skin with one hand and placing gentle traction on the suture/cannula with the other) until the mushroom end of the tube comes to rest against the stomach wall.
XIII. Secure the gastrostomy tube to the skin using traction sutures, and mark the tube at the skin margin so it can be monitored for signs of migration.
XIV. Place an adapter and three-way stopcock at the end of the tube to allow for intermittent feedings, and apply a light abdominal bandage over the tube.
XV. The tube should remain in place for a minimum of 10 to 14 days to decrease the incidence of peritonitis after tube removal.
XVI. To remove the tube, cut the sutures using one of the two following methods.
  A. Apply steady outward traction to the tube until the mushroom tip collapses and the tube can be pulled out through the abdominal wall.
  B. Pull the tube up against the body wall and then cut it flush at the skin, allowing the mushroom tip to fall back into the stomach and pass out the gastrointestinal tract (medium to large dogs) or be retrieved endoscopically (small dogs and cats).
XVII. An alternative method is blind percutaneous gastrostomy tube placement.
  A. Positioning and preparation is the same as for endoscopic placement.
  B. The device (see Box 3-1) is blindly and carefully advanced into the stomach lumen, until the tip can be seen pushing on the skin behind the last rib.
  C. The plunger on the handle is depressed until the trocar penetrates the skin.
  D. Pass a suture through a hole in the tip of the trocar, and withdraw the device from the animal.
  E. Placement of the tube from this point is identical to the endoscopic placement.
XVIII. For prolonged tube feedings (>12 to 16 weeks), the original PEG tube can be replaced by a low-profile silicone or Foley-type gastrostomy tube, which is less likely to be dislodged or removed by the animal.
  A. Manually insert the tube through the existing stoma.
  B. Sedation or anesthesia may be needed for the insertion.
  C. Silicone tubes may be used as long as 1 year, without requiring replacement.

Complications

I. Bloody or purulent peristomal discharge, peristomal swelling and inflammation (dermatitis)
II. Discomfort and chewing at the device
III. Premature removal of the tube, leakage around the tube, peritonitis
IV. Migration of the mushroom catheter tip into the pyloric antrum, causing vomiting
V. Splenic or intestinal laceration if either organ slips between the stomach and body wall during cannulation (higher incidence with the blind placement method)
VI. Pneumoperitoneum
VII. Vomiting from feeding of cold liquids or too rapid administration
VIII. Damage to the gastric mucosa from feeding of hot foods

BLOOD PRESSURE MEASUREMENT

Definition

I. Direct methods of measuring blood pressure involve insertion of a saline-filled catheter into an artery and using a pressure transducer.
II. Indirect methods of measuring blood pressure involve using an inflatable cuff and measuring arterial wall motion or blood flow after arterial occlusion.
III. The following discussion is limited to indirect blood pressure measurement.

Indications

I. Monitoring of surgical and critically ill animals
II. Shock assessment
III. Detection of hypertensive states

A. Cardiovascular and renal disease
B. Endocrine disorders
C. Neurologic and ocular disease
D. Hypercalcemia
E. Anemia and polycythemia
F. Obesity and aging

IV. Monitoring of animals on antihypertensive therapy
V. Monitoring of animals on drugs that may be hyper- or hypotensive

Restraint

I. Animals must be relaxed and minimally restrained
II. Measurements are performed in lateral or sternal recumbency or on some animals while they are standing.
III. Chemical restraint is not used, because blood pressure may be affected.

Technique

I. Oscillometric
   A. Place an inflatable cuff between the elbow and carpus on the foreleg or just below the hock on the hind leg.
   B. The width of the cuff is approximately 40% of limb circumference.
   C. The cuff is automatically inflated and deflated at a predetermined rate.
   D. The machine automatically displays pulse rate and systolic, diastolic, and mean arterial blood pressure.
   E. Five consecutive readings are obtained.
      1. The highest and lowest measurements are discarded, and the remaining three are averaged.
      2. Alternatively, three measurements can be used if the results are fairly consistent.
   F. This method is most accurate in animals >15 lb.
II. Doppler
   A. Place an inflatable cuff in one of the following locations:
      1. Mid-foreleg
      2. Just distal to the hock
      3. Around the tail base
      4. Below the stifle (cats)
   B. The width of the cuff is approximately 40% of limb circumference.
   C. A patch of hair is clipped distal to the cuff over the palpable artery on the palmar or plantar surface.
   D. The ultrasound transducer with coupling gel is placed over the clipped skin and positioned so that arterial flow is audible, and the transducer is taped or held in place.
   E. The cuff is inflated by a sphygmomanometer until arterial flow ceases and audible flow has disappeared.
   F. Cuff pressure is slowly reduced until flow is reestablished and flow sounds can be heard, which indicates the systolic blood pressure.
   G. Continued reduction of cuff pressure results in a change in sound quality that corresponds to diastolic pressure.
   H. Several readings are taken for accuracy.
   I. Diastolic blood pressure measurements may not be accurate or obtainable in many animals.

Complications

I. Stress may cause a falsely elevated blood pressure.
II. Inappropriate cuff size or placement may give erroneous results.
III. Doppler readings are somewhat subjective in relying on auditory signals for measurements.
IV. Oscillometric measurements may be difficult to determine in low-flow states.

FINE-NEEDLE ASPIRATION

Definition

Fine-needle aspiration involves the introduction of a small-gauge needle into a tissue or organ and removal of a small amount of tissue by suction.

Indications

I. Differentiate causes of organomegaly involving lymph nodes, spleen, liver, and other organs
II. Differentiate between inflammation, hyperplasia, and neoplasia
III. Differentiate benign from malignant neoplasia
IV. Differentiate carcinomas, sarcomas, and round (discrete) cell tumors

Restraint and Technique

I. Manual restraint alone is sufficient in most animals.
II. Attach a small-gauge needle (23 to 25 gauge) to a 12- to 20-mL sterile syringe.
III. A needle alone (not attached to a syringe) can be used in some tissues to minimize damage to the cells and peripheral blood contamination.
   A. Lymph nodes
   B. Cutaneous masses
   C. Subcutaneous masses
IV. If the mass is superficial, sterile preparation is not mandatory.
V. Aseptic technique is required when aspirating masses or organs within body cavities.
VI. Advance the needle into the tissue; apply 6 to 8 mL of suction if using a syringe.
VII. Redirect the needle is redirected two to three times, release suction , and withdraw the needle.
VIII. Detach the needle, aspirate air into the syringe, reattach the needle, and express the sample onto a slide, making a smear.
IX. Several samples may be needed to obtain a diagnostic smear.

Complications

I. Minor hemorrhage
II. Tissue damage

BONE MARROW ASPIRATE/BIOPSY

Definition

Bone marrow samples may be obtained by aspiration through a bone marrow needle or by punch-type biopsy through a trephine instrument (core biopsy).

Indications

I. Aspirate or core biopsy
   A. Nonregenerative anemias
   B. Suspected bone marrow disease: myeloid or erythroid suppression, neoplasia
   C. Certain clotting disorders, especially involving platelets
II. Core biopsy
   A. To study the structural architecture of the bone marrow
   B. When aspiration biopsies have been unsuccessful
   C. When searching for metastatic or occult neoplasia
   D. Certain metabolic disorders of bone

Restraint

I. Most biopsies may be performed using local anesthesia, with or without mild sedation.
II. The position of restraint is determined by the site to be biopsied.
   A. Wing of ilium (Figure 3-7)
      1. Large dog: standing or sternal recumbency
      2. Small dog or cat: sternal recumbency with hind legs drawn up alongside the abdomen
   B. Proximal femur: lateral recumbency (Figure 3-8)
   C. Rib: sternal or lateral recumbency (Figure 3-9)
   D. Proximal humerus: lateral recumbency (Figure 3-10)
   E. Other less commonly used sites: ischial tuberosity, sternum

Technique

I. Shave the hair over the biopsy site, which is then prepared aseptically and infiltrated with local anesthesia down to periosteum.
II. Make a small stab incision in the skin with a scalpel blade.
III. Aspirate bone marrow.
   A. Select a 16- or 18-gauge, 1.5-inch Osgood or Rosenthal (see Box 3-1) biopsy needle.
   B. With the stylet in place, advance the needle through the soft tissues until it meets resistance at bone.
   C. Push the needle through the bone by applying pressure with a simultaneous rotating motion.

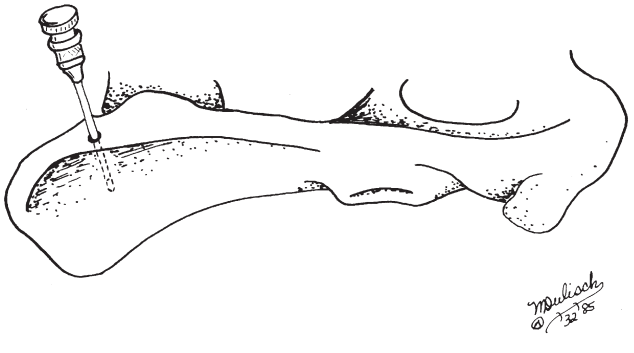

FIGURE 3-7 Insertion of bone marrow needle through the dorsal iliac spine into the marrow cavity of the wing of the ilium. The medial and lateral aspects of the spine are localized with the thumb and forefinger of one hand. With the other hand, the needle is directed ventrally and slightly laterally into the central portion of the wing of the ilium.

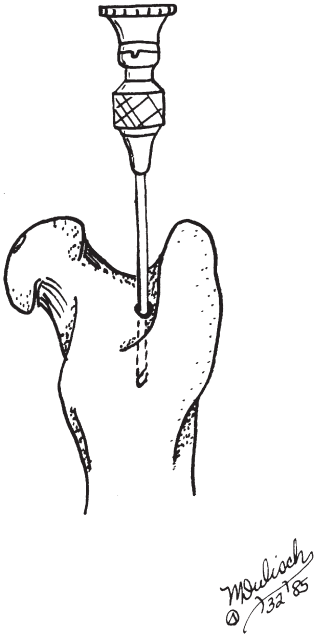

FIGURE 3-8 To retrieve a sample from the marrow cavity of the proximal femur, a bone marrow needle is advanced through the trochanteric fossa caudal and medial to the greater trochanter and directed laterally in a line parallel to the shaft of the femur.

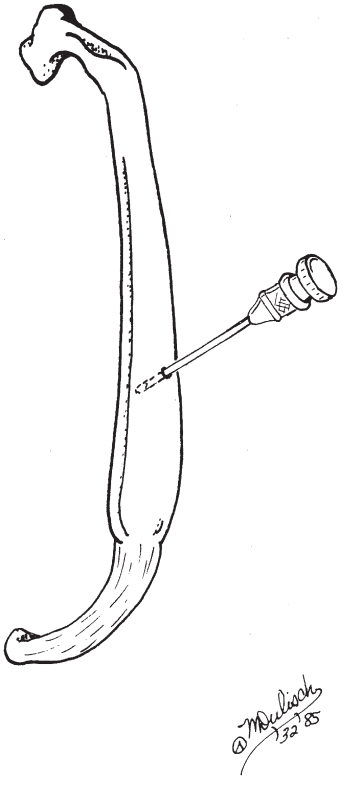

FIGURE 3-9 Bone marrow aspiration from a rib. Usually the 7th, 8th, or 9th rib is chosen. The biopsy needle is inserted at a slightly ventral angle at a point midway from the neck of the rib to the costal cartilage.

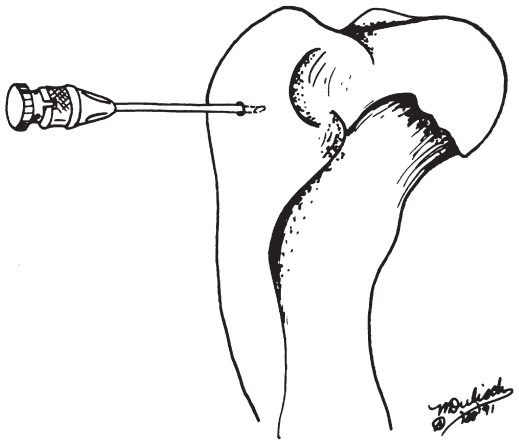

FIGURE 3-10 Bone marrow from the humerus is obtained by palpating the bony prominence of the greater tubercle lateral to the biceps tendon. The needle is inserted at a spot perpendicular to the long axis of the bone.

D. Decreased resistance indicates that the needle has passed through the cortex into the marrow cavity.
E. After advancing the needle into the marrow, remove the stylet, attach a 12-mL syringe, and exert negative pressure on the syringe.
   1. Evidence of pain with aspiration usually indicates that the needle is located within the marrow cavity.
   2. When marrow appears in the syringe, aspiration is halted and the syringe disconnected.
   3. Overzealous aspiration may lead to contamination of the sample with peripheral blood.
   4. Smears are quickly made on glass slides, and any clot is saved in formalin for histologic examination.
   5. A sample may also be submitted for culture.
F. If adequate marrow is retrieved, withdraw the needle.
G. The skin incision may be sutured or left to heal by second intention.

IV. Core biopsy
   A. Using a core biopsy instrument (e.g., Jamshidi bone marrow needle), advance the needle, with the stylet in place, through the soft tissues and then into bone, with steady pressure and a back-and-forth rotating motion.
   B. Once through the cortex, remove the stylet and push the trephine instrument into the marrow, advanced for 1 to 2 cm and then rotated around its long axis several times.
   C. Remove the needle, retrieve the core sample using the extending probe, and place the sample in formalin.

Complications

I. Complications are rare.
II. Damage to adjacent structures may occur.
   A. Poor positioning of the needle in the trochanteric fossa may damage the sciatic nerve.
   B. Accidental pneumothorax or laceration of intercostal vessels may accompany rib biopsies.
III. Infiltration of the trochanteric fossa with local anesthetic may result in transient paresis of the sciatic nerve.

ARTHROCENTESIS

Definition

Arthrocentesis is the percutaneous placement of a needle into a synovial cavity for the collection of synovial fluid for laboratory analysis.

Indications

I. As a diagnostic aid in suspected cases of inflammatory joint disease
   A. Septic or infectious arthritis
   B. Immune-mediated arthritis
   C. Hemarthrosis and traumatic synovial effusion
II. Insertion of contrast medium for radiographic evaluation (see Chapter 4)
III. Administration of therapeutic agents intrasynovially

Restraint

I. Local anesthesia and mild chemical sedation may be necessary depending on the temperament of the animal.
II. Lateral recumbency is used for centesis of the stifle, hock, elbow, and shoulder joints.
III. Centesis of the carpal joint may be performed in either lateral or sternal recumbency.

Technique

I. Clip the hair and aseptically prepare the skin over the affected joint.
II. Palpation of the distended joint capsule or the joint space must be precise before placing the needle.
III. A thorough knowledge of the joint and periarticular anatomy is essential for accurate needle placement (Figures 3-11 to 3-13).
IV. Attach a 22-gauge needle to a 3- or 6-mL syringe and advance it slowly through the skin, subcutaneous, periarticular, and synovial tissues to enter the synovial cavity.
V. Aspiration of the syringe results in collection of synovial fluid.
VI. Release suction is released and withdraw the needle when sufficient fluid (0.1 to 0.5 mL) has been collected.
VII. Place the fluid in EDTA tubes for cytologic study and in transport medium or thioglycolate broth for microbiologic analysis.
   A. Thin smears also are prepared and air-dried.
   B. Observe the viscosity of the fluid while preparing slides.
VIII. In suggested cases of polyarthritis, multiple joints are aspirated.

Complications

I. Inadequate preparation of the skin may result in bacterial inoculation of the joint or contamination of the specimen.
II. Intrasynovial trauma from the needle or repeated centesis may result in hemarthrosis or abrasion of the articular cartilage if technique is suboptimal.
III. Direct needle-induced damage to the periarticular blood vessels or nerves may occur if anatomical considerations are overlooked.

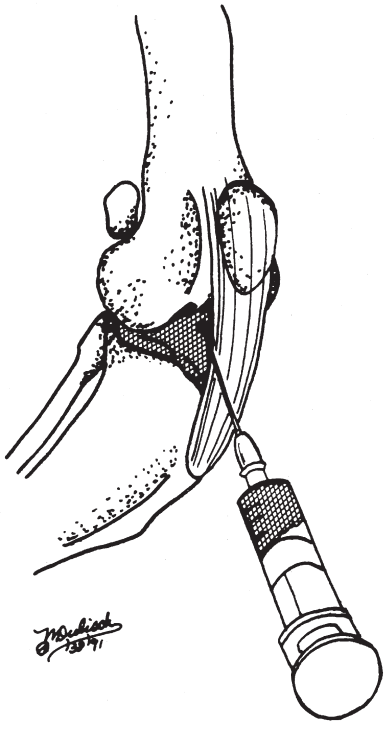

FIGURE 3-11 With the stifle joint partially flexed, the distal edge of the patella and proximal edge of the tibial tuberosity are palpated. The joint is entered at a spot approximately one third of the way between these two structures. Insert the needle into the joint just lateral to the straight patellar ligament and direct it slightly medially into the area between the two femoral condyles.

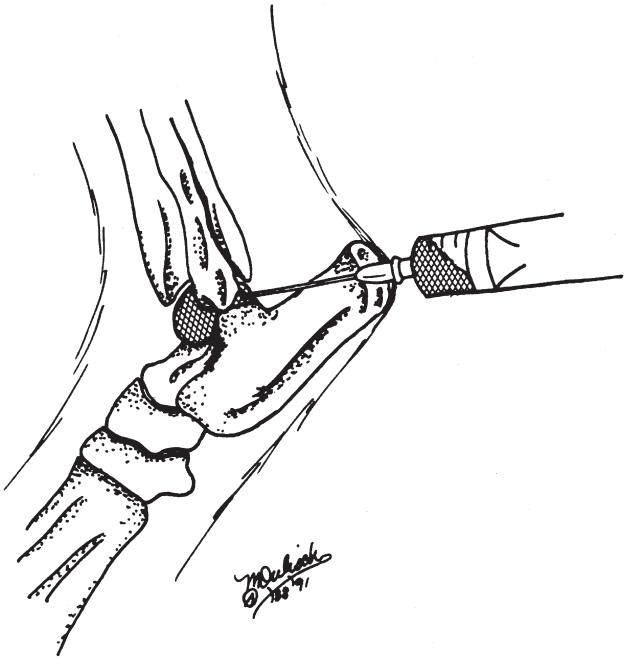

FIGURE 3-12 With the hock partially flexed, the tibiotarsal joint is entered laterally by inserting the needle under the malleolus from the plantar side. Care is taken to avoid the caudal branch of the lateral saphenous vein.

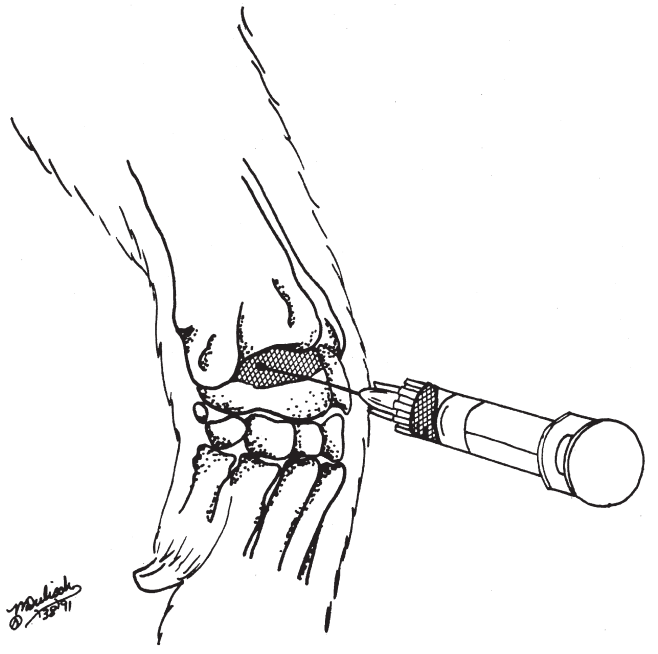

FIGURE 3-13 With the carpus partially flexed, the carpal joint is aspirated by inserting a needle into the medial radiocarpal space or between any of the palpable intercarpal spaces.

IV. Contamination of the sample with iatrogenic hemorrhage may necessitate centesis of another joint or repeated centesis of the same joint 48 hours later.

BONE BIOPSY

Definition

A trephine bone biopsy is the collection of a full-thickness specimen of bone for histopathologic and microbiologic analysis.

Indications

I. Obtaining a specimen for histological examination after radiographic evidence of a lesion involving bone, in certain suspected cases
   A. Primary or secondary neoplasia
   B. Bacterial, mycotic, or parasitic infection
   C. Developmental (idiopathic) or degenerative diseases of bone: panosteitis, hypertrophic osteodystrophy, hypertrophic pulmonary osteoarthropathy, and others.

II. Obtaining material for culture

Restraint and Technique

I. General anesthesia is required.
II. A wide area of skin around the affected site is clipped and prepared for aseptic surgery.
III. Radiographs are used to select an appropriate site to insert and direct the biopsy instrument.
IV. Make a 1-cm incision over the selected site.
V. Retract the subcutaneous, muscle, tendon, and deep fascial tissues to gain access to the periosteal surface.

VI. Using an appropriately sized Michel trephine biopsy instrument without stylet (see Box 3-1), use an oscillating, twisting motion to advance the instrument through the cortical bone, across the medullary cavity, and through the opposite cortex.
VII. Palpation of the trephine in the subcutaneous tissues indicates complete full-thickness biopsy.
VIII. Withdraw the trephine and insert the stylet to eject the core into bacteriologic transport medium or 10% formalin solution for microbiologic or histopathologic examination, respectively.
IX. Bleeding from the biopsy site is controlled with direct pressure and closure of the deep tissues.
X. Additional specimens may be collected until the surgeon is comfortable that a diagnostic sample has been obtained.

Complications

I. False-negative results may be obtained if inadequate or inappropriate tissues are collected.
   A. Careful radiographic analysis and collection of multiple samples minimize this complication.
   B. When samples are obtained for histopathology, avoid soft, necrotic bone and locate the biopsy site close to the junction with radiographically normal tissue.
II. Pathologic fractures may result from weakening of the bone.
   A. Such problems may be avoided by selecting smaller trephines and limiting the number of samples taken.
   B. External coaptation is used postoperatively if a secondary pathologic fracture is feared.

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CHAPTER 4

Contrast Radiography

Lance Rozear

GENERAL CONSIDERATIONS

Purpose

I. To identify and characterize anatomical and pathologic findings that are not adequately evaluated on survey radiographs
II. To provide qualitative information on the function of selected systems

Contrast Agents

I. Positive and negative contrast agents
  A. Positive contrast agents contain atoms of high atomic number (barium and iodine) that attenuate x-rays with great efficiency, increasing their radiographic opacity.
  B. Negative contrast agents are gases with low physical density (carbon dioxide, room air, nitrous oxide) and low x-ray attenuation, therefore decreasing radiographic opacity.
  C. Double-contrast studies use a small amount of positive contrast medium to coat mucosal surfaces in combination with a larger volume of negative contrast medium to inflate the structure and enhance surface visualization.
II. Barium sulfate (Table 4-1)
  A. High atomic number and density that attenuates the majority of incident x-rays and appears opaque (white) on radiographs
  B. Insoluble compound that passes unchanged and unabsorbed as a suspension through the gastrointestinal (GI) tract with a predictable transit time
  C. Nonirritating to mucosal surfaces; provides good mucosal coating
  D. Used in routine imaging of the GI tract
  E. Available formulations
    1. Barium sulfate powder (USP)
      a. Mixed on site for reconstitution at desired volume and concentration
      b. Inexpensive
      c. Tends to precipitate and flocculate, confusing mucosal detail
    2. Commercially prepared barium sulfate suspension
      a. Most commonly used, inexpensive
      b. Provided in 100% weight/volume (w/v) colloidal suspension; diluted to desired concentration
      c. For GI studies
      d. Provides good mucosal detail
    3. Barium sulfate paste
      a. Viscous
      b. Good for evaluation of the esophagus, because the paste coats the mucosa for longer periods
      c. Not useful for stomach or intestinal studies
    4. Solid radiopaque markers or barium-impregnated polyethylene spheres (BIPS; Med ID, Grand Rapids, Mich.)
      a. Spheres available in differing sizes in gelatin capsules
      b. Uniformly sized spheres or a combination of sizes in capsules
      c. Used to evaluate GI transit time and for the diagnosis of GI obstruction
  F. Potential adverse effects and complications
    1. Aspiration
      a. If the amount is small and confined to the major airways, it is removed via the mucociliary apparatus and swallowed.
      b. If a small amount reaches the alveoli, it may cause a local granulomatous reaction or be sequestered in regional lymph nodes.
      c. Inadvertent passage of orogastric tube into the trachea or aspiration of a large volume may cause a severe inflammatory reaction and possibly death.
    2. Leakage
      a. If barium leaks into the peritoneal, pleural, or mediastinal space, it can cause a severe granulomatous inflammation.
      b. It is *not* recommended in cases of suspected GI perforation.
    3. May cause constipation (rare)
III. Ionic water-soluble contrast media (ICM) (see Table 4-1)
  A. Characteristics
    1. ICM are monomeric or dimeric derivatives of benzoic acid containing iodine that have a high atomic number and appear opaque (white) on radiographs.
    2. They include sodium or methylglucamine (meglumine) salts.
    3. They have variable osmolality (580 to 2100 mOsm/kg H_2O) and generally higher osmolality than nonionic compounds.

TABLE 4-1

Examples of Contrast Agents, Including Some Basic Chemical Properties

CONTRAST CLASS	GENERIC NAME	BRAND NAME	MANUFACTURER	CONCENTRATION*	OSMOLALITY (mOsm/kg H_2O)
Nonionic contrast media (NICM)	Iohexol	Omnipaque	GE Healthcare	140	322
				180	408
				240	520
				300	672
				350	844
	Iopamidol	Isovue	Bracco Diagnostics	200	413
				250	524
				300	616
				370	796
	Ioversol (not labeled for intrathecal use)	Optiray	Mallinckrodt	160	355
				240	502
				300	651
				320	702
				350	792
Ionic contrast media (ICM)	Diatrizoate meglumine (Meg)/sodium (Na)	Renograffin-60	Bracco Diagnostics	292.5	1450
		Renocal-76	Bracco Diagnostics	370	1870
		MD-76R	Mallinckrodt	370	1551
	Diatrizoate Meg	Hypaque Meglumine-60	GE Healthcare	282	1415
		Reno-dip	Bracco Diagnostics	141	588
		Reno-30	Bracco Diagnostics	141	673
		Reno-60	Bracco Diagnostics	282	1404
	Diatrizoate Na	Hypaque Na-20	GE Healthcare	120	
	Iothalamate Meg	Cysto-conray	Mallinckrodt	81	N/A
		Cysto-conray II		282	1400
		Conray		141	600
		Conray30		202	1000
		Conray43			
Barium	Iothalamate Na	Conray400	Mallinckrodt	400	2300
	BaSO4 suspension	Liquid Polibar	E-Z-EM	100	N/A
	BaSO4 paste	Intropaste	Lafayette	70	N/A
	Barium-impregnated polyethylene spheres (BIPS)	BIPS	Med ID	N/A	N/A

*For aqueous iodine solutions (NICM and ICM), concentrations are given in milligrams of iodine/milliliter solution (mg I/mL). For barium products, concentration is given in percent weight in grams of barium/100 mL final solution (% w/v).

   a. Monomeric agents have high osmolality (1200 to 2100 mOsm/kg H_2O).
   b. Dimeric agents are lower in osmolality, and are therefore less toxic (≈600 mOsm/kg H_2O).
4. Most agents are excreted predominantly by the kidneys because of low protein binding.
5. An alternate route of excretion through the GI tract and liver occurs in cases of renal dysfunction (vicarious excretion).
6. Higher protein-binding agents (e.g., ioxaglate) are excreted by the liver in the bile.
7. They are relatively inexpensive.

B. Uses
1. IV contrast studies: angiography, IV urography
2. Retrograde lower urinary tract imaging: cystography, urethrography
3. Fistulography, pleuro/peritoneography, lymphangiography, arthrography
4. *Not for intrathecal use*

C. Formulations
1. Provided in sterilized single- or multiple-dose vials
2. Sodium or meglumine salts, or a combination of both
   a. Sodium salts are lower in viscosity and easier to inject; however, they are more toxic.
   b. Meglumine salts are higher in viscosity and more difficult to inject rapidly, but they are less toxic.

c. Combinations with varying proportions of each salt are commonly used to compromise between viscosity and toxicity.

D. Adverse effects/complications (rare)
1. Primarily related to hypertonicity
a. Irritating to tissues if extravasated
(1) Possible soft tissue slough
(2) Treated with cold compresses ± local infiltration of physiological saline as a diluent
b. Pain at injection site
c. Salivation, nausea, vomiting: IV or oral administration
d. Sequestration of fluid in GI tract (if orally administered), creating fluid/electrolyte imbalances; *not* recommended for GI studies
e. Transient increase in blood volume from increased plasma osmotic pressure: danger for animals with cardiac disease
f. Peripheral vasodilation: danger for animals with cardiac disease
g. Osmotic diuresis: danger for animals with cardiac or renal disease
h. Increased capillary permeability: can alter blood-brain barrier
i. Crenates red blood cells (RBCs) that can then obstruct capillaries: most serious for myocardium, brain, and kidneys
j. Pulmonary edema as a result of hypertonicity if aspirated
2. Contrast-induced renal failure
a. Varies from clinically insignificant to anuric renal failure
b. Generally reversible with IV fluid therapy
3. Chemotoxicity
a. Sodium salts more toxic than meglumine salts
b. Damage to blood-brain barrier, heart, and kidneys
c. Electrolyte imbalances
4. Idiopathic, anaphylactoid, or pseudoallergic reactions
a. Unpredictable, variable in severity
b. Do not require previous exposure to contrast media
c. Signs: urticaria, sneezing, decrease in blood pressure, tachycardia, facial swelling, laryngeal edema, pulmonary and cerebral edema, bronchospasm, and cardiovascular collapse
5. Potential risk factors: multiple myeloma; diabetes mellitus; advanced age; chronic renal, hepatic, or cardiac disease

IV. Nonionic water-soluble contrast media (NICM) (see Table 4-1)
A. Characteristics
1. Monomeric (most common) and dimeric derivatives of benzoic acid
2. Generally lower osmolality than ionic compounds (300 to 1000 mOsm/kg H_2O)
3. Excreted almost exclusively by the kidneys
4. Relatively expensive
5. Safest of the positive contrast media; associated with the fewest adverse effects

B. Uses
1. Same as ICM
2. Labeled for intrathecal injection (except for Ioversol)
3. Safest media to use near nervous system (myelography, epidurography, discography)
4. Do not cause fluid sequestration in GI tract as do ICM; safer for oral use

C. Adverse effects
1. Idiopathic reactions are similar to those of high-osmolar ionic media, but with much lower incidence.
2. Dimeric agents are viscous, and difficult to use in veterinary myelography (Widmer and Blevins, 1991).
3. In neurologic imaging procedures, rare adverse reactions include seizures, convulsions, radicular pain, and transient exacerbation of neurologic signs.
4. If extravasated or aspirated, NICM cause a less severe reaction than do ICM.

V. Negative contrast agents
A. Characteristics
1. Gases: room air, carbon dioxide (CO_2), nitrous oxide (rarely used)
2. Low physical density and relatively low atomic number
3. Attenuate few incident x-rays; appear radiolucent (black) on radiographs

B. Uses
1. Can be instilled into the lower urinary or GI tract for single-contrast studies
2. Most often used in double-contrast studies to inflate the lower urinary or GI tract precoated with positive contrast for visualization of mucosal detail

C. Adverse effects
1. Venous gas embolization can occur.
a. CO_2 is more soluble than room air and is therefore safer.
b. With animal in left lateral recumbency, small amounts of gas are trapped in the right side of the heart and do not travel into the pulmonary artery.
2. Pneumoabdomen/pneumomediastinum may develop if the gas extravasates.

ESOPHAGOGRAPHY

Definition

I. Dynamic or static contrast study of the pharynx and esophagus
II. Dynamic study performed with fluoroscopy; static study performed with radiographs
III. Evaluates swallowing reflex, motility, and structural aspects of the pharynx and esophagus

Indications

I. Dysphagia, regurgitation, gagging or retching, recurrent aspiration pneumonia
II. Suspected esophageal rupture or bronchoesophageal fistula
III. Stricture, ulceration, foreign body, mass, or diverticulum
IV. Localizing esophagus in relation to normal or abnormal mediastinal structures
V. Evaluation of possible esophageal lesion seen in survey radiographs
VI. Evaluation of motility, sphincter function, and swallowing reflex

Contraindications

I. Increased risk of aspiration (altered mental state, intractable vomiting)
II. With suspected rupture or fistulation, risk of barium entering the mediastinum or lung
III. Probable transient hypomotility/dilation from aerophagia, dyspnea, pain, or sedation

Alternative Imaging Procedures

I. Mediastinal/cervical ultrasonography: can evaluate paraesophageal structures in the neck and ventral mediastinum
II. Endoscopy: cannot assess motility, but can evaluate lumen and mucosa and obtain biopsy
III. Computed tomography: cannot assess motility

Preparation of Animal

I. Fasted 12 to 24 hours to encourage voluntary consumption of contrast agents
II. Survey thoracic and cervical/pharyngeal radiographs
III. May require sedation; however, this is undesirable because of effects on motility

Technique

I. Place animal in lateral recumbency.
II. Administer contrast medium per os into the buccal pouch.
  A. Barium sulfate liquid suspension (30% w/v)
  B. Barium sulfate paste
  C. Moist food mixed with barium paste
  D. Kibble mixed with barium paste
III. Begin with liquid, followed by paste, then soft food, and finally contrast-coated kibble.
IV. For each administration of contrast medium, monitor swallowing and transport of contrast to the stomach with fluoroscopy or with orthogonal radiographs made post-swallowing.

Normal Findings

I. Oropharyngeal phase
  A. Formation of bolus at base of tongue
  B. Rapid propulsion of bolus from base of tongue to cricopharyngeal sphincter over a closed glottis via peristaltic contraction of the pharynx
  C. Simultaneous opening of the cricopharyngeal sphincter to accept bolus
II. Esophageal phase
  A. Primary peristaltic waves begin upon acceptance of a bolus from the oropharynx, and may continue to the stomach. Primary waves are stimulated by the oropharyngeal phase.
  B. Secondary peristaltic waves are initiated to carry incompletely delivered boluses to the stomach. These waves are independent of the oropharyngeal phase.
III. Gastroesophageal phase
  A. Opening of the lower esophageal sphincter and passage of bolus into the stomach
  B. May see transient reflux of small amount in normal animals, but clears quickly
IV. Mucosal appearance
  A. Smooth and intact
  B. Mucosal folds: linear striations
    1. Dogs: longitudinally oriented throughout the length of the esophagus
    2. Cats: oblique or "herringbone" striations in the distal one third of the esophagus

Abnormal Findings

I. Diverticula: congenital or acquired
II. Abnormalities of oropharyngeal phase
  A. Incoordination of bolus propulsion and glottis closing, or opening of cricopharyngeal sphincter (dyssynergia)
  B. Mass in pharynx, preventing bolus formation or passage (neoplasia, abscess, granuloma, cyst)
  C. Stricture or spasm at cricopharyngeal sphincter, preventing opening (achalasia)
  D. Neuromuscular disorder or anesthesia-induced failure of the cricopharyngeal sphincter to contract (chalasia)
III. Abnormalities of peristalsis
  A. Delayed primary or secondary peristalsis
  B. Aperistalsis (diffuse vs focal)
    1. May be accompanied by esophageal dilatation (megaesophagus)
    2. Mechanical: vascular ring anomaly, gastroesophageal achalasia, foreign body, or mass
    3. Neuromuscular: idiopathic megaesophagus, myasthenia gravis, lead toxicity, thymoma, others
  C. Gastroesophageal reflux: possibly increased with sedation
IV. Mass effects
  A. Intraluminal: foreign body, gastroesophageal intussusception, polypoid mass
  B. Mural: stricture, mass (abscess, neoplasm, granuloma)
  C. Extramural
    1. Mediastinal, pulmonary or heart base mass: abscess, granuloma, neoplasm, lymphadenopathy
    2. Hiatal hernia: sliding, permanent
V. Extravasation: perforation, fistulation
VI. Mucosal abnormalities
  A. Ulceration
    1. Retention of barium; may see a crater ± increased wall thickness
    2. May be benign or associated with neoplasia

B. Esophagitis
   1. Irregular mucosal pattern
   2. Secondary to vomiting, reflux, or mechanical or chemical irritation

Complications

I. Aspiration is the major concern. Discontinue the procedure and obtain thoracic radiographs to determine the location and amount of aspirated material.
II. Leakage of barium into mediastinum through an unanticipated perforation is also possible.

GASTROGRAPHY

Definition

I. Gastric contrast procedure using negative (pneumogastrography) or both positive and negative contrast media (double-contrast gastrography)
II. Allows detailed examination of gastric mucosa, lumen, and wall
III. Does not evaluate motility

Indications

I. Chronic vomiting
II. Suspected gastric wall lesion (ulcer, mass)
III. Suspected gastric foreign body
IV. Abnormal appearance on survey radiographs

Contraindications

I. Increased risk of positive contrast media aspiration (altered mental state, intractable vomiting)
II. High suspicion of gastric rupture, perforation, or wall necrosis
III. Unable to pass gastric tube because of pharyngeal or esophageal disease

Alternative Imaging Procedures

I. Upper GI series
II. Ultrasonography
III. Endoscopy
IV. Nuclear scintigraphy: evaluation of motility, localization of GI bleeding
V. Computed tomography

Preparation of Animal

I. Fasted for 12 to 24 hours and cleansing enemas to empty GI tract
II. Sedation or anesthesia (for double-contrast study)
III. Administration of glucagon to decrease gastric motility, allowing visualization of structure without peristalsis (optional for pneumogastrography)
   A. Dogs: 0.1 to 0.35 mg/kg IV (lower doses in smaller animals); cats: 0.1 mg IV
   B. Maximum dose: 1 mg
   C. Lasts approximately 15 minutes; may be repeated
   D. Contraindications to glucagon: pheochromocytoma, uncontrolled diabetes mellitus

Technique

I. Double-contrast gastrography
   A. Via orogastric tube, administer barium sulfate suspension (30% w/v) at 1.5 to 3 mL/kg in dogs (higher dose for smaller dogs), and 3 mL/kg in cats.
   B. Inflate stomach with approximately 20 mL/kg gas (dogs) until stomach is distended.
   C. Withdraw the tube and rotate animal 360° about the longitudinal axis of the body.
   D. Obtain ventrodorsal (VD), dorsoventral (DV), and right and left lateral views.
II. Pneumogastrography
   A. Via orogastric tube, inflate stomach with approximately 20 mL/kg gas (dogs) until stomach is distended.
   B. Alternatively, administer 60 mL of a carbonated beverage.
   C. Kink and quickly withdraw tube.
   D. Obtain VD and left lateral abdominal radiographs immediately, with additional views as needed.

Normal Findings

I. Rugal folds: linear striations running parallel to the axis of the stomach
II. Lower esophageal sphincter: "star" pattern of rugae on lesser curvature (may not see with pneumogastrography)
III. Smooth, uninterrupted mucosal surface
IV. Normal shape and orientation

Abnormal Findings

I. Double-contrast gastrography
   A. Ulceration: craters of barium retention in the mucosa ± wall thickening; may be benign or neoplastic
   B. Wall masses, circumferential or eccentric: neoplasia, polypoid gastritis, granuloma
   C. Thickened wall: gastritis or neoplasia
II. Pneumogastrography
   A. Luminal foreign bodies
   B. Wall masses, circumferential or eccentric: neoplasia, polypoid gastritis, granuloma

Complications

I. Regurgitation/aspiration
II. Iatrogenic damage from intubation or overdistention of diseased organ
III. Discomfort from dilation of stomach (reintubate to decompress)

UPPER GASTROINTESTINAL SERIES

Definition

I. Contrast procedure designed to opacify stomach and small intestine (upper GI tract)
II. Allows evaluation of the lumen, mucosal surfaces, motility, and contents

Indications

I. Signs of gastric or small intestinal disease: acute or chronic vomiting, small bowel diarrhea, anorexia, weight loss, abdominal pain

II. Suspected intestinal obstruction
III. Evaluation of GI transit time
IV. Abdominal mass localization
V. Abnormal appearance of stomach or small intestine on survey radiographs

Contraindications

I. Increased risk of aspiration (altered mental state, intractable vomiting)
II. Suspected perforation (use NICM)
III. Obvious surgical condition on survey radiographs
IV. Unmanageable animal (many radiographs required, sedation undesirable)

Alternative Imaging Procedures

I. Ultrasonography
II. Endoscopy
III. Scintigraphy: motility study, localization of GI bleeding

Preparation of Animal

I. Fasted for 12 to 24 hours and cleansing enemas to empty GI tract
II. Survey orthogonal abdominal radiographs
III. Sedation (if needed) using agents with minimal impact on motility
   A. Dogs: acepromazine 0.025 to 0.05 mg/kg IV, SC, or IM
   B. Cats: ketamine 2 to 4 mg/kg IV with acepromazine 0.05 mg/kg IV or diazepam 0.44 mg/kg IV

Technique

I. Orogastric intubation: preferred over PO administration
II. Barium sulfate suspension (20% to 30% w/v)
   A. Dogs: 6 to 12 mL/kg (larger dose for smaller dogs)
   B. Cats: 12 to 16 mL/kg
III. Questionable GI integrity: NICM used
   A. Use 10 mL/kg to total dose of 240 to 300 mg iodine/mL NICM diluted 1:2 or 1:3 in water.
   B. ICM is *not* recommended because of hypertonic effects on fluid/electrolyte status.
IV. Radiographic views to be obtained
   A. Increase kVp by 5% to 10%
   B. Typical timing of radiographic exposures
      1. Dogs
         a. Immediate VD, DV, and right and left lateral
         b. Lateral and VD views at 30 minutes, 1, 2, 3, and 4 hours
      2. Cats
         a. Immediate VD, DV, and right and left lateral
         b. Lateral and VD at 15 and 30 minutes, then 1, 1.5, and 2 hours
      3. Normal exam: complete when barium clears stomach and reaches colon
      4. Exam with abnormalities: continue as needed to obtain diagnosis

Normal Findings

I. Generalized smooth or finely fimbriated mucosal surfaces
II. Normal focal mucosal irregularities

TABLE 4-2

Typical Times of GI Events for Dogs and Cats With Barium Sulfate Suspension and NICM

EVENT	TIME OF OCCURRENCE	
	DOG	CAT
Contrast Begins To Leave Stomach		
Barium	Immediately to 15 min, maximum 30 min (Moon and Meyer, 1986)	Immediately to 15 min (Morgan, 1981)
NICM	Immediately (Augt et al., 1993)	Immediately (Moon and Meyer, 1986)
Gastric Contents Cleared		
Barium	30-20 min, maximum 4 hr (Miyabayashi et al., 1986; Miyabayashi and Morgan, 1991)	15-60 min, maximum 2 hr (Morgan, 1977, 1981)
NICM	30-120 min (Augut et al., 1993)	30-90 min (Williams et al., 1993)
Contrast Reaches Colon		
Barium	30-120 min (Miyabayashi et al., 1986)	30-60 min, maximum 2 hr (Hogan and Aronson, 1988; Morgan, 1977, 1981)
NICM	60-90 min (Augt et al., 1993)	15-75 min (Williams et al., 1993)
Contrast Clears Small Intestine		
Barium	3-5 hr (Miyabayashi et al., 1986)	Not reported

GI, Gastrointestinal; *NICM,* nonionic water-soluble contrast media.

A. Gastric rugal folds: parallel folds in mucosa running parallel to the greater curvature
B. Lower esophageal sphincter: "star" pattern of rugae on lesser curvature of stomach
C. Peyer's patches: focal outpouchings of contrast into the mucosa of the antimesenteric border of the descending duodenum (dogs only)

III. Transit times (Table 4-2)
IV. Contrast column
A. Peristaltic waves should propel the contrast through the small intestine, showing a contrast column of varying diameters. This can be dramatic in the normal cat duodenum, causing a "string-of-pearls" appearance.
B. Areas of peristaltic activity are transient. Repeatable focal narrowing of the contrast column is an indicator of focal disease.

Abnormal Findings

I. Increased gastric emptying time (motility decreased or transit slowed)
A. Emptying time >4 hours in dogs and >2 hours in cats
B. Mechanical pyloric outflow obstruction
1. Pyloric hypertrophy or stenosis
2. Pyloric mass: neoplasia, granuloma, polyp
3. Foreign body
C. Functional obstruction: pyloric spasm, inflammation, or ulceration
D. Hypomotility from stress, pain, anticholinergic medication, neurological damage, or ischemia or other motility disorder
E. Insufficient dose of barium to initiate peristalsis

II. Increased small intestinal transit time (motility decreased or transit slowed)
A. Generalized
1. Functional ileus from stress, pain, anticholinergic medication, neurologic damage, ischemia, or inflammation
2. Mechanical ileus from obstruction in distal small intestine: foreign body, intussusception, neoplasm, extra-GI masses, entrapment, others
3. Mesenteric volvulus or infarction
B. Focal
1. Mechanical ileus (complete or partial obstruction): focal dilatation of intestine proximal to obstruction
2. "Gravel sign": accumulation of debris and barium immediately proximal to a partially obstructive lesion

III. Decreased small intestinal transit time (faster transit)
A. Enteritis
B. Maldigestion/malabsorption syndrome

IV. Increased contrast column diameter (GI distention)
A. Generalized
1. Functional ileus
2. Distal small intestinal obstruction (chronic)
B. Focal
1. Stomach only: pyloric outflow obstruction (acute or chronic)
2. Small intestine: proximal to obstruction (acute, chronic, partial, or complete)

V. Irregular contrast border
A. Infiltration and rigidity of mucosa
B. Potential causes
1. Inflammation
a. Inflammatory bowel disease
b. Granulomatous enteritis
c. Focal inflammation: irritation from foreign body, parasites
2. Neoplastic infiltration
3. Scarring

VI. Contrast column filling defects
A. Intraluminal
1. Foreign body
2. Parasites
3. Mucosal mass: polyp, neoplasia
B. Mural
1. Circumferential
a. Stricture
b. Neoplasia, most common: lymphoma and adenocarcinoma
2. Eccentric
a. Neoplasia: as lymphoma, adenocarcinoma leiomyoma, leiomyosarcoma, etc.
b. Abscess, granuloma, hematoma
C. Extramural
1. Mass or adjacent structure: lipoma, lymphadenopathy, prostatomegaly, full bladder, etc.
2. Internal hernia

VII. Eccentric outpouching of contrast column and wall defects
A. Ulceration
1. "Crater" of retained barium ± increased surrounding intestinal wall thickness
2. May be benign or associated with neoplasia
B. Diverticulum

Complications

I. Vomiting and aspiration
II. Leakage of contrast at perforation site
III. Barium-induced constipation (rare)
IV. Drooling or emesis with oral NICM
V. Iatrogenic damage
A. Trauma to oral cavity, pharynx, esophagus, or stomach from intubation
B. Rupture of diseased stomach from overdistention
C. Inadvertent deposition of barium into lungs

Solid Radiopaque Marker (BIPS) Study

I. Used when full upper GI study is not necessary or is contraindicated
II. Specific considerations
A. Can be used when obstruction is the primary differential diagnosis
1. Administer BIPS, and obtain radiographs 4 to 12 hours later.
2. BIPS will accumulate proximal to obstruction.
B. Good for uncooperative animals (can hide BIPS in food or administer as pill)
C. Can be used to evaluate GI transit time

1. Variably sized spheres proceed through the GI tract at different rates depending on method of administration (pill form or mixed in soft or dry food).
2. The manufacturer includes information describing normal transit patterns.

COLONOGRAPHY

Definition and Indications

I. Positive, negative, and double-contrast studies of the colon
II. Used in identification and localization of the colon in relation to other abdominal structures
III. Used to evaluate colonic structure, including the wall, lumen, and mucosal surface

Contraindications

I. Inability or unwillingness to sedate or anesthetize the animal
II. Suspected perforation: use NICM *only;* not barium or gas
III. Risk of iatrogenic perforation: severe colitis, known ulceration, or post-biopsy

Alternative Imaging Procedures

I. Ultrasonography
II. Colonoscopy
III. Computed tomography

Preparation of Animal

I. Cleansing enemas, then a 2-hour wait to clear introduced gas and fluid
II. Survey radiographs of abdomen and pelvis

Technique

I. Pneumocolon (for identification/localization purposes only)
   A. Sedation is often unnecessary.
   B. Via a red rubber or tomcat catheter, inject room air or other negative contrast agent at 1 to 3 mL/kg body weight into the rectum.
   C. Obtain VD and lateral abdominal radiographs; both lateral views may be beneficial.
II. Positive and double-contrast colonography (for thorough evaluation of structure)
   A. Anesthesia is required.
   B. A balloon catheter is placed in the rectum and inflated to occlude the anal sphincter.
   C. With the animal in left lateral recumbency, infuse barium sulfate suspension until colon is full (5 to 15 mL/kg body weight).
   D. Use NICM if colonic integrity is questionable.
   E. Obtain VD and lateral radiographs (increase kVp by 5% to 10%).
   F. Remove barium and administer sufficient negative contrast to distend the colon.
      1. Dose is approximately 10 mL/kg.
      2. *Do not overdistend;* monitor with fluoroscopy or radiographs.
   G. Obtain VD, DV, and both lateral radiographs.

Interpretation of Pneumocolon

I. Identifies location of the colon in relation to other abdominal structures
II. Differentiates colon from small intestine

Interpretation of Double-Contrast Colonography

I. Normal findings
   A. Mucosa smooth and intact
   B. Wall thin and regular
   C. Cecum sometimes inflated, without retrograde flow of contrast into distal small intestine (unless overdistended)
II. Abnormal findings
   A. Mucosal defects: ulceration
   B. Filling defects
      1. Intraluminal: unevacuated feces, mucosal mass (e.g., polyp), intussusception
      2. Mural: neoplasia, stricture, abscess, granuloma, hematoma
      3. Extramural: mass or adjacent structure (e.g., bladder, prostate, uterus, lumbar lymph nodes, neoplasm, granuloma, abscess)
   C. Diverticula
   D. Herniation

Complications

I. Intraperitoneal leakage of barium from loss of colon wall integrity
II. Iatrogenic perforation

EXCRETORY UROGRAPHY

Definition

I. Contrast procedure designed to enhance visualization of the kidneys, renal pelvis, and ureters
II. Gives qualitative information on renal function
III. Also known as *intravenous urography* and *intravenous pyelography* (IVP)

Indications

I. To evaluate morphology and location of the kidneys, ureters, and bladder
II. To identify and localize urinary tract disease or dysfunction
III. To assess the effect of masses or trauma on the urinary tract
IV. As a crude assessment of renal function and urinary tract patency

Contraindications

I. Dehydration: associated with contrast-induced renal failure
II. Renal disease
   A. As renal function decreases, the quality of the study decreases.
   B. With blood urea nitrogen >50 to 75 mg/dL, the contrast agent dose may be doubled to increase quality of imaging.
   C. With severe azotemia, the study may be poor regardless of contrast agent dosage.

D. Increasing the dose in the face of decreased renal function leads to increased risk of renal toxic effects and systemic reactions.

III. Known sensitivity to contrast agents

Alternative Imaging Procedures

I. Ultrasonography
II. Nuclear scintigraphy: evaluation of glomerular filtration rate
III. Computed tomography

Preparation of Animal

I. Fasted for 12 to 24 hours, and cleansing enemas to empty GI tract
II. Peripheral venous indwelling catheter
III. Urinary catheter if trigone morphology to be investigated or cystography performed
IV. Anesthesia or sedation if necessary (recommended for evaluation of trigone)
V. Well-hydrated circulatory status
VI. Survey abdominal radiographs

Technique

I. Intravenous bolus of ICM or NICM (800 mg iodine/kg body weight)
II. Radiographic views to be obtained
  A. Ventrodorsal and lateral views immediately and at 5, 20, and 40 minutes
  B. Oblique views at 10 minutes to visualize trigone, if needed
III. Modifications if ureteral ectopia suspected
  A. Anesthesia is required.
  B. Perform a negative contrast cystogram with a retention cuff catheter prior to excretory urography to increase contrast at the trigone.
  C. Fluoroscopy or multiple radiographs are often necessary to visualize contrast in the ureters at the trigone.

Normal Findings

I. Nephrogram (renal opacification)
  A. Opacity peaks at 10 to 20 seconds post-injection and gradually fades over 1 to 3 hours.
  B. Less than 25% of normal dogs have opacification remaining at 2 hours (Feeney et al., 1979).
  C. The nephrogram is best visualized on immediate and 5-minute radiographs.
  D. There are two components of the nephrogram:
    1. Vascular nephrogram: contrast in the renal vasculature
      a. Cortex more opaque than medulla (5 to 10 seconds post-injection)
      b. Occurs immediately and then quickly obscured by tubular phase
    2. Tubular nephrogram: contrast within Bowman's capsules and renal tubules
      a. Kidney uniformly opaque
      b. Most typically seen phase of the nephrogram
  E. Degree of renal opacification depends on hydration, contrast dose, renal blood flow, and relative renal function.

II. Pyelogram (renal pelvis, pelvic diverticula, and ureter opacification)
  A. Opacification begins at 1 to 3 minutes and persists for several hours.
  B. It is best visualized within the first hour.
  C. The pyelogram is more opaque than nephrogram because of contrast media concentration.
  D. Normal pelvic diverticula are often not visible without abdominal compression.
  E. Normal peristalsis causes transient filling defects in the ureteral contrast column.

Abnormal Findings

I. Nephrogram
  A. Morphological changes: size, shape, location, number, margination (Table 4-3)
  B. Opacification sequence changes: onset, degree of opacification, and fading (Box 4-1)
II. Pyelogram (Table 4-4)
  A. Changes in onset or degree of opacification
    1. Onset of opacification is dependent on renal excretion and ureteral patency.
    2. An absent or delayed pyelogram can result from reduced renal blood flow (e.g., shock, hypovolemia, renal infarction), renal disease (decreased excretion, ± decreased concentration), or ureteral outflow obstruction.
  B. Decreased peristalsis: obstruction, infection, or ectopia
  C. Ureteral obstruction: calculi, hematoma, neoplasia, abscess/granuloma, or stricture
  D. Changes in size, shape, location, lumenal contents (filling defects)
  E. Ectopic ureters
    1. The ureter may be dilated.
    2. Unilateral or bilateral ectopia may be found.

Box 4-1

Nephrographic Opacification Sequence Changes and Associated Disorders

Poor Initial Opacification	Fair to Good Initial Opacification
Gradual increase in opacity	Increasing opacity
Acute extrarenal obstruction	Systemic hypotension
Systemic hypotension	Acute renal obstruction
Renal ischemia	Contrast-induced renal failure
Persistent poor opacity	Persistent opacity
Primary glomerular dysfunction (chronic)	Acute tubular necrosis
Severe generalized renal disease	Contrast-induced renal failure
Gradual decrease in opacity	Systemic hypotension
Primary polyuric renal failure	Ethylene glycol toxicosis
Acute pyelonephritis	Decreasing opacity
Inadequate dose	Normal

Modified from Feeney et al: Advances in canine excretory urography. Gaines Vet Symp 30:8, 1981; with permission.

TABLE 4-3

Nephrographic Findings During Excretory Urography, Including Limited Differential Diagnosis

FINDING	SMOOTH MARGIN		IRREGULAR MARGIN	
	UNIFORM OPACITY	NONUNIFORM OPACITY	UNIFORM OPACITY	NONUNIFORM OPACITY
Kidney size increased	Compensatory hypertrophy Infiltration by inflammatory or neoplastic cells	Renal cyst Perirenal pseudocyst Polycystic disease Neoplasia Hydronephrosis Other non–capsule-deforming mass effects	Neoplasia Other	Neoplasia Renal cyst Polycystic disease Granuloma Abscess Hematoma
Kidney size normal	Normal Acute glomerular disease	Neoplasm Hydronephrosis Infarction Pyelonephritis Intrarenal hemorrhage Polycystic disease Renal cyst	Pericapsular hematoma Neoplasia	Neoplasia Intrarenal hemorrhage Renal cyst Polycystic disease Infarction
Kidney size decreased	Hypoplasia Dysplasia	Glomerular disorders Dysplasia	Hypoplastic kidneys with superimposed disease Chronic renal failure	Chronic generalized and/or tubulointerstitial disease Multiple infarcts
Nephrogram absent Renal aplasia Infarction or avulsion of renal artery Nephrectomy Inadequate dose (if bilateral)				

Modified from Feeney DA, Barber DL, Osborne CA: Advances in canine excretory urography. Gaines Vet Symp 30:8, 1981; with permission.

TABLE 4-4

Pyelographic Opacification Sequence and Structural Changes and Associated Disorders

DELAYED ONSET/ DECREASED OPACITY	STRUCTURAL CHANGES		
	FILLING DEFECTS	SIZE/SHAPE CHANGES	LOCATION
Obstruction Renal failure/insufficiency Inadequate dose	Calculi Hemorrhage	Hydronephrosis Obstructive Functional (ectopic ureter) Pyelonephritis Compression/distortion from renal parenchymal mass Ureteral ectopia Ureteral stricture Ureterocele	Ectopia Deviation by retroperitoneal mass

3. The ureter may enter the urethra, vagina, uterus, or vas deferens.
4. The ureter may enter the bladder wall and have one orifice into the bladder, then "tunnel" through the wall to have a second orifice into the urethra.

F. Extravasation of contrast material into the retroperitoneal space: rupture

Complications

I. Contrast reaction (rare)
II. Risk reduced by ensuring adequate hydration of the animal

CYSTOGRAPHY/URETHROGRAPHY

Definition

I. Contrast study designed to enhance visualization of the urinary bladder and urethra
II. Single- or double-contrast studies
  A. Positive or negative contrast study for evaluating location, shape, patency, wall thickness, and integrity
  B. Double-contrast cystogram for mucosal detail and to visualize lumenal contents

Indications

I. Stranguria/dysuria
II. Recurrent cystitis
III. Suspected radiolucent calculi
IV. Suspected anatomic malformation
V. Suspected rupture of the lower urinary tract

Contraindications

I. Inability to safely sedate or anesthetize animal
II. Emphysematous cystitis
III. Hematuria: negative contrast agents avoided because of risk of venous embolization
IV. Suspected small perforation: negative contrast study less sensitive than positive contrast study
V. Known sensitivity to contrast agents

Alternative Imaging Procedures

I. Ultrasonography
II. Computed tomography
III. Cystoscopy

Preparation of Animal

I. Fasted for 12 to 24 hours and warm water enemas to empty GI tract
II. Survey abdominal and pelvic radiographs

Technique

I. Place animal in left lateral recumbency.
II. Insert urinary catheter and drain urine.
III. Perform a single-contrast cystogram.
  A. Inject ICM, NICM, or negative contrast media until bladder is palpably turgid (approximately 5 mL/kg).
  B. Obtain VD and lateral radiographs.
IV. Alternatively, perform a double-contrast cystogram.
  A. Distend the bladder with negative contrast, then inject low-volume ICM or NICM (0.5 to 1 mL for cats, 1 to 4 mL for dogs).
  B. Gently roll animal about its long axis to coat all mucosal surfaces.
  C. Obtain lateral radiographs and oblique radiographs, ± VD view.
V. Perform a urethrogram.
  A. Retrograde urethrogram (preferred)
    1. Ensure the bladder is full to provide adequate pressure (use saline or contrast media to fill if necessary).
    2. Advance a balloon catheter to the proximal (pelvic) urethra and inflate cuff.
    3. Obtain lateral and VD radiographs during injection of ICM or NICM (dose to effect).
    4. Withdraw catheter to distal urethra and repeat.
  B. Antegrade urethrogram
    1. Perform IVP and allow contrast to accumulate in bladder, or inject ICM or NICM into the bladder.
    2. Obtain VD and lateral radiographs while applying pressure to the bladder, forcing urine to flow antegrade through the urethra.

Normal Findings

I. The bladder mucosal surface is smooth and the wall is thin (≈1 to 2 mm).
II. Positive contrast forms a small, uniform, opaque pool in the dependent central bladder; small air bubbles may be seen at the periphery of this pool.
III. Normal ureteral reflux may be seen in normal young animals, with anesthesia, or with excessive distention.
IV. A normal urethrogram has the following characteristics:
  A. Males
    1. With a full bladder under sufficient pressure, the prostatic urethra is the widest section; however, with an empty bladder the prostatic urethra will be the narrowest.
    2. Mild prostatic reflux may be seen if the bladder is distended.
    3. The small longitudinal dorsal filling defect at the neck of the bladder and in the prostate is the normal colliculis seminalis.
  B. Females
    1. Uniform diameter of contrast column
    2. Smooth mucosal borders

Abnormal Findings

I. Abnormal shape/location: urachal diverticulum, pelvic bladder, herniation
II. Filling defects
  A. Air bubbles: round lucencies at the periphery of the contrast pool in the bladder or transient round filling defects in the urethra.
  B. Calculi or blood clots: repeatable filling defects, usually in the central contrast pool or urethra
    1. Blood clots: amorphous; can change shape with manipulation

2. Calculi: may change position with manipulation, but shape is typically consistent

C. Mural mass protruding into the lumen: neoplasm, abscess, granuloma, hematoma

D. Circumferential narrowing of urethra

1. Physiologic spasm: may be relieved by flushing 1 to 3 mL lidocaine through catheter
2. Stricture

III. Extravasation: rupture or avulsion

IV. Wall thickening/irregularity

A. General: cystitis/urethritis (± cobblestone appearance to mucosa)

B. Focal: cystitis (possibly polypoid) or neoplasia

1. Cranioventral: more likely cystitis
2. Dorsal trigone region: more likely neoplasia

V. Prostatic/ureteral reflux

A. Can be seen in a small percentage of normal animals

B. May indicate prostatic or ureteral disease/dysfunction

Complications

I. Air embolization: rare; risk reduced by placing animal in left lateral recumbency and using CO_2

II. Iatrogenic bladder or urethra damage

A. Do not force catheter (may damage or penetrate the wall).

B. Distend bladder only until palpably turgid; *do not overdistend.*

III. Iatrogenic infection introduced with catheterization

IV. Changes in urinalysis results: artifactually increased urine specific gravity and protein for 24 to 72 hours, which altered culture/sensitivity results

V. Contrast reaction (rare)

MYELOGRAPHY

Definition and Indications

I. The introduction of a positive contrast agent into the subarachnoid space (SAS) for delineation of the SAS and, indirectly, the spinal cord

II. Indicated when neurological signs are present referable to the spinal cord

III. Allows evaluation of the location and extent of spinal cord compressive lesions

IV. Allows evaluation of the effect of vertebral disease on the neural canal

Contraindications

I. Inability to anesthetize animal safely

II. High intracranial pressure: cisternal puncture possibly leading to brain herniation

III. Meningitis: possible exacerbation of inflammation or spread of infection

IV. Dehydration: increased contrast clearance time, thereby increasing complications

V. Known sensitivity to contrast agents

Alternative Imaging Procedures

I. Magnetic resonance imaging

II. Computed tomography

Preparation of Animal

I. General anesthesia is required.

II. Do not premedicate with phenothiazine derivatives because they may lower the seizure threshold.

III. Obtain survey lateral and VD radiographs of the spine with oblique views of suspicious regions.

Technique

I. Injection site: chosen based on neurologic localization of suspected lesion

A. Cervicothoracic spinal cord segments: cerebellomedullary cistern injection

B. Thoracolumbar and sacral spinal cord segments: lumbar injection (between the 5th and 6th, or 4th and 5th lumbar vertebrae)

II. *With NICM only*

A. Cervical study: dose = 0.3 mL/kg

B. Thoracolumbar study: dose = 0.3 to 0.4 mL/kg

C. Whole-spine study: dose = 0.45 mL/kg

III. Injection method

A. Aseptically prepare injection site.

B. Perform dural puncture and collect cerebrospinal fluid (CSF), if appropriate.

C. Administer injection slowly in the dorsal SAS for cisternal puncture, and ventral SAS for lumbar puncture.

D. CSF may not flow into the needle hub with lumbar puncture.

IV. Views to be obtained

A. Cervical study

1. Lateral and DV views (both lateral views possibly useful)
2. VD ± DV oblique views of lesions
3. Traction, extension, and flexion views if dynamic lesion (cervical vertebral instability) suspected

B. Thoracolumbar study

1. Lateral and VD views
2. Oblique views of lesions

Normal Findings

I. Uniform contrast medium columns (Figure 4-1, *A*)

II. May see slight undulation of ventral column in lumbar region of small dogs

III. May see asymmetrical columns (dorsal column wider than ventral or vice versa), but no complete attenuation of both columns on one view in any region

IV. Slight attenuation of contrast columns with circumferential widening of the spinal cord at the cervical and lumbosacral (L-S) intumescences

V. Occasional central canal filling: thin linear opacity parallel to and in the center of the cord

Abnormal Findings

I. Extradural compressive lesion (see Figure 4-1, *B*)

A. Eccentric deviation and attenuation of SAS

B. Type I or II intervertebral disk disease (IVDD), spinal ligament hypertrophy, stenotic myelopathy

C. Hemorrhage

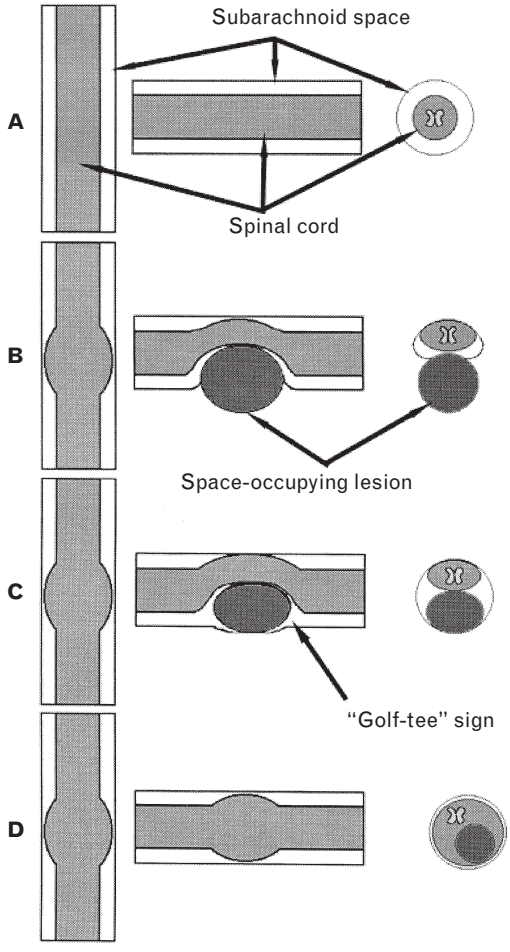

FIGURE 4-1 Myelographic findings associated with various space-occupying lesions. Orthogonal myelographic views and a cross-sectional view are shown. **A,** Normal. **B,** Extradural compressive lesion. **C,** Intradural-extramedullary lesion. **D,** Intramedullary lesion.

D. Neoplasia, cyst, abscess, granuloma
E. Displaced vertebral fracture or fracture fragment

II. Intradural/extramedullary space-occupying lesion (see Figure 4-1, *C*)
A. Characteristic "golf tee" sign to one contrast column as contrast medium flows around space occupying lesion, with attenuation of the other columns
B. Hemorrhage
C. Neoplasia, arachnoid cyst, abscess, granuloma

III. Intramedullary space-occupying lesion (see Figure 4-1, *D*)
A. Widening of the cord with circumferential SAS deviation and attenuation
B. Spinal cord swelling (edema or inflammation)
C. Hemorrhage
D. Neoplasia, abscess, granuloma

IV. Epidural injection
A. Wide, undulating ventral column with circular opacities at intervertebral foramina
B. Injection repeated after 30 minutes if needed (allows contrast medium to clear)

V. Contrast within cord
A. Wide central canal (>1 mm)
1. Hydromyelia: naturally occurring or iatrogenic from direct injection into central canal
2. Myelomalacia: poor to grave prognosis
B. Injection into cord parenchyma: no effect to worsening of signs; usually transient

Complications

I. Temporary worsening of clinical signs
II. Seizures
III. Apnea or changes in anesthetic plane during injection
IV. Radicular pain
V. Contrast reaction (rare)
VI. Injection into cord parenchyma
VII. Introduction of infection: rare, minimized by aseptic technique
VIII. Brain herniation through foramen magnum after cervical puncture in presence of high intracranial pressure

EPIDUROGRAPHY

Definition and Indications

I. Introduction of positive contrast agent into the caudal epidural space for opacification and delineation of the epidural space
II. Indicated for clinical signs referable to the cauda equina or L-S region

Contraindications

I. Inability to safely anesthetize animal
II. Infection (e.g., discospondylitis) and risk of iatrogenic dissemination
III. Known sensitivity to contrast agents

Alternative Imaging Procedures

I. Magnetic resonance imaging
II. Computed tomography
III. Myelography
IV. Discography

Preparation of Animal

I. General anesthesia: required
II. Survey VD and lateral radiographs

Technique

I. Injection site
A. L-S junction: palpable space between last lumbar and sacral spinous processes
B. Caudal vertebrae
1. Sagittal plane between vertebral arches anywhere between the 3rd sacral and 5th caudal vertebrae
2. Sacrocaudal junction easiest

II. Injection technique
A. Aseptically prepare the injection site.
B. Insert a 22-gauge spinal needle (length variable depending on size of animal) into interarcuate space, advancing to the floor of the canal.
C. Inject NICM 0.15 mL/kg initially, then 0.1 mL/kg if needed between subsequent exposures.

III. Radiographic views to be obtained
  A. Increased kVp by 5% to 10% over that used for survey radiographs
  B. Neutrally positioned lateral radiographs
  C. Lateral radiographs with hips extended and flexed
  D. DV radiographs for lateralization, if necessary

Normal Findings

I. Contrast columns are symmetrical with no filling defects.
II. The ventral column is immediately adjacent to the dorsal aspect of the vertebral bodies at the L-S junction.

Abnormal Findings

I. Elevation or deviation of the epidural contrast medium column with compression of >50% of the vertebral canal diameter or complete obstruction to contrast medium flow
  A. Lumbosacral IVDD
  B. Lumbosacral stenosis
  C. Ventral longitudinal ligament hypertrophy resulting from L-S instability
  D. May differentiate static versus dynamic lesion with flexion/extension views
II. Filling defects: neoplasia, hemorrhage, granuloma/abscess, cyst

Complications

I. Introduction or dissemination of infection
II. Contrast reaction (rare)

ARTHROGRAPHY

Definition

I. Contrast procedure for evaluation of joint space, capsule, and articular cartilage
II. Performed in many joints, but most often done in the shoulder joint

Indications

I. Lameness localized to joint, without specific survey radiographic findings
II. Osteochondritis desiccans (OCD): used to diagnose and determine number and location of cartilage flaps/fragments in the joint and/or tendon sheath
III. Wound near joint: used to determine communication of joint with the wound

Contraindications

I. Inability to safely anesthetize animal
II. Known sensitivity to contrast agents

Alternative Imaging Procedures

I. Ultrasonography
II. Computed tomography
III. Magnetic resonance imaging

Preparation of Animal

I. General anesthesia is required.
II. Obtain survey orthogonal radiographs of affected joint(s).

Technique

I. Perform aseptic arthrocentesis using 22-gauge spinal needle (see Chapter 3).
II. Aspirate joint fluid for culture and cytology.
III. Inject NICM or ICM, diluted 1:3 with sterile saline (NICM recommended).
  A. Shoulder: 2 to 4 mL, or until resistance (Muhumuza et al., 1988)
  B. Stifle: 0.3 to 0.4 mL/cm width of stifle joint (Hay et al., 1996)
  C. Elbow: 2 mL (Lowry et al., 1993)
IV. Hypertonic ICM may draw fluid into joint, thereby diluting contrast media quickly.
V. Gently flex and extend joint to evenly distribute contrast.
VI. Obtain orthogonal views with stress and oblique views as needed, thereby increasing kVp by 5% to 10% over survey radiographs.

Normal Findings

I. Smooth capsular and cartilage surfaces
II. Intraarticular tendons (e.g., bicipital tendon) visualized as linear filling defects

Abnormal Findings

I. Irregularity to cartilaginous surface: OCD or erosion
II. Intraarticular filling defects
  A. Cartilage flap secondary to OCD
  B. Joint bodies
  C. Osteochondroma/osteochondromatosis
  D. Adhesions
III. Irregularity to internal joint capsule surface
  A. Synovial hyperplasia/proliferative synovitis
  B. Osteochondroma/osteochondromatosis
  C. Adhesions

Complications

I. Infectious arthritis
II. Synovial irritation and influx of fluid by high-osmolar monomeric ICM; NICM safer
III. Synovial rupture if excessive pressure used
IV. Contrast reaction (rare)

PORTOGRAPHY

Definition and Indications

I. Contrast study used to visualize the portal vascular system
II. Used to identify portosystemic shunting
III. Practical methods: splenoportography and jejunal vein portography

Contraindications

I. Inability to safely anesthetize animal and possibly perform laparotomy
II. Known sensitivity to contrast agents
III. Coagulopathy

Alternative Imaging Procedures

I. Ultrasonography
II. Nuclear scintigraphy: transrectal portal scintigraphy, transsplenic portal scintigraphy

Preparation of Animal

I. Fasted 12 to 24 hours ± cleansing enemas to empty GI tract
II. Survey VD and lateral abdominal radiographs
III. General anesthesia required

Technique

I. Splenoportography
   A. Place the animal in right lateral recumbency and aseptically prepare site of injection.
      1. Evaluate location of spleen by palpation or with ultrasonography.
      2. Prepare area from hypaxial musculature to midline, parallel to the last rib—a region approximately 6 to 7 cm wide.
   B. Insert an over-the-needle catheter into splenic parenchyma (guided with ultrasonography, if possible), aiming toward hilus. Venous backflow will indicate proper needle placement.
   C. If ultrasonography is not available and palpation of the spleen is not possible, perform laparotomy to visualize the spleen for catheter placement, or perform jejunal venography.
   D. Perform a 1- to 2-mL test injection and record results with either fluoroscopy or radiography; if needle is in the proper location, proceed.
   E. Inject 5 to 15 mL of ICM or NICM.
   F. Obtain two to four radiographs in rapid succession 2 to 4 seconds post-injection.
   G. Repeat, if necessary; orthogonal studies may improve visualization.
II. Jejunal vein portography
   A. Perform a ventral midline laparotomy and isolate a loop of jejunum.
   B. Insert an over-the-needle catheter into a jejunal vein and secure with ligatures.
   C. Temporarily close the abdominal incision for transport and positioning, if needed.
   D. With the animal in dorsal recumbency, rapidly inject 1 to 2 mL/kg body weight ICM or NICM.
   E. Monitor flow with fluoroscopy or obtain radiograph at middle to end of injection.
   F. Reposition the animal in lateral recumbency and repeat injection and radiograph.

Normal Findings

I. Opacification of the portal branches associated with injection
   A. Splenoportography: splenic and cranial portal veins
   B. Jejunal vein: jejunal, cranial mesenteric, and portal veins
II. Arborization of portal vein as it enters the hepatic parenchyma

Abnormal Findings

I. Portosystemic shunt
   A. Single or multiple vessels connecting portal system to caudal vena cava or azygous vein
   B. May have decreased or complete lack of hepatic arborization
II. Shunt caudal to the 13th thoracic vertebra: high likelihood of extrahepatic shunt (Birchard et al., 1989)
III. Shunt cranial to the 13th thoracic vertebra: high likelihood of intrahepatic shunt (Birchard et al., 1989)
IV. Misdiagnosis
   A. With splenoportography, only the portal vein and its branches at and cranial to the splenic vein entrance can be evaluated. A shunt caudal to this point may be missed if hepatofugal flow is not present.
   B. With jejunal vein portography, a shunt arising from the caudal mesenteric vein or its branches may be missed if hepatofugal flow is not present.

Complications

I. Splenic laceration
II. Hemoabdomen
III. Contrast reaction (rare)

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CHAPTER 5

Introduction

Kristin MacDonald

HEART DISEASE

Heart Failure

I. In moderate to severe cardiac disease, normal cardiovascular functions cannot be maintained.
II. The first change is elevation in capillary and venous pressures, leading to tissue edema (pulmonary edema, peripheral edema, ascites), which is termed *congestive heart failure (CHF)*.
   A. CHF occurs in the setting of moderate or severe cardiac disease.
   B. Often, cardiac disease is present without CHF.
   C. Increased preload (increased filling pressures) occurs when there is hypotension that activates the renin-angiotensin-aldosterone system.
   D. Increased aldosterone and antidiuretic hormone levels lead to increased fluid retention and increased preload.
III. Cardiac output is then reduced, which leads to exercise intolerance weakness, slow capillary refill time, hypothermia, and reduced pulmonary venous oxygen content.
   A. Initially the sympathetic nervous system is activated by reduced blood pressure.
      1. This activation leads to beta receptor stimulation, increased heart rate, and contractility.
      2. Alpha adrenergic stimulation leads to arteriolar vasoconstriction and maintenance of blood pressure.
   B. After 1 to 3 days, the beta receptors downregulate, and the short-term benefit of increased cardiac output is blunted.
IV. Maintenance of blood pressure is the last cardiovascular priority to fail in heart failure.
V. Cardiogenic shock occurs when the cardiovascular system cannot maintain adequate blood pressure, most often in acute heart failure.

Pathophysiology of Cardiac Diseases

I. Volume overload
   A. Many cardiac diseases lead to volume overload (e.g., atrioventricular valve disease, left-to-right shunting congenital heart defects).
   B. Increased preload occurs when there is increased blood volume and venous return to the ventricle, which leads to diastolic stretching of the cardiomyocytes.
   C. The initial response is Starling's law, with increased contractility to eject the excess volume.
   D. Chronic increased preload leads to eccentric hypertrophy and increased left ventricular chamber size, which help to normalize stroke volume and cardiac output.
   E. Eccentric hypertrophy is identified as increased end-diastolic diameter or volume on the echocardiogram.
   F. Sequelae to volume overload are increased diastolic filling pressure and development of CHF.
II. Pressure overload
   A. It occurs secondary to many cardiac diseases (e.g., pulmonic stenosis, aortic stenosis, systemic hypertension, pulmonary hypertension).
   B. Concentric hypertrophy (increased wall thickness) develops to normalize the increased systolic wall stress.
   C. Severe overload may lead to myocardial ischemia and fibrosis, which results in life-threatening ventricular arrhythmias.
   D. Systolic or diastolic failure may ensue.
   E. Concentric hypertrophy is identified on the echocardiogram as increased diastolic ventricular wall thickness.
III. Systolic myocardial failure
   A. Primary myocardial failure arises from idiopathic dilated cardiomyopathy.
   B. There are many secondary causes of systolic myocardial failure.

C. The primary abnormality of systolic myocardial failure is a reduction in contractility, which is seen as an increased end-systolic diameter or volume, reduced fractional shortening, and increased E point to septal separation on the echocardiogram.
D. The chronic compensatory mechanism of systolic myocardial failure is development of eccentric hypertrophy, which helps improve stroke volume and cardiac output.

IV. Diastolic dysfunction
A. Relaxation is the early phase of diastole.
1. Early, rapid filling is influenced by relaxation and by left atrial pressure.
2. Delayed early relaxation is the first abnormality in diastolic dysfunction.
B. Passive diastolic filling occurs in middle to late diastole, is influenced by compliance of the ventricle, which can be reduced by concentric hypertrophy, myocardial fibrosis, and myofiber disarray.
C. Diastolic dysfunction may lead to an elevated ventricular filling pressure and may cause CHF.
D. Systolic function usually remains normal.
E. Hypertrophic cardiomyopathy, unclassified cardiomyopathy, and restrictive cardiomyopathy are cardiac diseases that cause diastolic dysfunction.
F. Echocardiography (pulsed wave Doppler, tissue Doppler technique) is useful to identify diastolic dysfunction.

V. Arrhythmias
A. Sustained tachyarrhythmias (supraventricular or ventricular) may reduce cardiac output and lead to weakness, syncope, or collapse.
B. Bradyarrhythmias may also lead to reduced cardiac output and clinical signs as a result of severely reduced heart rate.

Clinical Assessment

I. Signalment
A. Useful to evaluate diseases with known breed, age, and sex predilections
B. Useful for diseases with known heritability patterns

II. Cardiovascular physical examination
A. Auscultation
1. Murmurs are classified based on location, timing, and grade of intensity.
2. Often the location of a murmur and its timing may be pathognomonic for a defect or may refine the differential list of possible defects.
3. The rhythm may be too slow, too fast, or irregular.
4. Lung sounds (rales, crackles) may be heard if there is pulmonary edema; dampened lung sounds occur with pleural effusion.
B. Precordial pulse palpation
C. Femoral arterial pulse palpation
1. Dampened, hypokinetic pulses: subaortic stenosis, cardiogenic shock, cardiac tamponade
2. Bounding pulses: patent ductus arteriosus, aortic insufficiency
D. Jugular venous distension or pulsation: tricuspid regurgitation, pulmonic stenosis, cardiac tamponade
E. Mucous membrane color and capillary refill time

III. Thoracic radiography
A. Assessment of overall heart size and quantification of heart size by vertebral heart scale
B. Assessment of great vessels: aorta, pulmonary artery, caudal vena cava
C. Assessment of pulmonary vasculature
D. Assessment of pulmonary parenchyma

IV. Echocardiography
A. It is the cornerstone for establishing a definitive diagnosis of a specific heart disease.
B. It is essential to evaluate cardiac function, chamber size, anatomical abnormalities, and valvular competence.
C. Noninvasive estimation of pressures between two chambers is possible using continuous wave Doppler and the modified Bernoulli's principle.

V. Electrocardiography (ECG)
A. It is used when an arrhythmia has been ausculted and is necessary for diagnosis of the specific arrhythmia.
B. Holter monitors are ambulatory, 24-hour ECG recorders that are useful for diagnosis of arrhythmias and monitoring antiarrhythmic therapy.
C. Event monitors are continuous loop recorders used in syncopal animals to determine whether an arrhythmia is causative.

VI. Cardiac catheterization is rarely necessary for diagnosis of a cardiac defect, but it is used before interventional catheter-based therapies.

CHAPTER 6

Cardiac Arrhythmias

Marc S. Kraus | Anna R.M. Gelzer

GENERAL CONSIDERATIONS

Cardiac Arrhythmias

Definition and Causes

I. Cardiac arrhythmias are defined as variations of rhythm from the normal sinus rhythm.
II. Some arrhythmias are clinically insignificant and require no specific therapy, whereas others may cause severe clinical signs or degenerate into serious arrhythmias (e.g., ventricular fibrillation [VF]) that lead to cardiac arrest and sudden death.

Pathophysiology

I. Mechanisms for cardiac arrhythmias can be grouped into abnormalities of impulse formation and impulse propagation.
II. Automaticity refers to the ability of cardiac cells to spontaneously and repetitively depolarize in the absence of external stimulation.
    A. Normal automaticity is dictated by the rate of phase 4 depolarization (balance of calcium, potassium, and sodium ions that cause spontaneous depolarization).
    B. Abnormal automaticity occurs when acceleration of phase 4 activity develops at some location or a region of the heart that normally is not capable of spontaneous depolarization (e.g., atrioventricular [AV] node) and gives rise to spontaneous depolarizations.
III. Reentry represents a potential circular path in which membrane potentials may be conducted.
    A. It is a phenomenon of recurring and self-perpetuating depolarization around a circuit.
    B. It accounts for many clinically significant tachyarrhythmias, such as atrial flutter and fibrillation; intraatrial sinoatrial (SA) and AV nodal tachycardias; tachycardia via accessory pathways; and some ventricular tachycardias.
IV. Triggered activity has some features of automaticity and reentry.
    A. Abnormal potentials, called *after-depolarizations,* follow closely on a previous normal action potential.
    B. The repolarization of a cardiac action potential may be interrupted or followed by another depolarization or after-depolarization.
    C. After-depolarizations that interrupt repolarizations are called *early after-depolarizations,* and those that follow repolarizations are called *delayed after-depolarizations.*

Clinical Signs

I. The end result of severe arrhythmias is inadequate cardiac output and subsequent hypotension with decreased brain perfusion, syncope, or organ damage (especially kidney and liver).
II. Common clinical signs are as follows:
    A. Weakness and/or collapse (syncope)
    B. Exercise intolerance
    C. Sudden death
III. Heart failure can develop from severe bradyarrhythmias or tachyarrhythmias.
    A. Long-standing ventricular tachycardia (VT) and supraventricular tachycardia (SVT) can produce a reversible, left ventricular dysfunction.
    B. The onset of cardiomyopathy and the severity of post-tachycardic changes depend on at least three parameters (type, rate, duration) of the tachycardia.

Diagnosis

I. Although a specific diagnosis may be suggested by auscultation and physical examination, electrocardiography (ECG) is required for a definitive diagnosis.
II. A systematic approach is also required for rhythm diagnosis (Figures 6-1, 6-2, and 6-3).
    A. Criteria used in assessing arrhythmias include the following:
        1. Whether the rate is fast or slow (tachycardia or bradycardia)
        2. Whether the rhythm is regular or irregular
        3. If irregular, whether the rate is slow or fast, or whether premature beats are present
        4. Whether P waves are present and normal (upright in lead II, suggestive of SA nodal origin)
        5. Whether there is a P wave for every QRS complex, and a QRS complex for every P wave
        6. Whether the QRS complexes are normal or abnormal in appearance
    B. Supraventricular arrhythmias must be differentiated from ventricular arrhythmias (Table 6-1).

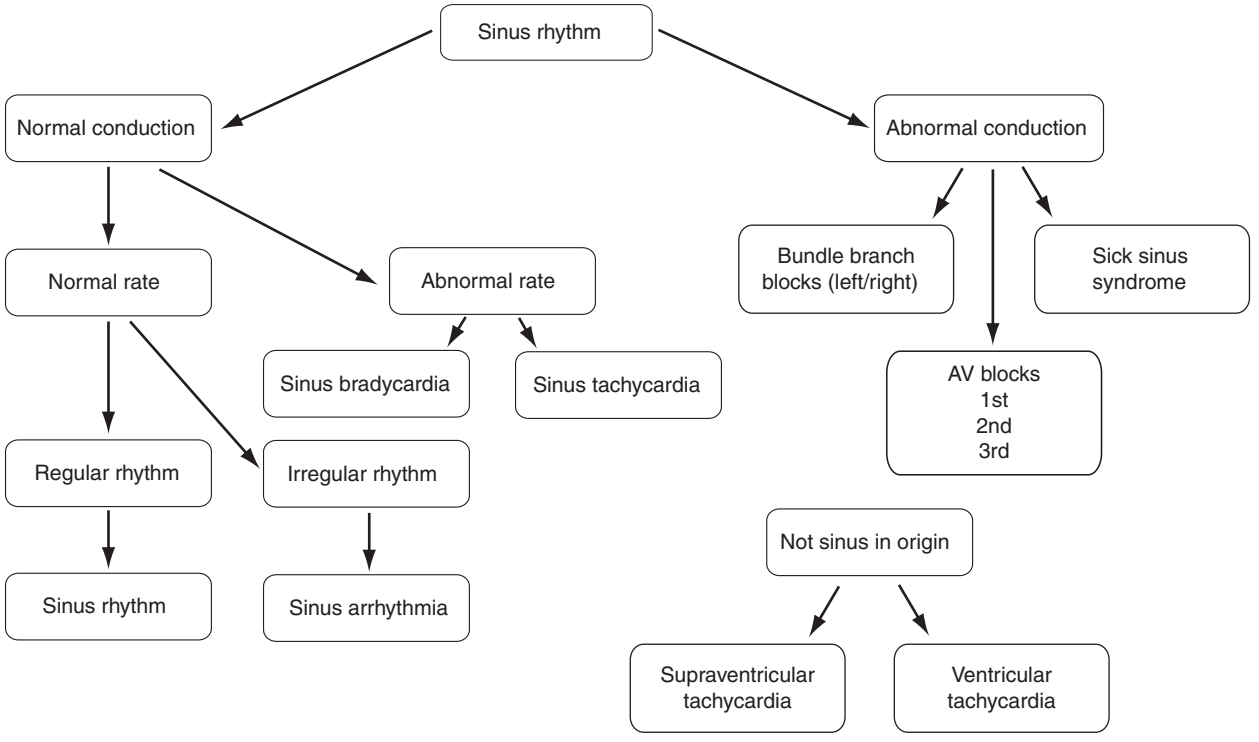

FIGURE 6-1 An algorithm for rhythm analysis if P waves are present on the ECG. If no P waves can be identified, the rhythm probably does not originate in the sinus node, unless it is a rapid supraventricular tachycardia (P wave may be hiding in preceding T waves). *AV,* atrioventricular.

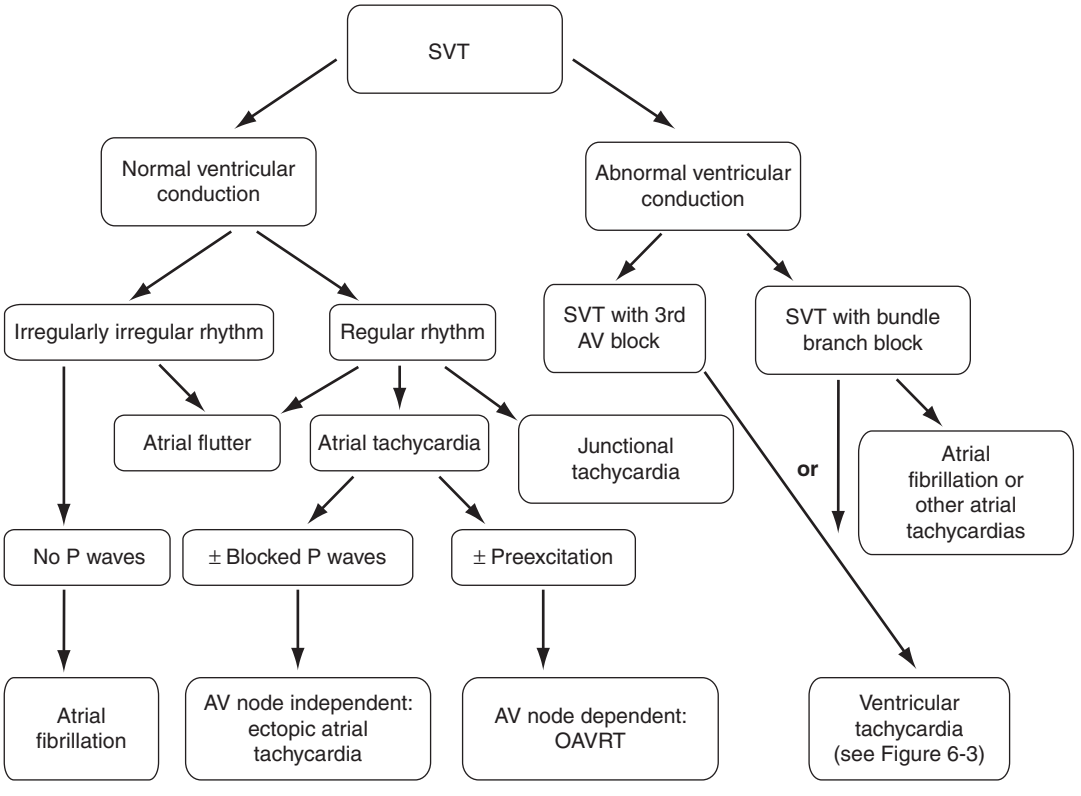

FIGURE 6-2 An algorithm for rhythm analysis of supraventricular tachycardia (SVT). SVT with narrow, upright QRS complexes implies normal ventricular conduction. *AV,* Atrioventricular; *OAVRT,* orthodromoc atrioventricular reciprocating tachycardia.

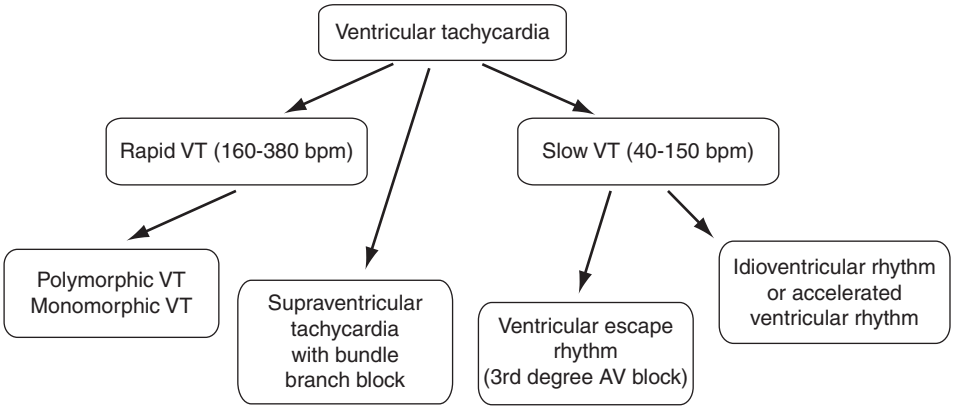

FIGURE 6-3 An algorithm for analysis of ventricular tachycardia (VT). *AV,* Atrioventricular; *bpm,* beats per minute.

TABLE 6-1

Features That Differentiate Supraventricular from Ventricular Arrhythmias

ELECTROCARDIOGRAPHIC FEATURE	SUPRAVENTRICULAR ARRHYTHMIA	VENTRICULAR ARRHYTHMIA
Size of QRS complex	Narrow	Wide
Premature complex has similar appearance to a sinus beat	Yes	No
P waves are associated with the QRS complex	Yes	No
Fusion beats are present	No	Yes

Sinus Arrhythmia

Definition

I. Sinus arrhythmia is a physiological, autonomically mediated cyclical change in sinus rate.
II. The P-P intervals are irregular from fluctuations in autonomic tone that result in phasic changes in the rate of SA node discharge.
III. Sinus arrhythmia is normal in the dog and abnormal in the cat.

Causes

I. Respiratory sinus arrhythmia: fluctuation associated with respiration
II. Nonrespiratory sinus arrhythmia
  A. Cyclic change in P-P interval is independent of respiration and arises from increased vagal tone.
  B. Causes include respiratory, central nervous system (CNS), increased intracranial pressure, ocular, and gastrointestinal (GI) diseases.

Pathophysiology

I. Respiratory sinus arrhythmia
  A. SA node discharge rate is regulated by the autonomic nervous system.
  B. Inspiration decreases vagal tone and increases sympathetic tone, resulting in an increased heart rate.
  C. On expiration, vagal tone increases and sympathetic tone decreases, resulting in a decreased heart rate.
II. Nonrespiratory sinus arrhythmia
  A. Autonomic influences can also cause sinus arrhythmia independent of respiration.
  B. Diseases most commonly associated with high vagal tone include respiratory, CNS, and GI disorders.

Clinical Signs

I. Respiratory sinus arrhythmia does not cause clinical signs.
II. In nonrespiratory sinus arrhythmia, clinical signs are usually related to the underlying disease.

Diagnosis

I. Physical examination findings
  A. Slow to normal heart rate
  B. Irregular heart rhythm that varies with respiration
  C. Normal pulse strength; may vary in intensity (based on R-R interval)
II. ECG characteristics (Figure 6-4)
  A. Heart rate is normal to slow (usually <140 beats per minute [bpm] in the dog).
  B. Variability in P-P interval is >10%.
  C. P wave morphology is normal, and every P wave is followed by a QRS complex.
  D. A wandering pacemaker is often seen (see Figure 6-4).
  E. QRS complexes are normal in appearance.

Differential Diagnosis

I. Slow AF: no P waves, irregularly irregular rhythm
II. Sick sinus syndrome: longer pauses between sinus beats
III. Atrial premature contractions: may interrupt a sinus rhythm

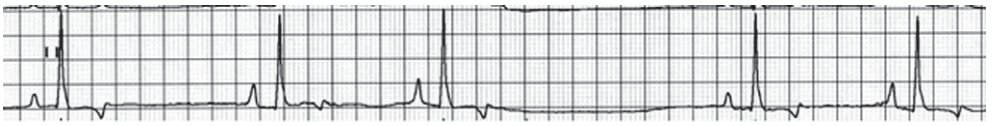

FIGURE 6-4 Electrocardiogram (Lead II, 50 mm/sec, 10 mm/mV) example of sinus arrhythmia. A wandering pacemaker is demonstrated by the variable amplitude of the P wave.

Treatment

I. Sinus arrhythmia does not warrant specific therapy.
II. Specific treatment is directed toward the underlying etiology.

SUPRAVENTRICULAR ARRHYTHMIAS

Atrial Premature Contractions

Definition and Causes

I. Atrial premature contractions (APCs) originate in the atria in a location other than the SA node.
II. They often indicate underlying cardiac pathology, particularly atrial enlargement (chronic valvular disease, cardiomyopathy, congenital heart disease).
III. Noncardiac causes include electrolyte abnormalities, sepsis, and organ failure (e.g., liver, kidney, pancreatitis).

Pathophysiology

I. The prematurity of the APC leads to an instantaneous decrease in stroke volume and ventricular filling.
II. A single APC is not hemodynamically significant.

Clinical Signs

I. Clinical signs are not observed with single APCs.
II. Clinical signs are observed (syncope, lethargy) if APCs progress to SVT.

Diagnosis

I. Physical examination findings
   A. Auscultation often reveals an irregular heart beat.
   B. A pulse deficit may be detected.
II. ECG characteristics
   A. QRS morphology looks similar to a normal sinus impulse.
   B. The QRS complex of the APC occurs earlier than expected, compared with the normal sinus rhythm.
   C. P wave morphology often appears different from the normal sinus P wave.
   D. Echocardiography and thoracic radiography are needed to evaluate underlying structural heart diseases and for presence of heart failure.

Differential Diagnosis

I. Ventricular, premature contraction with a narrow QRS morphology (originating near the bundle of His)
II. Multiple APCs: atrial tachycardia, atrial fibrillation

Treatment and Monitoring

I. No treatment is necessary for occasional APCs.
II. Appropriate therapy is indicated for underlying heart disease or failure.
III. Periodic ECGs or Holter monitoring is needed to assess the frequency of APCs and the presence of more severe arrhythmias (e.g., SVT).

Atrial Fibrillation

Definition

I. Atrial fibrillation (AF) is the bombardment of the AV node with multiple, disorganized atrial impulses.
II. Rapid atrial activation occurs, and the atrial rate can exceed 500 depolarizations per minute.
III. Abnormal automaticity and reentry are possible electrophysiological mechanisms that initiate and maintain AF.

Causes and Pathophysiology

I. AF is usually a chronic, permanent arrhythmia associated with underlying heart disease.
II. It is associated with advanced stages of atrial enlargement secondary to dilated or hypertrophic cardiomyopathy, or to volume overload (e.g., chronic AV valve regurgitation, uncorrected patent ductus arteriosus).
III. Idiopathic AF is diagnosed when no overt cardiovascular disease or other precipitating illnesses are present.
   A. It has low mortality initially.
   B. It may be a sign of occult heart disease and can become clinically significant over time.
   C. Occasionally the administration of narcotics has been associated with the induction of AF in large dogs (Moise et al., 2005).

Clinical Signs

I. Clinical signs are associated with rapid heart rates, usually >200 bpm.
II. Signs include exercise intolerance, coughing, weakness, and syncope.

Diagnosis

I. Physical examination findings
   A. Rapid irregular heart rate and heart sounds of variable intensity
   B. Weak pulses of variable intensity and pulse deficits
   C. Signs of congestive heart failure (CHF): murmur, gallop rhythm, harsh lung sounds
II. ECG characteristics (Figure 6-5)
   A. QRS complexes are usually narrow and upright in leads II, III, and aVF.

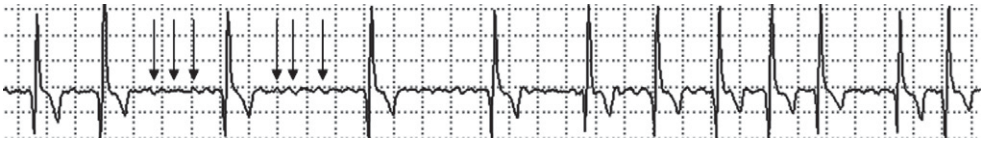

FIGURE 6-5 Electrocardiogram (Lead II, 25 mm/sec, 10 mm/mV) of atrial fibrillation showing a supraventricular rhythm with variable R-R intervals (irregularly irregular) and absence of identifiable P waves. An undulating baseline is present between QRS complexes, with small fibrillatory (f) waves *(arrows)*.

B. The QRS complex can be wide if a bundle branch block is present.
C. P waves are absent.
D. Atrial activity is represented by fibrillatory (f) waves of varying amplitudes.
E. Ventricular rhythm is irregular.
F. At very rapid rates, the rhythm can appear regular.

Differential Diagnosis

I. Rapid supraventricular arrhythmias with variable AV node conduction
II. Frequent APCs

Treatment

I. Management depends on the average heart rate.
II. Acquiring a baseline 24-hour Holter recording is ideal for establishing an accurate average heart rate before initiating treatment.
III. Medical conversion to a sinus rhythm is very difficult and rarely achieved in dogs.
IV. Ventricular rate is controlled via slowing of AV node conduction with diltiazem ± digoxin (Table 6-2).
   A. Although atenolol has been proposed as a treatment, it is avoided if significant myocardial failure (e.g., severe, dilated cardiomyopathy) is present.
   B. Diltiazem XR is well-tolerated in dogs with severe, systolic myocardial dysfunction.
   C. Digoxin as a monotherapy rarely controls the ventricular response rate adequately, especially during times of stress, exercise, or excitement.
V. Electrical cardioversion may be performed under anesthesia.
   A. Best results are seen in dogs with mild structural heart disease or idiopathic AF.
   B. The goal of cardioversion is to avoid structural or functional remodeling of the atria from chronic AF.
   C. The rate of recurrence is high, and related morbidity from transthoracic cardioversion (requires general anesthesia) makes this approach impractical in animals with significant structural heart disease.
   D. Pretreatment with sotalol, amiodarone, and/or angiotensin-converting enzyme inhibitors may improve the chance of cardioversion.

Monitoring of Animal

I. Evaluate heart rate 1 week after initiating treatment.
   A. Ideally this includes 24-hour Holter monitoring.
   B. Target heart rate is 90 to 120 bpm in dogs and 130 to 150 bpm in cats.
   C. If mean heart rate is >140 bpm in dogs, increase the dose of diltiazem/digoxin by 25% and repeat ECG 5 to 7 days later.
   D. Check for bradyarrhythmias (pauses >4 seconds) and, if present, decrease the dosage of the diltiazem/digoxin by 25%.
II. Measure serum digoxin levels (6 to 8 hours post-pill) 5 to 7 days after starting therapy.
   A. Ideal level is 1 to 2 ng/mL.
   B. Lower serum levels (0.6 to 0.8 ng/mL) may successfully control heart rate in some dogs.

Atrial Flutter

Definition and Causes

I. Atrial flutter is a form of reentry tachycardia that utilizes the anatomy of the right atrium to sustain a loop of continuous depolarization.
II. The causes are the same as for AF.
   A. Anything that causes atrial enlargement can predispose to this arrhythmia.
   B. It is uncommon in dogs and cats.
III. Atrial flutter can predispose to AF owing to the electric remodeling that occurs with continuous, rapid activation of the atrial myocardium.
IV. It is unknown if animals undergo a phase of atrial flutter before developing permanent, chronic AF.

Clinical Signs

I. Clinical signs are those associated with rapid heart rates.
II. Signs include exercise intolerance, coughing, weakness, and syncope.

Diagnosis

I. Physical examination findings: similar to AF
II. ECG characteristics (Figure 6-6)
   A. Rapid rhythm, which may be regular or irregular
   B. Sawtooth undulation of the baseline (flutter waves)
   C. Atrial rate usually >300 bpm
   D. Supraventricular appearance of QRS complexes

Differential Diagnosis

I. Rapid ectopic atrial tachycardia with 1:1 conduction is indistinguishable from atrial flutter.
   A. One-to-one conduction may be lethal.
   B. Ectopic atrial tachycardia with variable AV conduction appears similar, but the atrial rate is slower (200 to 250 bpm).
II. AF with course fibrillatory waves may appear similar.

TABLE 6-2

Drugs Used for Supraventricular Arrhythmias

DRUG *(BRAND NAME)*	PER OS ADMINISTRATION	INTRAVENOUS ADMINISTRATION	INDICATION
Diltiazem XR *(Dilacor-XR)*	*Dog:* 3-4 mg/kg BID *Cat:* 30-60 mg SID-BID (start with 30 mg SID)	NA	Atrial fibrillation, flutter, tachycardia OAVRT
Diltiazem *(Cardizem, Cardazem-CD)*	*Dog:* 0.5 mg/kg TID titrated to maximum dose of 1.5-2 mg/kg TID *Cat:* 10 mg/kg SID *(Cardazem-CD)*	*Dog:* 0.1-0.2 mg/kg bolus, then CRI at 2-6 µg/kg/min	Acute atrial fibrillation or flutter OAVRT
Atenolol *(Tenormin)*	*Dog:* 0.25-1 mg/kg SID-BID *Cat:* 6.25-12.5 mg SID-BID	NA	Atrial flutter or tachycardia OAVRT
Esmolol *(Brevibloc)*	NA	*Dog, cat:* 50-100 µg/kg bolus, repeated up to maximum 500 µg/kg or CRI of 50-200 µg/kg/min	Acute atrial fibrillation, flutter or tachycardia OAVRT
Sotalol *(Betapace)*	*Dog:* 1-2.5 mg/kg BID *Cat:* 10 mg BID	NA	Atrial fibrillation, flutter or tachycardia
Digoxin *(Lanoxin)*	*Dog:* 0.005 mg/kg BID Maximum dose for Doberman pinschers is 0.25 mg BID *Cat:* 0.31 mg q 3 days	NA	Atrial fibrillation
Procainamide *(Procain)*	*Dog:* 10-20 mg/kg TID-QID *Cat:* 2-5 mg/kg BID-TID	*Dog:* 10-15 mg/kg IV bolus slowly over 2 minutes or CRI of 25-50 µg/kg/min	Atrial tachycardia Tachycardia via accessory pathway
Amiodarone *(Cordarone)*	*Dog:* 10 mg/kg BID for 1 week (anecdotal loading dose) and 5 mg/kg SID (anecdotal maintenance dose)	*Dog:* 5-10 mg/kg IV bolus (anecdotal dose)	Atrial fibrillation and tachycardia
Lidocaine	NA	*Dog:* 2 mg/kg IV bolus, repeated if needed *Cat:* 0.25-1 mg/kg IV bolus (use with *extreme* caution)	Atrial fibrillation secondary to narcotics

NA, Not available; *OAVRT,* orthodromic atrial reciprocating tachycardia; *CRI,* constant rate infusion.

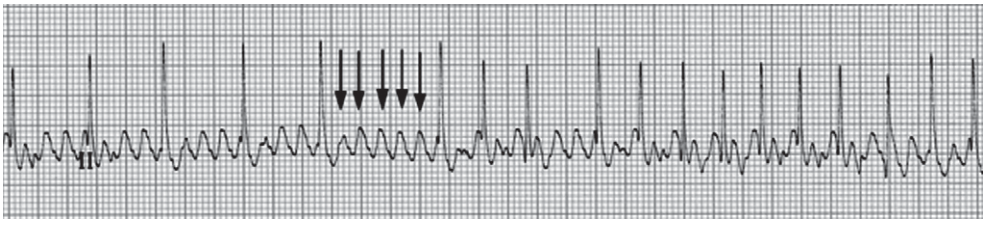

FIGURE 6-6 Electrocardiogram (Lead II, 25 mm/sec, 10 mm/mV) of atrial flutter demonstrating a sawtooth pattern of atrial flutter waves *(arrows)*. Atrial flutter waves are characterized by the absence of isoelectric diastolic intervals (no return to a smooth baseline) between atrial activations.

Treatment

I. A baseline 24-hour Holter tracing is recommended to determine if the arrhythmia is paroxysmal or chronic.
   A. If the arrythmia is chronic, drug therapy is indicated (see Table 6-2).
   B. If it is paroxysmal and infrequent, treatment may be postponed with reevaluation 3 to 6 months later.

II. Therapy is aimed at suppressing the atrial reentry circuit by using sotalol, amiodarone, or procainamide.

III. Attempts to abolish atrial flutter with drugs are often unsuccessful.

IV. Control of ventricular rates by slowing conduction through the AV node with calcium channel or beta blockers is often effective in dogs.
   A. Diltiazem XR is initially given at 3 mg/kg PO BID then titrated based on the ventricular rate.
   B. If the heart rate is consistently >150 bpm, increase the diltiazem to 4 mg/kg PO BID.

C. Alternatively, atenolol is started at 1 mg/kg PO BID, but must be used with caution if systolic function is impaired.
D. Digoxin monotherapy is usually ineffective in controlling the fast heart rate.

Monitoring of Animal

I. Evaluate the heart rate 1 week after initiating treatment, preferably via Holter monitoring or ECG.
II. Goal of therapy is to maintain the ventricular rate at <150 bpm.

Atrial Tachycardia

Definition

I. Atrial tachycardia (AT) occurs when localized regions in the atria (other than the sinus or AV node) develop the ability to fire rapidly (abnormal automaticity).
II. Clinically significant arrhythmia occurs with heart rates >180 bpm in the dog and >240 bpm in the cat.
III. AT differs from APCs primarily in that AT is sustained.

Causes and Pathophysiology

I. Causes can be the same as for AF.
II. AT may also occur in animals with no obvious cardiac or systemic abnormalities.
III. Untreated, chronic AT can lead to myocardial dysfunction (tachycardia-induced cardiomyopathy).

Clinical Signs

I. Clinical signs (exercise intolerance, panting, coughing, weakness, syncope) depend on the heart rate, duration of arrhythmia, and cardiac function.
   A. Chronically sustained heart rates >180 bpm (dogs) or >240 bpm (cats) often cause clinical signs and deterioration of myocardial function.
   B. With lower rates or sporadic AT, no clinical signs may be noted.
II. Signs of CHF may be present, including exercise intolerance, coughing, weakness, dyspnea, and syncope.

Diagnosis

I. Physical examination findings
   A. A rapid heart rate is ausculted and may be regular or irregular, depending on AV node conduction.
   B. Signs of CHF may be present.
II. ECG characteristics (Figure 6-7)
   A. Ectopic P waves are different in morphology from sinus P waves.
   B. Arrhythmias caused by abnormal automaticity usually show gradual acceleration and deceleration (warm-up and cool-down phenomena).
   C. Atrial rate is usually >180 bpm in dogs.
   D. Usually, QRS complexes are narrow and upright.
      1. Tachycardia may cause a functional bundle branch block, whereas the QRS complexes are wide but are associated with a P wave.
      2. In rapid tachycardia, a P wave may be buried in the preceding T wave and not visible.
      3. The ventricular rhythm is irregular when there is physiological second-degree AV block (the atrial rate is so rapid that not every atrial beat is conducted to the ventricles).

Differential Diagnosis

I. Atrial flutter, AF
II. AV junctional tachycardia
III. Sinus tachycardia
IV. Ventricular tachycardia
   A. AT with bundle branch block appears similar to VT.
   B. Visualization of a P wave associated with a wide QRS complex confirms a bundle branch block.
   C. VT is often suppressed by IV lidocaine, but AT with bundle branch block is not.

Treatment

I. Suppression of the rapidly firing atrial focus is attempted with sotalol, amiodarone, or procainamide (see Table 6-2).
II. Amiodarone must be used with caution because of its side effects, which include hepatic toxicity, GI disturbances, and blood dyscrasias in dogs.
III. If AT cannot be terminated with these drugs, a secondary goal is to control the ventricular rate with calcium channel blockers, beta blockers, or digoxin (see Table 6-2).
IV. The goal of therapy is to maintain a ventricular rate <150 bpm.

Monitoring of Animal

I. Evaluate heart rate 1 week after initiating treatment, with Holter monitoring or ECG.
II. If amiodarone is used, periodic complete blood counts and serum biochemistries are performed to monitor for blood dyscrasias and elevated hepatic enzymes.
III. Measure serum digoxin levels (6 to 8 hours post-pill) 1 week after starting digoxin.
   A. Target range is 0.7 to 2 ng/mL.
   B. Decrease the digoxin dose by 50% if amiodarone is given concurrently.

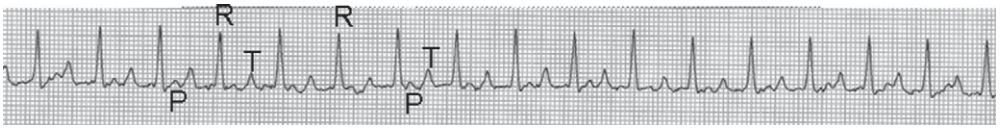

FIGURE 6-7 Electrocardiogram (Lead II, 50 mm/sec, 10 mm/mV) of atrial tachycardia displaying a rapid supraventricular rhythm, with P waves (P) superimposed on the ST segment of the preceding QRS complex. *R,* R wave; *T,* T wave.

C. High digoxin levels (>2 ng/mL) may cause inappetence, lethargy, GI signs, and may potentiate arrhythmias.

IV. Repeat an echocardiogram in 2 to 3 months to assess cardiac function in animals with myocardial failure.

V. Tachycardia-induced cardiomyopathy may improve with control of the heart rate, and systolic function may normalize over several weeks.

Atrioventricular Reentrant Tachycardia

Definition and Causes

I. Atrioventricular reciprocating tachycardia travels a circuit through the AV node and an accessory pathway (that can conduct impulses from the atria to the ventricles directly), and bypasses the AV node and the His Purkinje system.

II. During typical orthodromic AV reciprocating tachycardia (OAVRT), electrical activity proceeds from the atria to the ventricles through the AV node and then moves back up to the atria in a retrograde direction via the accessory pathway (bypass tract).

III. An accessory pathway can behave like a two-way street for electrical conduction.

IV. During early activation of the ventricle via the accessory pathway (if it conducts in an antegrade direction), a delta wave may be seen on the ECG.

A. Antegrade conduction is uncommon in the dog.

B. Accessory pathways are embryonic, muscular remnants that allow conduction from the atria to the ventricles and bypass the normal pathway of activation.

C. Labrador retrievers with tricuspid valve dysplasia occasionally have accessory pathways and OAVRT.

Clinical Signs

I. Clinical signs depend on the heart rate and duration of the abnormal rhythm.

II. Clinical signs are associated with rapid heart rates and include exercise intolerance, coughing, weakness, and syncope (rarely).

III. AV reciprocating tachycardia can be paroxysmal, and the animal may be asymptomatic.

IV. Signs of CHF may be present, such as cough, exercise intolerance, weak and rapid pulses, harsh lung sounds from pulmonary edema, and syncope (potentially).

Diagnosis

I. Physical examination findings

A. Rapid heart rate may be ausculted.

B. Signs of CHF may be present.

C. A right apical holosystolic murmur may be detected in Labrador retrievers with tricuspid valve dysplasia and OAVRT.

II. ECG characteristics

A. A short PR interval may be seen if antegrade conduction occurs (Figure 6-8).

B. A delta wave, with slurring and notching of the QRS complex, may be detected (ventricular pre-excitation).

C. In OAVRT, QRS complexes are narrow and the retrograde P wave (negative P wave) may be embedded into the early portion of the T wave.

D. One-to-one AV association is a requisite of atrioventricular reciprocating tachycardia because the atria and ventricles are both integral parts of the arrhythmia circuit.

Differential Diagnosis

I. Wide QRS tachycardia

A. QRS complexes are wide and bizarre, but the arrhythmia originates in the atria.

B. This term is used when differentiation between ST with aberrancy and VT cannot be made.

II. VT

Treatment

I. Treatments of choice are oral diltiazem or atenolol (see Table 6-2).

II. For acute management, IV diltiazem or esmolol is often effective.

III. For refractory cases, sotalol, procainamide, or amiodarone may be added; however, do not combine sotalol with atenolol.

IV. For dogs that do not adequately respond to medications (persistent tachycardia), transvenous catheter ablation of the accessory pathway using radiofrequency energy can be attempted.

V. Ventricular preexcitation without accompanying SVT requires no therapy.

Monitoring of Animal

I. Heart rate and presence of SVT are periodically assessed by Holter monitoring or ECG.

II. If ventricular response rate is >150 bpm, do the following:

A. If using monotherapy, increase drug dosage to the maximum tolerated dose.

B. Consider switching to another antiarrhythmic drug.

C. Combination therapy may be needed (e.g., sotalol, procainamide).

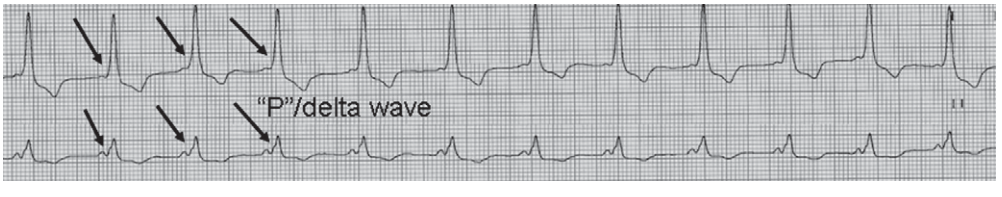

FIGURE 6-8 Electrocardiogram (Leads I and II, 50 mm/sec, 10 mm/mV) of ventricular preexcitation showing a sinus rhythm, with a short PR interval and wide QRS complexes that have a distinct notch in the upstroke of the R wave (delta wave, *arrows*). The delta wave is evidence of early activation of the ventricle via an accessory pathway.

III. Control of the arrhythmia usually eliminates the clinical signs.
IV. Ventricular preexcitation is permanent but does not appear to be progressive.

BRADYARRHYTHMIAS/ CONDUCTION DISTURBANCES

Sinus Bradycardia

Definition

I. Sinus bradycardia is a sinus rhythm in which the SA node discharge rate is low (≤60 bpm in an awake dog, ≤120 bpm in cats).
II. Sinus bradycardia of 45 to 60 bpm during sleep is normal.
III. Pathologic bradycardia often persists during excitement or exercise.
IV. Sinus bradycardia may occur as a pronounced sinus arrhythmia or a regular sinus bradycardia.

Causes and Pathophysiology

I. Sinus bradycardia may occur as a primary disorder.
II. It may arise secondarily.
  A. Drug toxicity: narcotics, overdose of beta blockers, calcium channel blockers or digoxin
  B. Excessive vagal tone from a systemic disease: CNS, ocular, respiratory, or GI diseases, head trauma
  C. Metabolic disorders: hyperkalemia, hypothyroidism, hypothermia
III. Chronic, severe bradycardia may lead to left-sided volume overload and subsequent CHF.
IV. It may exacerbate ventricular volume overload of other cardiac diseases (e.g., myxomatous AV valvular disease).

Clinical Signs

I. Clinical signs may be absent, or dogs may display weakness, exercise intolerance, or syncope.
II. Mild exercise intolerance is often underrecognized by owners.
III. Concurrent signs of CHF (coughing, lethargy, inappetence) may be present if heart rate has been slow for several months.

Diagnosis

I. Physical examination findings
  A. Findings may be unremarkable, except for a slow heart rate.
  B. A soft, left apical holosystolic murmur may be present if there is functional (secondary) mitral regurgitation from left ventricular enlargement.
II. ECG characteristics (Figure 6-9)
  A. Sinus rhythm with upright P waves in leads II, III and aVF
  B. Normal, upright, narrow QRS complexes, unless concurrent conduction disorder present
  C. Slow sinus discharge rate: ≤60 bpm in dogs; ≤120 bpm in cats
  D. ± Escape beats from AV node or ventricular Purkinje fibers

Differential Diagnosis

I. Marked sinus arrhythmia
II. Sick sinus syndrome

Treatment

I. The decision to treat a sinus bradycardia is based on clinical signs and the degree of bradycardia present.
II. Sinus bradycardia often requires no therapy.
III. In animals with syncope or episodic weakness, pacemaker insertion is indicated, even if the underlying disease may be curable.
IV. If pacemaker therapy is not an option, medical therapy is aimed at abolishing the increased vagal tone.
  A. An atropine response test helps identify animals that may benefit from medical management.
  B. Following injection of atropine (0.01 to 0.04 mg/kg IM, IV), the heart rate should increase by 50% to 100% within 5 to 10 minutes (initial transient AV block is normal).
  C. Animals experiencing at least a partial response to atropine may be candidates for medical management.
  D. Treatment options include the following:
    1. Vagolytic drugs: propantheline bromide 0.25 to 0.5 mg/kg PO BID
    2. Sympathomimetics: albuterol 0.02 to 0.05 mg/kg PO BID to TID or terbutaline 0.2 mg/kg PO BID to TID
    3. Phosphodiesterase inhibitors: theophylline 20 mg/kg PO BID
    4. Disadvantages: erratic or poor efficacy, adverse effects (anxiety, excessive panting, anorexia, GI signs)
  E. Other agents may be tried in emergency situations, but they may initiate other arrhythmias.
    1. Dogs, cats: epinephrine 0.05 to 0.2 mg IV

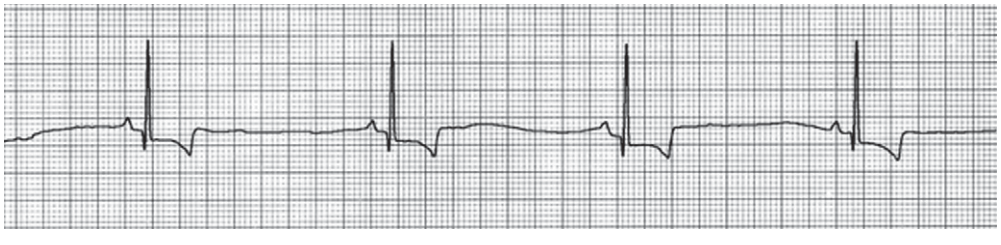

FIGURE 6-9 Electrocardiogram (Lead II, 50 mm/sec, 10 mm/mV) of sinus bradycardia showing a regular, slow sinus rhythm.

2. Dogs, cats: dopamine 1 to 3 μg/kg/min IV as a constant rate infusion (CRI)
3. Dogs: dobutamine 5 to 20 μg/kg/min IV CRI
4. Cats: dobutamine 2 to 5 μg/kg/min IV CRI
5. Dogs, cats: isoproterenol 0.01 to 0.2 μg/kg/min IV CRI

Monitoring of Animal

I. With medical therapy, 24-hour Holter monitoring is done to determine whether the heart rate has increased to an acceptable level (>70 bpm) and whether it increases during exercise.
II. Alternatively, an ECG is used to monitor response to therapy.
III. Pacemaker implantation usually requires long-term monitoring of battery life and function.
   A. The pacemaker is usually set at a fixed rate for 1 month, which allows the owner to easily assess the heart rate at home; it is then changed to a rate-responsive mode.
   B. Reevaluations are done at 3, 6, and 12 months for the first year, and then once or twice yearly.
IV. Prognosis after pacemaker implantation is excellent, with most animals living years after implantation; however, ventricular function may worsen with time (after long periods of ventricular pacing).

Sick Sinus Syndrome

Definition and Causes

I. Sick sinus syndrome (SSS) is a disease in which spontaneous SA node discharge is either slower than normal (primary sinus bradycardia) or intermittently absent (sinus arrest).
II. Subsidiary pacemaker tissue (AV node, Purkinje fibers) is usually also abnormal, resulting in inadequate escape beats so that asystole (pauses) can be >6 seconds.
III. SSS occurs primarily in small-breed dogs, such as the miniature schnauzer, American cocker spaniel, West Highland white terrier, and dachshund.
IV. Doberman pinschers and boxers may have syncope associated with long sinus pauses, suggestive of SSS.
V. The underlying cause is unknown, but it may be associated with fibrous replacement of the SA node.

Clinical Signs

I. Clinical signs include exercise intolerance, lethargy, and syncope.
II. Dogs with primary sinus bradycardia may show only mild exercise intolerance, which is often unrecognized by owners.

Diagnosis

I. Because of the intermittent nature of the sinus pause, Holter monitoring or use of an event monitor may be necessary to definitively identify SSS.
II. Definitive diagnosis requires documentation of SA node dysfunction with clinical signs of SSS.
III. Periods of bradycardia or asystole followed by paroxysms of SVT are typical (Figure 6-10).

Differential Diagnosis

I. Sinus bradycardia
II. Sinus arrest

Treatment

I. Pacemaker insertion is the treatment of choice for syncopal or lethargic animals, because medical management is rarely a long-term solution.
II. Some cases have supraventricular tachyarrhythmias (atrial tachycardia, flutter, or fibrillation) in addition to the sinus pauses, so antiarrhythmic therapy also may be needed.
III. Insert a pacemaker before initiation of antiarrhythmic therapy (diltiazem, atenolol, or sotalol) for SVT.

Monitoring of Animal

I. Monitoring is similar to that for sinus bradycardia.
II. If a pacemaker is implanted, periodic examinations are necessary.
III. Most animals respond well to pacing with the resolution of clinical signs and improved energy.

Atrial Standstill (Asystole)

Definition and Causes

I. Atrial standstill is a lack of ECG evidence of atrial depolarization (no P waves are visible on the ECG).
II. Two main reasons exist for atrial standstill.
   A. Hyperkalemia: urethral obstruction, hypoaldosteronism, reperfusion syndrome in arterial thromboembolic disease
   B. Primary atrial muscle disease: neoplasia, atrial myopathy, scapulohumeral muscular dystrophy of English springer spaniels (Miller et al., 1992; Smith, 1997; Buchanan, 2005).

Clinical Signs

I. Weakness, lethargy, and/or syncope
II. Signs relating to low cardiac output and CHF
   A. Lethargy, coughing, syncope, possible abdominal distension from ascites

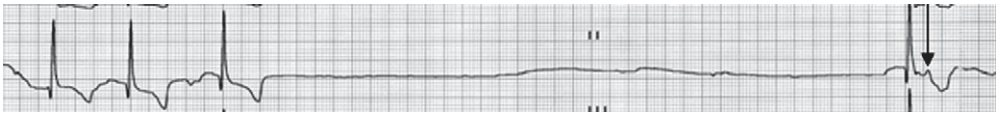

FIGURE 6-10 Electrocardiogram (Lead II, 50 mm/sec, 10 mm/mV) of sick sinus syndrome illustrating an abrupt pause in electrical activity (sinus arrest). A junctional escape beat (narrow QRS) has a P wave *(arrow)* appearing in the ST segment.

B. Occur with significant bradycardia (<50 bpm)

III. Signs related to neuromuscular disease in English springer spaniels with scapulohumeral muscular dystrophy (Miller et al., 1992)

Diagnosis

I. Physical examination findings: slow, irregular heart rate

II. ECG abnormalities (Figure 6-11)
   A. P waves are absent.
   B. The escape rhythm may be junctional (60 to 80 bpm, narrow QRS) or ventricular (20 to 40 bpm, wide QRS) in origin.
   C. If associated with hyperkalemia, tall T waves and wide, bizarre QRS complexes may occur.

Treatment

I. If hyperkalemia is documented, IV fluids are required to lower potassium via dilution and increased excretion.
   A. Acceptable fluids include 0.9% saline, 0.45% saline with 2.5% dextrose, or 5% dextrose in water.
   B. Dextrose increases insulin secretion, which drives potassium into the cells.

II. Regular insulin (0.5 U/kg) may be given with 50% dextrose (2 g/U insulin) by slow IV infusion, followed by monitoring for hypoglycemia.

III. Calcium gluconate 10% (0.5 mL/kg IV very slowly) may be given to make more cardiac sodium channels available for activation.

IV. Correction of the underlying disease process is also important.

V. Pacemaker implantation is required for atrial muscle diseases.

Monitoring of Animal

I. Hyperkalemia-induced atrial standstill requires repeated monitoring of potassium levels.

II. If atrial muscle disease is present, the prognosis is guarded as the myopathy may progress to CHF, and despite pacemaker therapy the underlying disease often worsens within several months.

Atrioventricular Conduction Abnormalities

Definition

I. These abnormalities arise from prolonged or complete failure of conduction between the atria and ventricles via the AV node.

II. First-degree AV block is prolongation of conduction through the AV node that results in a PR interval of ≥ 0.13 seconds in the dog and ≥ 0.1 seconds in the cat.

III. Second-degree AV block has morphologically normal P waves and QRS complexes, and a constant PR interval, but intermittently a P wave is not followed by a QRS complex.
   A. Mobitz type I (Wenckebach): PR interval gradually increases until a dropped ventricular beat occurs.
   B. Mobitz type II
      1. A fixed PR interval is present until a nonconducted P wave occurs.
      2. It is a more advanced degree of block that often occurs in the AV junction or His bundle.
   C. High-grade, second-degree AV block
      1. There are more than two P waves for each QRS complex.
      2. There is a fixed PR interval of the conducted P waves.
      3. This type of block indicates severe AV disease.

IV. In third-degree (complete) AV block, none of the P waves conduct through the AV node.
   A. Atrial and ventricular activities are independent of each other.
   B. There is no consistent PR interval.

Causes and Pathophysiology

I. The exact cause of AV block is undetermined in most cases.
   A. Neoplastic and infectious causes have been implicated.
   B. Lyme myocarditis has been reported as a cause in a dog (Levy and Duray, 1988).
   C. Systemic diseases that cause hyperkalemia (e.g., hypoadrenocorticism, urethral obstruction) may induce AV block that is reversible with normalization of potassium levels.
   D. Drugs, such as beta-blockers, calcium channel blockers, and digoxin, may depress AV conduction.

II. Complete AV block is often a primary abnormality of the AV node.

III. Prolonged bradycardia can lead to volume overload and subsequent CHF.

Clinical Signs

I. Clinical signs depend on the type and severity of AV block.

II. First-degree AV block is an incidental finding on the ECG and does not cause symptoms.

III. With second-degree AV block, animals are usually asymptomatic; however, syncope and lethargy can occur with slow heart rates (<40 to 50 bpm).

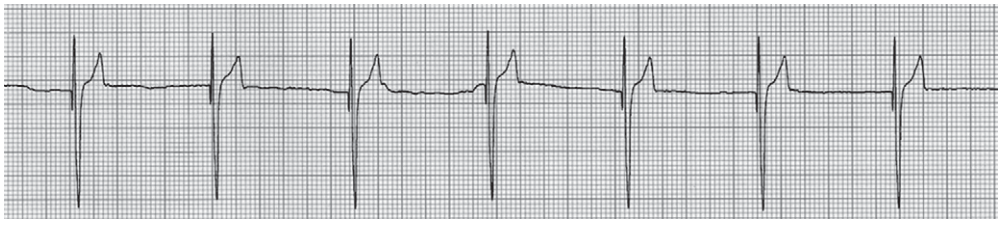

FIGURE 6-11 Electrocardiogram (Lead II, 50 mm/sec, 10 mm/mV) of atrial standstill, with the characteristic absence of P waves and a slow ventricular escape rhythm.

IV. With high-grade, second-degree, or third-degree AV block, lethargy, exercise intolerance, collapse, and syncope are common.

Diagnosis

I. ECG is required for definitive diagnosis.
II. First-degree AV block is characterized by a PR interval ≥0.13 second, and normal P waves and QRS complexes that occur at a 1:1 ratio (Figure 6-12).
III. With second-degree AV block P waves and QRS complexes are normal, but P waves are not always followed by QRS complexes (Figure 6-13).
IV. Complete AV block is characterized by the following (Figure 6-14):
   A. The atrial and ventricular rates are unrelated to each other, with P waves dissociated from the QRS complexes.
   B. The atrial rate is faster than the ventricular rate.
   C. If the ventricular rate is faster than the atrial rate, AV dissociation is present (not AV block).
   D. The rhythm is usually regular.
   E. Escape beats may arise from subsidiary pacemakers (AV node, bundle of His below the site of AV block, Purkinje fibers, etc.).
      1. AV nodal escape beats have a narrow, upright QRS morphology (supraventricular), and their rate is usually 40 to 60 bpm in dogs, and 80 to 120 bpm in cats.
      2. Ventricular escape beats have wide, bizarre QRS complexes and are usually slower (30 to 50 bpm) in the dog.

Differential Diagnosis

I. Third-degree AV block must be differentiated from AV dissociation (frequency of the ventricular rhythm exceeds that of the atrial rhythm).
II. Ventricular premature complexes or idioventricular rhythms must be differentiated from third-degree AV block with ventricular escape beats, as suppression of any ventricular escape rhythm could be lethal.

Treatment

I. First-degree AV block requires no treatment.
II. Second-degree AV block may or may not require treatment.
   A. An atropine challenge test is performed (see Sinus Bradycardia) to assess whether vagal tone is contributing to the AV block and to identify animals that may be candidates for medical therapy.
   B. High-grade, second-degree AV block usually requires a pacemaker.
   C. Pacemaker therapy is indicated if clinical signs are observed.
   D. Medical management can be attempted similar to sinus bradycardia, but the efficacy of medical therapy is often erratic and short-lived.
III. Complete AV block requires pacemaker implantation.

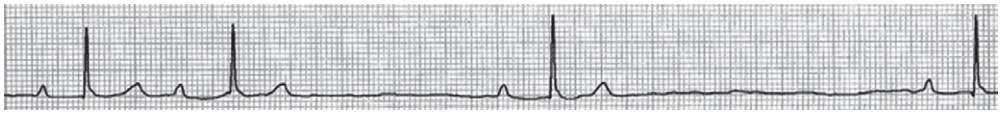

FIGURE 6-12 Electrocardiogram (Lead II, 50 mm/sec, 10 mm/mV) of first-degree atrioventricular (AV) block showing a prolonged PR interval (0.18 to 0.22 sec), which indicates slowed conduction through the AV node.

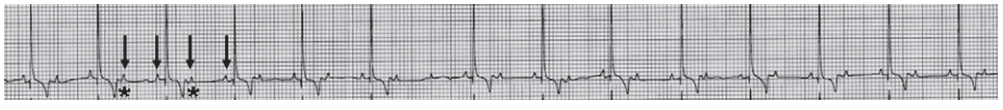

FIGURE 6-13 Electrocardiogram (Lead II, 25 mm/sec, 10 mm/mV) of second-degree atrioventricular (AV) block, which is intermittent conduction through the AV node. P waves *(arrows)* may or may not (*) be conducted.

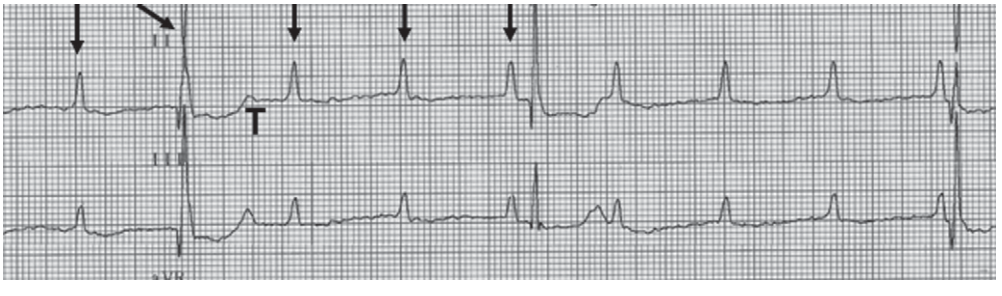

FIGURE 6-14 Electrocardiogram (Leads II and III, 50 mm/sec, 10 mm/mV) of third-degree atrioventricular (AV) block depicting a regular sinus node discharge rate, and no association between P waves *(straight arrows)* and the QRS complexes. An AV nodal escape beat results in a narrow QRS complex *(angled arrow)*. *T,* T wave.

IV. Ventricular antiarrhythmic therapy (lidocaine) or negative chronotropic antiarrhythmic drugs (beta blockers, calcium channel blockers, and digoxin) are contraindicated in third-degree AV block before pacemaker implantation, as they may be lethal.

Monitoring of Animal

I. Monitoring is similar to that for sinus bradycardia.
II. First- or second-degree AV block may progress to third-degree block.
III. Sudden death may occur in dogs with third-degree block.
IV. Third-degree block in cats does not appear to be as life-threatening, and cats with collapsing episodes may live for >1 year without pacemaker implantation (Kellum and Stepien, 2006).

VENTRICULAR ARRHYTHMIAS

Ventricular Premature Contractions/ Tachycardia

Definition

I. Ventricular arrhythmias are abnormal depolarizations that originate from any location in the ventricle.
II. Three or more ventricular premature contractions (VPC) in succession is termed *VT*.
III. Accelerated idioventricular arrhythmia is a VT of slower rates (60 to 160 bpm) and does not cause significant hemodynamic abnormalities.
IV. Breed-specific ventricular arrhythmias occur in the boxer, Doberman pinscher, and German shepherd dog.
   A. Boxers with cardiomyopathy may develop ventricular arrhythmias at 4 to 6 years of age that often increase in frequency and severity over time.
   B. Doberman pinschers with dilated cardiomyopathy typically develop arrhythmias at 3 to 6 years of life, and their frequency and severity usually increase with time.
   C. The German shepherd dog may develop ventricular arrhythmias at 12 to 16 weeks of age.
      1. Frequency and severity often increase until 24 to 30 weeks of age.
      2. Some dogs remain severely affected, whereas others have a progressive decline in the frequency of the arrhythmias.

Causes

I. Cardiomyopathies are a common cause.
   A. Cardiomyopathy in the boxer and Doberman pinscher are inherited as autosomal dominant traits.
   B. The disease in German shepherd dogs has a polygenic mode of inheritance.
II. Dogs with congenital heart diseases (severe subaortic or pulmonic stenosis) are predisposed to develop ventricular arrhythmias, possibly from abnormal myocardial perfusion and fibrosis.
III. Other causes include the following:
   A. Chronic valvular disease
   B. Trauma: traumatic myocarditis
   C. Gastric dilatation-volvulus, certain surgeries (e.g., splenectomy)
   D. Pancreatitis, hyperthyroidism (cats), sepsis and other systemic diseases
   E. Severe electrolyte abnormalities: hypokalemia, hyperkalemia, hypercalcemia, hypomagnesemia
   F. Drugs: digoxin, tricyclic antidepressants, opioids, antiarrhythmic agents
   G. Neoplasia: cardiac and other
IV. In many cases, the cause is not identified (idiopathic).

Pathophysiology

I. Rapid VT (>180 bpm in the dog, >250 bpm in the cat) reduces cardiac output and blood pressure.
II. VT is potentially life-threatening because it may degenerate into ventricular fibrillation, resulting in sudden death.

Clinical Signs

I. Clinical signs vary depending on the number of VPCs, and the rate and duration of VT.
   A. Single VPCs cause no clinical signs.
   B. Rapid VT is associated with syncope, weakness, or sudden death.
   C. The animal may be asymptomatic if VT is not sustained (<30 seconds).
   D. Intermittent rapid breathing may coincide with rapid VT.
II. Clinical signs of CHF may be present.
III. In boxers syncope is often the first sign observed, especially during exercise, stress, or excitement.
   A. The boxer may tolerate multiple collapsing episodes before sudden death, whereas the Doberman pinscher may die suddenly during the first syncopal event.
   B. The incidence of sudden death in the Doberman pinscher before onset of CHF is between 30% to 50% (Calvert et al., 2000; Calvert and Wall, 2001).

Diagnosis

I. Physical examination findings
   A. Irregular cardiac rhythm, with variable intensity of heart sounds
   B. Variable pulse intensity with pulse deficits
   C. ± Signs of CHF or underlying systemic diseases
II. ECG characteristics (Figures 6-15, 6-16, and 6-17)
   A. QRS complexes are wide and abnormal in shape.
   B. No P wave is associated with the QRS complex.
   C. AV dissociation is common.
   D. Fusion beats are common and are characterized by a short PR interval and an intermediate QRS morphology (similar in shape to ectopic ventricular complex and the normal QRS).
   E. Normal, upright QRS complexes may occur if the arrhythmia originates near the septum, but the QRS duration is prolonged.
   F. Initial direction of the QRS complex is different from a normal QRS.

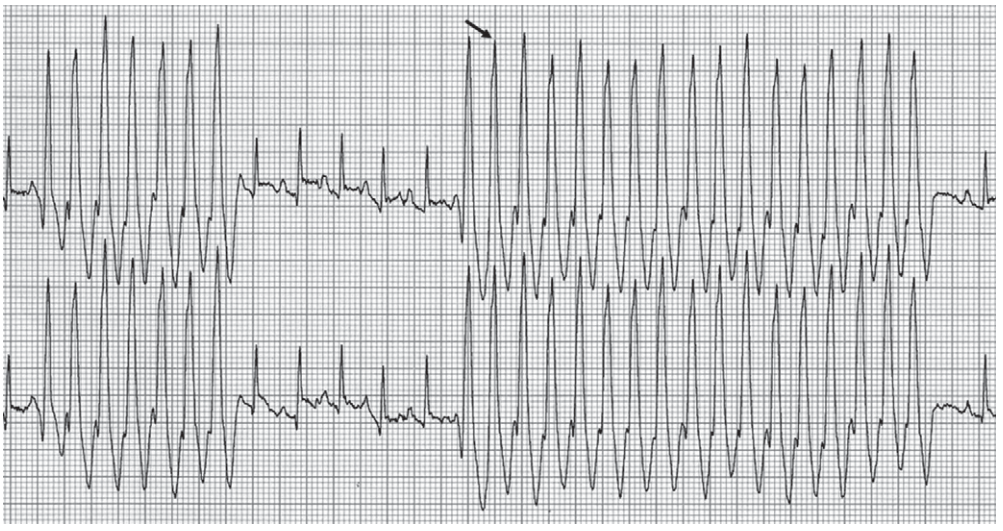

FIGURE 6-15 Electrocardiogram (Leads II and III, 25 mm/sec 10 mm/mV) of ventricular tachycardia showing rapid runs of ventricular complexes separated by five normal sinus beats. The *arrow* points to an occurrence of R on T phenomenon.

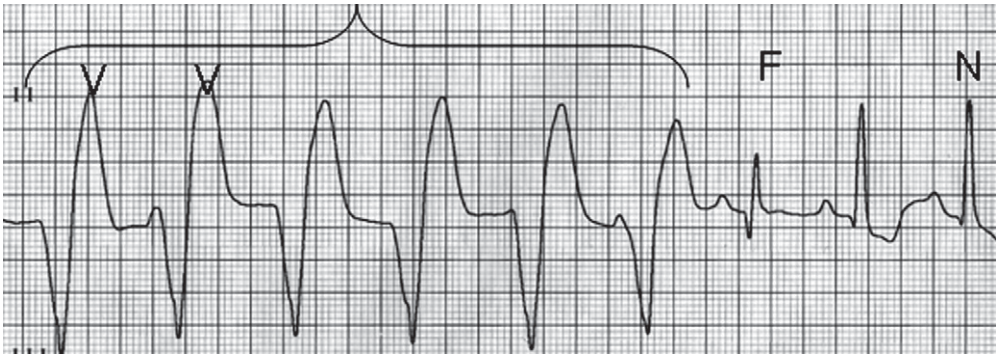

FIGURE 6-16 Electrocardiogram (Lead II, 50 mm/sec, 10 mm/mV) displaying multiple, consecutive ventricular premature beats (V, under bracket) that convert to a sinus rhythm (N) after a fusion beat (F).

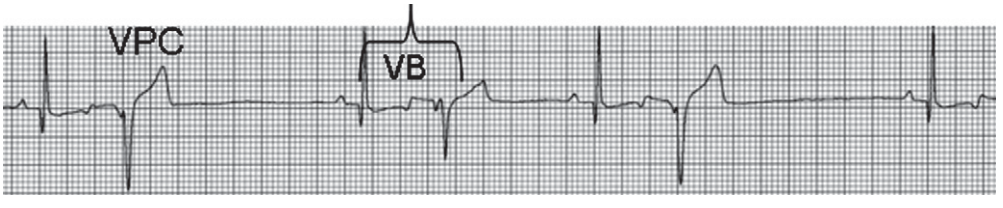

FIGURE 6-17 Electrocardiogram (Lead II, 50 mm/sec, 10 mm/mV) of single ventricular premature contractions (VPCs) that appear immediately after a normal sinus beat, which is termed *ventricular bigeminy* (VB).

G. Affected boxers have QRS complexes that are positive in leads II, III, and aVF (Kraus et al., 2002; see Figure 6-15).
H. Affected Doberman pinschers have QRS complexes with monomorphic and polymorphic characteristics.
I. Wide, bizarre T waves often have opposite polarity to QRS complexes.
J. Ventricular couplets, polymorphic complexes, R on T phenomenon (T wave embedded in R wave and not visible; see Figure 6-15), and VT are considered high-grade, more severe arrhythmias.

Differential Diagnosis

I. Supraventricular tachycardias (e.g., AF) with bundle branch block
II. APCs with aberrant conduction
III. Ventricular or AV nodal escape beats

Treatment

I. Treatment of VPCs
   A. Deciding when to treat VPCs is difficult because not all affected animals are at risk for sudden death.

TABLE 6-3

Drugs Used for Ventricular Arrhythmias

DRUG *(BRAND NAME)*	PER OS ADMINISTRATION	INTRAVENOUS ADMINISTRATION	INDICATION
Sotalol *(Betapace)*	*Dog, cat:* 0.5-2 mg/kg BID	NA	VT
Mexiletine *(Mexitil)*	*Dog:* 4-8 mg/kg TID	NA	VT, but not effective alone
Amiodarone *(Cordarone)*	*Dog:* 10 mg/kg BID for 1 week (anecdotal loading dose) and 5 mg/kg SID (anecdotal maintenance dose)	*Dog:* 5-10 mg/kg (anecdotal dose)	Refractory VT
Lidocaine	NA	*Dog:* 2 mg/kg IV bolus, repeated up to 3 times, followed by CRI of 30-90 µg/kg/min *Cat:* 0.25-1 mg/kg IV bolus (used with *extreme* caution)	Life-threatening VT
Procainamide	*Dog:* 10-20 mg/kg TID-QID *Cat:* 2-5 mg/kg BID-TID	*Dog:* 10-15 mg/kg IV bolus slowly over 2 minutes or CRI of 25-50 µg/kg/min *Cat:* 1-2 mg/kg IV bolus slowly or CRI of 10-20 µg/kg/min	Life-threatening VT
Atenolol *(Tenormin)*	*Dog:* 0.25-1 mg/kg SID-BID *Cat:* 6.25-12.5 mg SID-BID	NA	VT; effective only in combination with mexiletine
Esmolol *(Brevibloc)*	NA	*Dog, cat:* 50-100 µg/kg bolus, repeated to maximum dose of 500 µg/kg or CRI of 50-200 µg/kg/min	Life-threatening VT

NA, Not available; *VT,* ventricular tachycardia; *CRI,* constant rate infusion.

B. Considerations include the frequency and degree of prematurity and the presence of concurrent underlying diseases.
C. The following are suggested guidelines:
1. Unifocal, single VPCs (<30 to 50/hour) probably require no treatment, even if structural heart disease is present.
2. More frequent, unifocal, single VPCs (>50/hour) may require antiarrhythmic treatment, especially if an underlying heart disease (dilated cardiomyopathy) is present.
3. Unifocal, numerous VPCs (>100/hour) are usually treated with antiarrhythmic drugs.
4. Multiform VPCs and ventricular couplets in the presence of structural heart disease are usually treated.
5. R on T phenomenon is usually treated.
6. If normal blood pressure is not maintained, treatment is initiated.
D. For specific antiarrhythmic therapy, see Table 6-3 and Treatment of VT.

II. Acute, life-threatening ventricular arrhythmias in dogs (Table 6-3)
A. Administer lidocaine slowly in boluses of 2 mg/kg IV (up to 8 mg/kg total) until VT converts to sinus rhythm, then follow with CRI of 30 to 80 µg/kg/min IV.
B. If lidocaine therapy fails, administer procainamide slowly in boluses of 2 mg/kg IV (up to 20 mg/kg total) until VT resolves, then follow with CRI of 20 to 50 µg/kg/min IV or 8 to 20 mg/kg IM QID.
C. If no response occurs to either lidocaine or procainamide, CRIs of both drugs can be combined.
D. If no response occurs to combined therapy, administer boluses of esmolol (0.05 to 0.1 mg/kg IV slowly every 5 minutes) to a cumulative dose of 0.5 mg/kg, or as a CRI of 50 to 200 µg/kg/min IV.
E. Combination therapy with esmolol and procainamide/lidocaine may cause significant hypotension.

III. Life-threatening ventricular arrhythmias in cats (see Table 6-3)
A. They are less common than in dogs.
B. Use extreme caution when administering lidocaine.

IV. Chronic oral antiarrhythmic therapy in dogs
A. Baseline 24-hour Holter monitoring may be done before therapy (if not life threatening) to determine the number of VPCs, their duration and rate, the presence of episodes of VT, and the presence and length of pauses.
B. The preferred oral antiarrhythmic drug for VT in most dogs is sotalol, with the exception of German shepherd dogs (arrhythmogenic in this breed).
1. In German shepherd dogs, the combination of mexiletine and sotalol is usually the most effective.
2. If advanced myocardial systolic dysfunction (fractional shortening <15%) is present, sotalol may not be tolerated because of its beta-blocker effect.

FIGURE 6-18 Electrocardiogram (Lead II, 50 mm/sec, 10 mm/mV) of a slow idioventricular rhythm (V) that is temporarily interrupted by normal sinus beats (N).

C. Mexiletine in combination with atenolol is also very effective in boxers (Meurs et al., 2002).
D. For refractory VT, a combination of sotalol and mexiletine may be given, with sotalol started first, and mexiletine added after 2 to 3 days to avoid side effects (AV block, inappetence).
E. Amiodarone is used as a last resort for refractory VT.
1. In large-breed dogs, 200 mg PO SID is usually well-tolerated, but 400 mg PO SID consistently causes toxicity (Kraus et al., 2005).
2. Monitoring of biochemistry panels is recommended because elevated liver enzymes usually precede the onset of clinical signs associated with drug toxicity.
3. Amiodarone hepatopathy is reversible with reduction or discontinuation of the drug (usually within 3 months).
4. Other toxicities include neutropenia, hypothyroidism, and hyperthyroidism.

V. Chronic, oral, antiarrhythmic therapy in cats (see Table 6-3)

Monitoring of Animal

I. Holter recordings are used to evaluate treatment.
A. Adequate treatment involves an 80% reduction in VPCs and suppression of VT.
B. Presence of couplets, triplets, or multiform VPCs suggests inadequate therapy.

II. If a Holter monitor is not available, ECG is used to evaluate response to therapy.

III. Measurement of plasma drug levels (sotalol, mexiletine, amiodarone) is indicated if the arrhythmia is not controlled with standard dosages of these drugs.

Idioventricular Rhythm

Definition and Causes

I. Idioventricular rhythm is characterized by a ventricular rate that is slow or comparable to a normal sinus rate (60 to 150 bpm in the dog, >100 bpm in cats).

II. It has many causes.
A. Systemic diseases: anemia, septicemia, splenic hemangiosarcoma
B. Drug toxicity: digoxin, anesthetic agents (opioids) that can slow the SA node discharge rate
C. Electrolyte abnormalities: hypokalemia

III. Enhanced automaticity may be the electrophysiologic mechanism that causes the arrhythmia.

Clinical Signs

I. Generally, no clinical signs occur.

II. If clinical signs are present, they are often associated with the underlying illness.

Diagnosis

I. Physical examination findings: irregular cardiac rhythm, occasional pulse deficits

II. ECG characteristics (Figure 6-18)
A. The ventricular rate usually remains within 10 to 15 bpm of the sinus rate.
B. The cardiac rhythm switches back and forth between two competing pacemaker sites.
C. The QRS complexes are wide and bizarre.

Differential Diagnosis

I. Supraventricular rhythm with bundle branch block

II. VT with a relatively slow rate

Treatment

I. Idioventricular rhythms usually do not require treatment.

II. Management of the underlying cardiac disease or metabolic abnormality is needed.

III. If the animal is symptomatic or hemodynamically compromised (low blood pressure), increasing the sinus rate with an anticholinergic drug abolishes the idioventricular rhythm.

Ventricular Fibrillation

Definition

I. Ventricular fibrillation (VF) is an irregular, chaotic rhythm of the ventricles in which there is no effective ventricular contraction.

II. VF is a terminal rhythm if the animal is not successfully defibrillated.

Causes and Pathophysiology

I. Ventricular tachycardia can degenerate to VF.

II. VF can occur primarily from heart disease or secondary to systemic disorders, such as shock, hypoxemia, drug reactions, trauma, and electrolyte disturbances.

III. Dogs with congenital heart diseases that are predisposed to ventricular arrhythmias (e.g., subaortic and pulmonic stenosis) may develop VF during exercise.

IV. Electrocution may induce VF.

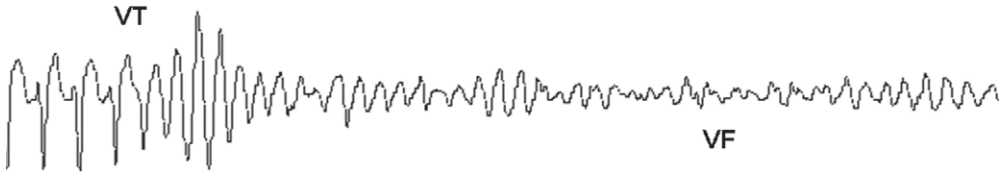

FIGURE 6-19 In this electrocardiogram (Lead II, 50 mm/sec, 10 mm/mV) ventricular tachycardia (VT) degenerates into ventricular fibrillation (VF), which is characterized by a low-amplitude, chaotic baseline, and contains no distinct waveforms.

Clinical Signs

I. Within seconds of onset, severe hypotension leads to collapse.
II. VF often occurs without forewarning.
III. Dyspnea or labored breathing may immediately precede VF.
IV. Sudden death is common.

Diagnosis

I. Physical examination findings
   A. No auscultable heart beat
   B. No palpable pulse
   C. Pale mucous membranes, slow or nonexistent capillary refill time
II. ECG characteristics (Figure 6-19)
   A. Chaotic and irregular deflections of varying amplitudes
   B. No P waves, QRS complexes, or T waves

Differential Diagnosis

I. ECG artifact
II. Rapid, polymorphic VT

Treatment and Monitoring

I. Immediate electrical defibrillation is the only viable treatment option (see Chapter 7).
II. VF has a grave prognosis if not corrected within 3 minutes of onset.

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CHAPTER 7

Cardiopulmonary Arrest

Sean Smarick

CARDIOPULMONARY ARREST

Definition

I. Cardiopulmonary arrest (CPA) is a lack of spontaneous respiration and circulation.
II. In most instances, it is the common pathway preceding death.

Causes

I. The possible causes are numerous and many of these causes are potentially reversible.
II. A memory aid suggested by the American Heart Association for reversible causes includes the following list of "H"s and "T"s, and can be adapted to small animals.
   A. Hypovolemia
   B. Hypoxia
   C. Hypoglycemia
   D. H^+ (acidosis)
   E. Hyperkalemia
   F. Hypothermia
   G. Tablets (drugs)
   H. Trauma (brain)
   I. Tamponade
   J. Tension pneumothorax
   K. Thromboembolism

Pathophysiology

I. An underlying disease or insult causes hypoxia or decreases perfusion and notably affects the coronary and cerebral circulations.
II. Decreased perfusion results in cell dysfunction or death, leading to cardiac arrest, neurological impairment, and whole-body ischemia.

Clinical Signs

I. Collapse
II. Unresponsiveness
III. Lack of chest wall movement or agonal respirations

Diagnosis

I. If any of the clinical signs are noted, confirmation of CPA is pursued without hesitation, simultaneous to initiating specific treatment.
II. Physical examination findings of an unconscious and unresponsive animal require ruling out CPA.
   A. Lack of respiratory effort indicates respiratory arrest.
   B. Auscultation reveals no or only intermittent agonal breath sounds and no heart sounds during cardiac arrest.
   C. In cardiac arrest, palpation does not yield an apex heart beat or a peripheral pulse.
III. Cardiac arrest is characterized by electrocardiographic (ECG) evidence of asystole, pulseless electrical activity, or ventricular fibrillation.
   A. Animals in respiratory arrest or early CPA may have other arrhythmias (Rush and Wingfield, 1992).
   B. Electrical activity on the ECG does not ensure mechanical activity, and bradycardic waveforms are interpreted as CPA.
   C. A lack of a discernible ECG rhythm also warrants the consideration of technical difficulties, such as poor electrode-patient coupling, machine malfunction, among others.
IV. Changes in anesthetic or critical-care parameters help support the presence of CPA.
   A. Arterial blood pressure or Doppler blood flow intensity drops precipitously.
   B. Capnometry shows acute downward trends of end-tidal carbon dioxide ($_{ET}CO_2$) or apnea.
   C. Pulse oximetry waveforms or light-emitting diode indicators decrease abruptly; however, a decrease in oxygen saturation (S_pO_2) is not a reliable indicator of CPA.

Differential Diagnosis

I. Coma or neurological event
II. Syncope
III. Technical difficulties with monitoring devices

Treatment

I. Treatment is based on the owner's informed consent or, in the absence of a documented "do-not-resuscitate" request, dependent on any obvious signs of irreversible death (rigor).
   A. People's expectations are often unrealistic because of emotional involvement or unrealistic impressions (Diem et al., 1996).
   B. In dogs, survival rates range from 4% for cardiac arrest to 28% for respiratory arrest (Kass and Haskins, 1992; Wingfield and Van Pelt, 1992).

C. In cats, survival rates range from 2% for cardiac arrest and 58% for respiratory arrest (Kass and Haskins, 1992; Wingfield and Van Pelt, 1992).
D. Most successful resuscitations are related to anesthetic complications (Gilroy et al., 1987; Kass and Haskins, 1992; Waldrop et al., 2004).

II. Resuscitation is aimed at restoring spontaneous circulation while mitigating cerebral ischemia.
A. Cardiopulmonary cerebral resuscitation (CPCR) has been suggested as the treatment for CPA, because it reflects the goal of survival with intact neurological function.
B. Return of spontaneous circulation has been correlated with maximizing coronary perfusion pressure.

III. Duration of treatment is determined for each case, but most successful resuscitations last <15 minutes (Gilroy et al., 1987; Kass and Haskins, 1992; Waldrop et al., 2004).

IV. A dedicated area, cart, or tackle box for CPCR supplies, and regular staff training increases the likelihood of successfully reversing CPA.

V. The letters *A* through *G* provide a mnemonic guide to treatment (Figure 7-1).

Access Airway

I. Extend the neck (in a nontraumatized animal); pull the tongue rostrally.

II. Place and secure an appropriately sized endotracheal tube, confirming initial and continued placement with capnometry, visualization, or palpation.

III. If an airway obstruction is suspected or the endotracheal tube cannot be passed, relieve the obstruction.
A. Suction any vomitus or secretions from the laryngeal/pharyngeal area.
B. Physically remove any foreign body or use a polypropylene urinary catheter as a stylet to guide the endotracheal tube around the obstruction.
C. For foreign bodies not visible, perform a Heimlich maneuver by sharply compressing the abdomen in a ventrodorsal direction, just cranial to the umbilicus.
D. A tracheostomy is performed if an upper airway obstruction cannot be relieved.

Breathing

I. If only respiratory arrest is present, provide positive-pressure ventilation with 100% oxygen at a rate of 20 breaths per minute.

II. If cardiac arrest is present, ventilate 8 to 10 times per minute.

III. Use Ambu-bags, Baines, or other nonbreathing circuits, anesthesia machines, and even mouth-to-nose breathing to ventilate the animal.

IV. Experimentally, dogs maintain an oxygen saturation >90% without positive-pressure ventilation for up to 4 minutes and maintain a partial pressure of arterial oxygen (P_aO_2) of 80 mm Hg during CPCR on room air; however, ventilation with 100% oxygen is still recommended.

Circulation

I. Generate forward blood flow to perfuse the heart and brain.

II. Begin external chest compressions.
A. Compression dynamics are as follows:
1. Compress the chest by about 30% of its diameter.
2. Maintain a 1:1 compression:relaxation ratio.
3. Perform at a rate of 100 beats per minute (bpm) and minimize interruptions.
B. Thoracic conformation and size determine the best position for external compressions.
1. Cats and small dogs are circumferentially compressed at the level of the 5th intercostal space while in lateral recumbency.
2. Medium-size dogs (<15 kg) with greater dorsal-ventral versus lateral dimensions are placed in lateral recumbency, with the hands placed one over the other at the 5th intercostal space.
3. In large dogs, hand placement is over the widest portion of the thorax with the dog in lateral recumbency, or just cranial to the xiphoid process with the dog in dorsal recumbency.
C. Changing compressors, placement of hands, varying the rate and depth may offer some benefit if unsatisfactory results are obtained (e.g., increased $_{ET}CO_2$, perfusion pressure, or return of spontaneous circulation.
D. Procedures to augment external compressions may be considered.
1. Interposed abdominal compressions are performed midway between the umbilicus and xiphoid to generate a pressure of 100 mm Hg.
2. Active compression-decompression ± inspiratory threshold impedance valves require specialized equipment.
3. Simultaneous ventilation-compression CPCR and the application of military antishock trousers or caudal abdominal binding are no longer recommended.

III. Internal cardiac compressions may be considered.
A. Despite on-going debate, it is universally accepted that internal cardiac compressions must be used within 2 to 5 minutes to have any benefit.
B. Indications include a chest wall defect, penetrating trauma, cardiac tamponade, ineffective external compressions (especially in large or barrel-chested dogs) loss of chest wall compliance, or pleural space disease.
C. The technique for internal compressions is described in Box 7-1.

Differential Diagnosis and Drugs

I. While instituting the "ABCs," also start appropriate therapy for reversible causes of CPA.

II. Vascular access is obtained to administer fluids and drugs.
A. Central IV catheters are best for administering drugs, but placement is technically difficult during CPCR, and their long length is not ideal for administering fluid boluses.
B. Intraosseous (IO) access of the humerus or femur is technically feasible, especially in young or small animals, and provides central access.

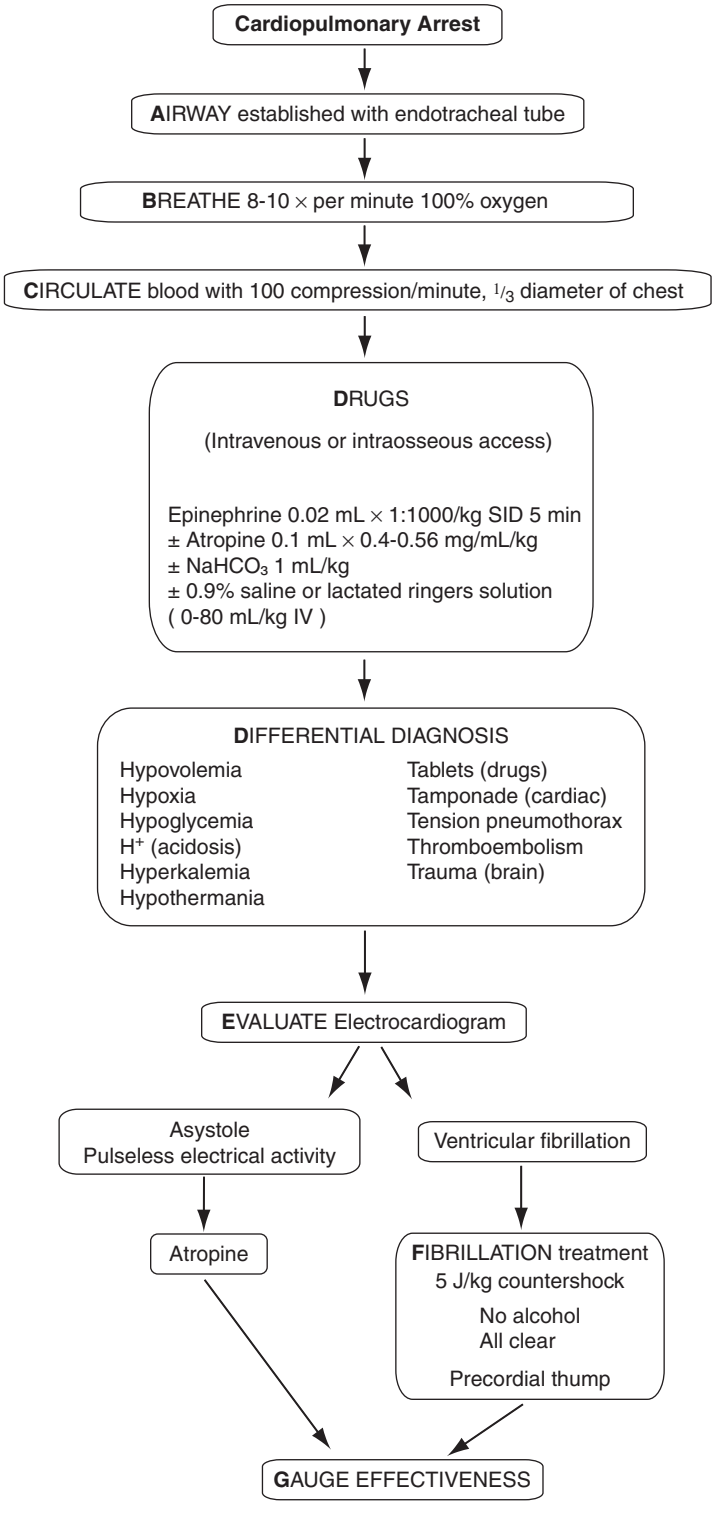

FIGURE 7-1 Algorithm for cardiopulmonary cerebral resuscitation for cardiopulmonary arrest.

C. Peripheral IV catheters are most often used but should be placed within the cephalic vein to minimize time to reach the heart during CPCR.
   1. Follow all drugs with a 20 mL bolus of IV fluids.
   2. Elevate the extremity afterward for 20 seconds.

III. Dosages of drugs administered intratracheally are at least doubled, except for epinephrine.

A. Drugs are dissolved in 5 to 10 mL of sterile water for injection or 0.9% saline, injected via a red rubber catheter at the level of the carina, and followed by two ventilated breaths.

B. *NAVEL* is the mnemonic for drugs that can be administered intratracheally (IT).
   1. **N**aloxone 0.04 mg/kg IT

Box 7-1

Technique for Performing Internal Cardiac Compressions

1. Animal is placed in right lateral recumbency.
2. Minimal to no surgical preparation is required over the left 6th intercostal space.
3. Incise the skin with a scalpel blade.
4. Make a controlled stab incision into the pleural space cranial to the rib with the tips of curved Mayo scissors.
5. Extend the incision by advancing the partially open Mayo scissors dorsally and ventrally, stopping short of the internal thoracic and vertebral arteries.
6. Insert Balfour or other self-retaining retractors.
7. Alternatively, incise the diaphragm during a celiotomy.
8. Incise the pericardial sac with the Mayo scissors to expose the heart.
9. Compression dynamics are as follows:
   a. Use the palmar surfaces of the fingers and hand(s).
   b. Compress the heart from apex to base.
   c. Compress at a rate of 100 to 150 beats/min.
10. Occlude the descending aorta by digital compression or by blunt dissection and occlusion with a red-rubber catheter, Penrose drain, or Rumel tourniquet.
11. If resuscitation is successful, release the aortic occlusion over 5 to 10 minutes while administering sodium bicarbonate empirically or as determined by blood gas analysis, and close the chest routinely after pleural lavage.

2. **A**tropine 0.08 mg/kg IT
3. **V**asopressin 1.6 U/kg IT
4. **E**pinephrine 0.2 mg/kg IT
5. **L**idocaine 4 mg/kg IT

IV. Sublingual administration of medications has been recommended only anecdotally.

V. Fluid administration in CPCR has been associated with worse outcomes in euvolemic animals, but if hypovolemia caused or contributed to CPA, appropriate boluses of isotonic crystalloids (0.9% saline, lactated Ringer's solution) are indicated.

VI. The administration of some drugs warrant ECG evaluation (see following section); however, others are immediately indicated.
   A. Antagonists for anesthetic agents during an anesthetic arrest (e.g., naloxone for a narcotic)
   B. Calcium gluconate 10% (0.6 mL/kg IV), insulin (0.2 U/kg IV), and dextrose (1 g/kg IV), and sodium bicarbonate (1 mEq/kg IV) for known hyperkalemia
      1. Calcium gluconate is only indicated for CPA associated with hyperkalemia, hypocalcemia, or calcium channel blocker intoxication.
      2. In other causes of CPA, calcium gluconate may worsen outcome.
   C. Epinephrine as a vasopressor
      1. Give 0.01 to 0.02 mg/kg IV every 3 to 5 minutes.
      2. High doses (0.1 to 0.2 mg/kg) have not been shown to be superior.
      3. Other alpha-2 agonists, such as phenylephrine or norepinephrine, have shown no increased benefit.
   D. Vasopressin 0.8 U/kg IV once: alternative to epinephrine (Schmittinger et al., 2005)
   E. Empirical vagolytic therapy
      1. Atropine may be given at 0.01 to 0.04 mg/kg IV.
      2. Empirical use is justified, as approximately 80% of the arrhythmias seen in CPA require atropine.
   F. Sodium bicarbonate ($NaHCO_3$)
      1. Dose: 1 mEq/kg IV initially, then 0.5 mEq/kg every 10 minutes
      2. Contraindicated in hypercarbia and requires adequate ventilation to avoid intracellular acidosis
      3. Indicated in animals with known metabolic acidosis or prolonged (>10 minutes) CPA

Evaluation of Electrocardiogram

I. Asystole (flat line) and pulseless electrical activity (wide, often bizarre bradyarrhythmia with no or ineffective mechanical cardiac activity) are most often observed.
   A. Administer atropine 0.04 mg/kg and repeat in 5 minutes.
   B. Transthoracic or transesophageal electrical pacing (available on many defibrillators) may be beneficial.
   C. Defibrillation is not indicated and can cause further myocardial insult.

II. Severe sinus bradycardia is often seen early in a vagal-induced arrest.
   A. Atropine is given at 0.004 to 0.01 mg/kg IV.
   B. Transthoracic or transesophageal pacing is indicated if bradycardia deteriorates or atrioventricular block occurs

III. Ventricular fibrillation (sawtooth waveform) accounts for approximately 20% of initial CPA rhythms and can occur during resuscitation efforts.

Fibrillation Treatment

I. Immediate defibrillation therapy is indicated, as survival is inversely proportional to the amount of time from onset to the first countershock.

II. Electrical defibrillation is the only effective therapy.
   A. Quickly clip area for electrodes to decrease impedance and potential for arcing.
   B. Electrode options include the following:
      1. Manually hold both standard paddles on opposite sides of the chest with the one marked "sternum" over the animal's right cranial thorax.
      2. Flat paddle marked "apex" is slid under the animal (in left lateral recumbency) while on a nonconducting table surface and the paddle marked "sternum" is placed on the animal's right cranial, lateral thorax.
      3. Self-adhesive electrodes are applied to the skin in the same areas as with hand-held paddles.
      4. Internal paddles are applied directly to either side of the heart (after thoracotomy).
      5. Select energy settings.
         a. Set at 5 to 10 J/kg for monophasic (older) defibrillators.

b. Newer biphasic defibrillators use approximately 40% less energy as the current flows from electrode to electrode and back again.
c. Internal defibrillation is done at approximately 10% of external settings.

6. Apply firm pressure to hand-held paddles to decrease transthoracic impedance.
7. Do not use alcohol; use coupling gel or saline-soaked gauzes.
8. Just before delivering a countershock, make sure everyone is clear of direct and indirect animal contact.
9. Administer one shock and then perform compressions, ventilation, and drug therapy for 1 minute before repeated attempts.

C. Pharmacological attempts at defibrillation have been very disappointing and are no longer recommended.
1. After unsuccessful countershocks, CPCR and vasopressor therapy, pharmacological intervention may be helpful in electroconversion before additional counter shocks.
2. Amiodarone 5 mg/kg IV is the drug of choice, and half of the initial dose may be repeated once.
3. Lidocaine may be used alternatively at 1 mg/kg IV and then 0.5mg/kg every 5 minutes to a maximum of 3 mg/kg.
4. Magnesium is only indicated in hypomagnesemic states or Torsades de pointes and is given at 20 mg/kg diluted in dextrose 5% in water (D_5W) over 5 minutes IV.

D. In the absence of a defibrillator, a precordial thump can be attempted but is not recommended for routine use.

Gauge Resuscitative Efforts

I. Monitor for return of spontaneous circulation.
II. $_{ET}CO_2$ values >10 mm Hg are evidence of effective oxygenation and circulation.
III. Diastolic arterial pressures >30 mm Hg correlate with coronary perfusion pressure of >15 to 20 mm Hg, which is adequate; however, indirect measurements (oscillometric, Doppler) are unreliable in CPCR.
IV. No other clinical indicators (pulse strength, pulse oximetry) have proven reliable for real-time evaluation of CPCR effectiveness.
V. If efficacy of CPCR is in question, do the following:
A. Confirm endotracheal tube placement.
B. Augment compressions.
C. Consider buffer therapy, such as $NaHCO_3$.
D. Reevaluate the ECG.
E. Revisit the differential diagnosis list to address any reversible causes.
F. Evaluate electrolytes, pH, and attempt to correct imbalances
VI. Consider discontinuing CPCR if there has been no return of spontaneous circulation and CPCR has lasted for 15 to 30 minutes, the animal was presented in CPA, or the underlying disease was already receiving maximal therapy.

Hypothermia

I. In successfully resuscitated animals, lowering the body temperature to approximately 91.5° F (33° C) by permissive means (not providing heat support), cooling blankets, or ice packs may improve neurological recovery in hemodynamically stable animals.
II. Intensive care and monitoring are usually required for successful recovery once spontaneous circulation is established.

Monitoring of Animal

I. Maintain oxygenation at P_aO_2 >80 mm Hg or S_pO_2 >95%, with supplemental oxygen or intermittent positive-pressure ventilation (IPPV).
II. Ventilation is assessed by measurement of arterial blood gas carbon dioxide (P_aCO_2), venous blood gas (P_vCO_2), or $_{ET}CO_2$ to maintain normocapnia (≈35 mm Hg).
III. Blood pressure is supported with vasopressors (norepinephrine 0.05 to 0.5 μg/kg/min, phenylephrine 1 to 10 μg/kg/min, or dopamine 10 to 40 μg/kg/min constant rate IV infusion) to maintain a mean arterial pressure >100 mm Hg or a Doppler systolic pressure >125 mm Hg for the first 12 hours, and then to maintain normotension.
IV. Monitor the ECG for arrhythmias that can affect cardiac output, blood pressure, and lead to rearrest.
V. Central venous pH is normalized by maximizing perfusion, maintaining normocapnia, and correcting acidosis with $NaHCO_3$ (0.3 mEq/kg/mmol × base deficit IV).
VI. Blood glucose is monitored to maintain euglycemia.
VII. Additional monitoring is warranted to identify the onset of coagulopathy, pneumonia, sepsis, renal failure, and seizures, with appropriate treatment instituted as needed.
VIII. Assess the animal for complications of external chest compression, such as rib or sternum separations or fractures, hemothorax, pneumothorax, pulmonary contusions, and hepatic and splenic lacerations.
IX. Prognostic factors for poor neurological outcome or death 24 hours post-resuscitation include the following:
A. Corneal reflex absent
B. Pupillary light response absent
C. Withdrawal response to pain absent
D. Motor response absent

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CHAPTER 8

Congenital Heart Disease

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OVERVIEW OF CONGENITAL HEART DISEASE

Definition

I. Congenital heart disease (CHD) is a developmental lesion of the heart or great vessels present at birth.
II. Malformations are the most common cause of cardiovascular disease in dogs and cats <1 year of age.

Causes

I. CHD can be caused by genetic, environmental, chromosomal, infective, toxicologic, or nutritional factors, or it may develop from teratogenic effects of drugs.
II. Most cases have a genetic basis, but the precise mode of inheritance is often unknown.
III. There are numerous examples of breed-related predispositions to specific cardiac malformations (Table 8-1).
IV. Penetrance of a lesion can be incomplete, making clinical recognition difficult or impossible.

Pathophysiology

I. CHD can be classified as left-to-right shunts, right-to-left shunts, outflow tract stenosis, atrioventricular (AV) valve malformations, and complex malformations.
II. Outcomes can include congestive heart failure (CHF), arrhythmias, syncope, or sudden death.
III. Right-to-left shunts and complex malformations create hypoxemia and secondary polycythemia, with clinical complications related to tissue hypoxia and blood hyperviscosity (e.g., hypertrophic osteopathy).
IV. Pulmonary hypertension (PH) can develop with large cardiac shunts or with mitral valvular stenosis.
   A. Pulmonary arterial injury creates a high-resistance vascular system, increased right ventricular (RV) pressures, and reduced venous return to the left atrium.
   B. Severe PH can lead to limited cardiac output, exercise intolerance, and syncope.
   C. A left-to-right shunt may become right-to-left with severe PH (Eisenmenger's physiology).
   D. Severe pulmonary vascular disease is generally irreversible, and surgical closure of a shunt that decompresses the right circulatory side can be fatal.
   E. Clinical evidence of PH includes RV hypertrophy, main pulmonary artery dilation, right atrial enlargement, and reduced size of the left heart chambers.

Clinical Signs

I. In most cases, the pet owner does not recognize overt clinical signs of heart disease.
II. Stunted growth is common with severe CHD.
III. CHD often leads to exercise-induced problems, such as tiring, collapse, and syncope.
IV. Signs of CHF can be observed, including tachypnea, orthopnea, coughing, respiratory distress, or abdominal distension (from ascites).
V. Cyanosis is common with right-to-left shunts and when severe pulmonary dysfunction accompanies left-sided or biventricular CHF.
VI. Death from CHD may occur from unmanaged CHF, severe hypoxemia, or a cardiac arrhythmia (ventricular fibrillation, asystole).

Diagnosis

I. The diagnosis is suspected from identification of a cardiac murmur in a young animal, particularly in a breed at risk for CHD.
   A. The pet may appear normal, even with serious CHD.
   B. When clinical signs of CHD are present, suspect a severe cardiovascular malformation.
   C. Once clinical signs have developed, the prognosis is generally poor unless definitive or palliative treatments are initiated.
   D. Noncardiac causes of the clinical signs (e.g., anemia, parasitism, or pneumonia) must be ruled out.
II. Physical examination findings can be suggestive of CHD.
   A. Precordial palpation may identify cardiomegaly via caudal displacement of the left ventricular (LV) apical impulse or as a prominent RV impulse (heave).
   B. A palpable vibration or thrill indicates the presence of a loud cardiac murmur (grade V or VI) and identifies the point of maximum murmur intensity.
   C. Cardiac murmurs are typical of CHD.
      1. Most murmurs associated with CHD are systolic.
      2. A continuous murmur occurs with patent ductus arteriosus (PDA) or, rarely, from an aorticopulmonary window.
      3. A diastolic murmur usually indicates aortic regurgitation and, rarely, AV valvular (or supravalvular) stenosis.
      4. Distinguishing an innocent (functional) murmur from one caused by CHD can be difficult, if not

TABLE 8-1

Common Breed Predispositions to Congenital Heart Disease

BREED	MALFORMATION
Airedale terrier	Pulmonic stenosis
Beagle	Pulmonic stenosis, pulmonary insufficiency
Bichon frise	Patent ductus arteriosus
Boykin spaniel	Pulmonic stenosis
Boxer	Subaortic stenosis, pulmonic stenosis, atrial septal defect
Bull terrier	Mitral valve dysplasia, aortic stenosis
Chihuahua	Patent ductus arteriosus, pulmonic stenosis
Cocker spaniel	Patent ductus arteriosus, pulmonic stenosis
Collie	Patent ductus arteriosus
Doberman pinscher	Atrial septal defect
English bulldog	Pulmonic stenosis, tetralogy of Fallot, ventricular septal defect, subaortic stenosis
English springer spaniel	Patent ductus arteriosus, ventricular septal defect
German shepherd dog	Patent ductus arteriosus, subaortic stenosis, mitral valve dysplasia, tricuspid valve dysplasia, persistent right aortic arch
German shorthair pointer	Subaortic stenosis
Golden retriever	Subaortic stenosis, mitral valve dysplasia, tricuspid valve dysplasia
Great Dane	Mitral valve dysplasia, tricuspid valve dysplasia, aortic stenosis, persistent right aortic arch
Irish setter	Persistent right aortic arch, patent ductus arteriosus
Kerry blue terrier	Patent ductus arteriosus
Keeshond	Tetralogy of Fallot, ventricular septal defect, patent ductus arteriosus
Labrador retriever	Tricuspid valve dysplasia, patent ductus arteriosus
Maltese	Patent ductus arteriosus
Mastiff	Mitral valve dysplasia, pulmonic stenosis, subaortic stenosis
Newfoundland	Subaortic stenosis, mitral dysplasia, patent ductus arteriosus
Old English sheepdog	Tricuspid valve dysplasia
Poodle breeds	Patent ductus arteriosus
Poodle (standard)	Atrial septal defect
Pomeranian	Patent ductus arteriosus
Rottweiler	Aortic stenosis, mitral dysplasia
Samoyed	Pulmonic stenosis, aortic stenosis
Schnauzer breeds	Pulmonic stenosis
Shetland sheepdog	Patent ductus arteriosus
Weimaraner	Tricuspid valve dysplasia, peritoneopericardial diaphragmatic hernia
West Highland white terrier	Pulmonic stenosis
Yorkshire terrier	Patent ductus arteriosus

impossible; however, murmurs caused by clinically significant CHD are typically louder and of longer duration.

5. A particularly difficult issue for breeders is the persistence of a soft ejection murmur in the absence of an echocardiographic lesion, which makes it impossible to determine the presence of CHD.
6. With the exception of ventricular outlet obstruction (aortic or pulmonic stenosis [PS]), murmur grade (intensity) and duration do not correlate well with the severity of the cardiac lesion.
7. A murmur can be soft or absent even in serious situations, such as right-to-left shunting defects with polycythemia; pulmonary or aortic atresia; large unrestrictive ventricular septal defect (VSD); tricuspid dysplasia; or severe PH.

D. Jugular venous distension or pulsations suggest right heart disease (e.g., PS, tricuspid regurgitation, right-sided CHF).
E. A hypokinetic or late-rising femoral arterial pulse suggests outflow obstruction, LV dysfunction, or heart failure.
F. A bounding (hyperkinetic or waterhammer) pulse is typical of PDA and aortic regurgitation.
G. Cyanosis can be a sign of CHD and is caused by either right-to-left shunting or pulmonary dysfunction from lung edema or pleural effusion.
   1. Concurrent bronchopneumonia may be the most common cause of cyanosis in CHD.

2. The term *differential cyanosis* generally refers to the condition of pink oral membranes and cyanotic caudal membranes (best seen in the vulva or prepuce) and is most typical of reversal of a left-to-right PDA.

III. Thoracic radiographs can identify cardiomegaly, dilation of the great vessels, alterations in pulmonary circulation, and findings compatible with CHF.
   A. Young puppies have a relatively prominent RV shadow until 6 to 8 weeks of age.
   B. Radiographs also provide objective proof of the presence of CHF and can help guide initial treatment plans.
   C. Routine 6-lead electrocardiography (ECG) may identify atrial or ventricular enlargement, but can be negative and is rarely definitive.

IV. Definitive diagnosis and appropriate staging of CHD requires advanced echocardiography with Doppler studies.
   A. Two-dimensional (2D) and motion-mode (M-mode) echocardiography precisely define lesions, cardiac and great vessel enlargement, and ventricular function.
   B. Doppler studies identify the direction and velocity of blood flow and can be used to estimate intracardiac pressures.
   C. Turbulence algorithms can delineate abnormal patterns of blood flow, such as shunting or valvular regurgitation.

V. Cardiac catheterization and angiocardiography are needed to diagnose ambiguous cases of serious CHD, particularly if significant coronary, systemic, or pulmonary vascular malformations are present.

VI. Cases of trivial CHD can escape detection or defy clear definition, even with advanced echocardiographic methods and expert examination.
   A. For many dogs with soft ejection murmurs, distinguishing a functional (innocent) murmur from definitive disease can be difficult.
   B. These situations are unimportant relative to the health of the affected dog, but they do cause consternation regarding breeding soundness.

Differential Diagnosis

I. The most important considerations and most common problems are as follows:
   A. Stunted growth: malformations of other organ systems, metabolic diseases, chronic infection, malnutrition, or severe parasitism
   B. Respiratory signs: infectious respiratory diseases (viral infections, respiratory parasites, bordetellosis, bacterial bronchopneumonia), developmental diseases of the respiratory tract
   C. Abdominal distension with fluid: right-sided CHF, obstruction of caudal vena caval entry (cor triatriatum dexter), noncardiac diseases
   D. Syncope: acquired cardiac rhythm disturbance, myocarditis in puppies

II. In a young animal, the differential diagnosis of a murmur includes functional or innocent murmurs in puppies and kittens as well as cardiomyopathy in cats.
   A. Soft ejection-type murmurs (<III and/or VI) in otherwise healthy puppies or kittens are often innocent and disappear over time.
   B. Increasing murmur intensity, other physical abnormalities (stunted growth, cyanosis), or any clinical signs (exercise intolerance, respiratory distress) should prompt immediate evaluation by a specialist in CHD.
   C. A loud systolic murmur, a diastolic murmur, or a continuous murmur is very unlikely to be innocent and needs prompt evaluation.
   D. A persistent, soft-ejection murmur is common in many breeds at risk for aortic stenosis (e.g., boxer, Bouvier de Flanders, golden retriever), but it can be difficult or impossible to distinguish trivial CHD from a normal physiologic variation.
   E. In young cats (<2 years) with a systolic murmur and echocardiographic evidence of a concentrically hypertrophied LV, the differential diagnosis includes genetic hypertrophic cardiomyopathy, mitral valve malformation with dynamic obstruction of the ventricular outflow tract, or (rarely) fixed aortic stenosis.

Treatment

I. Definitive or palliative therapy for CHD often requires surgery or catheter-based intervention.
   A. Before such treatments begin, a definitive diagnosis *must* be established.
   B. Specific treatments are described under individual malformations.
   C. Unfortunately, many cases of CHD require surgery during cardiopulmonary bypass, so definitive repair is rarely accomplished, except for PDAs.
   D. Medical therapy may be needed for complications of CHD (e.g., CHF, cardiac arrhythmias, PH, secondary polycythemia).

II. CHF is a consequence of progressive volume or pressure overload of the affected ventricle.
   A. Initial management of left-sided CHF involves furosemide (2 to 4 mg/kg IV, IM, SC), oxygen supplementation, possibly 2% nitroglycerin ointment, and sedation with butorphanol (0.25 mg/kg IM, SC) as needed.
   B. If CHF persists and the cause is a left-to-right shunt, nitroprusside (0.5 to 2.5 μg/kg/min IV infusion) can be used to reduce arterial blood pressure and the magnitude of shunting.
      1. Chronic therapy with enalapril (0.5 mg/kg PO BID), amlodipine (0.05 to 0.2 mg/kg PO SID), or hydralazine (0.5 to 2 mg/kg PO BID) may reduce blood pressure and left-to-right shunting.
      2. Amlodipine or hydralazine may be needed in addition to an angiotensin-converting enzyme (ACE) inhibitor.
      3. Maintain systolic blood pressure at 80 to 120 mm Hg, particularly in cases of aortic stenosis (hypotension reduces coronary perfusion).
   C. Long-term medical therapy of CHF in dogs and cats with CHD is identical to that described in Chapter 9.

D. The use of beta-blockers in treatment of dogs with CHF from CHD is unresolved, and care must be used to avoid bradycardia, especially in dogs with fixed obstructions, such as subaortic stenosis and PS.
E. In some cases (e.g., PDA), medical therapy for CHF can be discontinued if definitive repair of the defect is performed successfully.

III. Controlling arrhythmias in animals with severe CHD helps to maintain a compensated state and can prevent sudden death (see Chapter 6).
IV. Management of PH is difficult, as the vascular changes responsible often are irreversible.
A. PH usually develops rapidly in dogs with large left-to-right shunts (<6 months of age), but in cats it may develop more gradually and may be arrested by closure of the defect or management of a stenotic mitral valve.
B. When reactive vasoconstriction is identified, drugs that reduce pulmonary vascular resistance, such as sildenafil *(Viagra)* at initial doses of 0.5 to 2 mg/kg PO BID can be beneficial (although very expensive).
C. Arterial blood pressure must be monitored, as reduced systemic resistance leads to greater right-to-left shunting.
D. Controlling exercise is important to prevent exertional collapse or dyspnea.
V. Management of polycythemia may be required.
A. Balloon valvuloplasty or surgery decreases right-sided pressures and reduces shunting from anatomic obstruction (PS).
1. Drugs can be tried to reduce pulmonary vascular resistance (see above).
2. Care must be exercised with large VSDs, as florid left-to-right shunting can develop if RV pressures approach normal.
B. Phlebotomy may be required in animals with right-to-left shunting and secondary polycythemia (see Chapter 64).
1. While a packed cell volume (PCV) of 62% to 65% is often well tolerated, values >68% to 70% are likely to cause exercise difficulties or predispose to thrombotic stroke or sudden death.
2. Amount of blood removed (mL) = (body weight [kg] × 0.08) × 1000 mL/kg × (actual PCV – desired PVC ÷ actual PCV).
3. Simultaneously administer IV fluids at one to two times the volume removed.
4. Alternatively, remove 10% of blood volume in the morning and 2% to 10% in the afternoon without fluid replacement.
C. When the need for phlebotomy becomes too frequent, reversible bone marrow suppression with hydroxyurea (10 to 20 mg/kg PO SID) may be tried.

Monitoring and Prevention

I. Follow-up care is individualized and based on the specific defect, the severity of disease, prior treatments, and supervening complications.
II. No genetic tests are available to detect carriers of CHD, so genetic counseling for breeding dogs can be difficult.
A. Animals with even mild CHDs should not be bred.
B. Dogs with normal cardiac phenotype that produce CHD-affected puppies in more than one litter are removed from breeding programs.
C. Breeding dogs with equivocal cardiac status based on echocardiographic and Doppler studies are bred only if other important characteristics are considered normal or outstanding.

PATENT DUCTUS ARTERIOSUS

Definition

I. PDA is a persistent patency of the fetal ductus arteriosus, which connects the descending aorta and the main or adjacent left pulmonary artery.
II. This defect is present in approximately 2.5 of 1000 live canine births; it is rare in cats.

Causes

I. PDA is a genetic disorder in many breeds (see Table 8-1); the exact mode of inheritance is undetermined but may be related to multiple genes or modifying genes.
II. Females are predisposed, but both sexes are affected.

Pathophysiology

I. Left-to-right shunting leads to pulmonary overcirculation, volume overload of the left side of the heart, progressive LV dysfunction, and ultimately left-sided CHF.
II. Cardiomyopathy of chronic volume overload (myocardial failure, systolic dysfunction) and atrial fibrillation are common in large-breed dogs with untreated PDA.
III. In a small percentage of cases, reversed shunting is caused by pulmonary vascular injury (Eisenmenger's physiology).

Clinical Signs

I. Most puppies are asymptomatic.
II. Once tachypnea and exercise intolerance develop, left-sided CHF is likely.
III. Exertional rear limb weakness is typical of "reversed" PDA.

Diagnosis

I. A key finding is a continuous cardiac murmur that is loudest over the left craniodorsal cardiac base.
II. The diastolic component of the murmur is less prominent or absent in very young puppies, cats, or cases of progressive PH.
III. Arterial pulses are typically hyperkinetic.
IV. The LV can be enlarged, with palpable caudoventral apical displacement.
V. Pelvic limb weakness that improves with rest, differential cyanosis, loss of the continuous murmur, and a loud second heart sound are typical of reversed PDA.
VI. Radiographs identify pulmonary overcirculation with a left-to-right shunting PDA.
VII. Radiographs and 2D echocardiograms demonstrate dilation of the left atrium, LV, ascending aorta, descending aorta ("ductus bump"), and main pulmonary artery.

VIII. M-mode echocardiography demonstrates eccentric hypertrophy (increased diastolic diameter) and, possibly, reduced LV systolic function (decreased shortening fraction).
IX. Doppler studies demonstrate continuous blood flow in the main pulmonary artery, and mitral regurgitation and pulmonic insufficiency from chamber dilatation.
X. The echocardiogram typically shows enlargement of the LV and possibly the left atrium.
XI. In reversed PDA, diagnostic studies reveal mainly right heart enlargement, dilation of the main pulmonary artery, and reduced pulmonary blood flow, whereas contrast echocardiography (after cephalic vein injection) demonstrates contrast medium in the descending aorta.

Differential Diagnosis

I. Aortopulmonary communication (window) is a congenital connection between the ascending aorta and pulmonary artery, and it may produce a continuous murmur.
II. VSDs with aortic regurgitation, or aortic stenosis with aortic regurgitation can produce both systolic and diastolic murmurs that can be confused with a PDA murmur.
III. Multiple (bronchial artery) systemic to pulmonary fistulas can create a PDA-like situation; however, a continuous murmur is not evident, mandating angiography for diagnosis operation when performed by an experienced surgeon.
IV. Signs of reversed PDA can mimic neuromuscular diseases, particularly myasthenia gravis.

Treatment

I. Early closure is strongly recommended for left-to-right shunting defects, as the 1-year mortality for untreated dogs probably exceeds 60%.
II. For a reversed (right-to-left) shunting PDA, closure of the defect is contraindicated.
III. Thoracotomy and surgical ligation of the ductus is a successful operation when performed by an experienced surgeon.
   A. Closure generally results in complete resolution of signs.
   B. A postoperative murmur of mitral regurgitation is common, but generally subsides by the time of suture removal.
IV. Less-invasive transcatheter techniques for closure of PDAs include insertion of embolization coils and use of various Amplatzer occluding devices.
V. When CHF complicates PDA, medical management is needed (see Treatment under Overview of Congenital Heart Disease).
VI. Reversed PDA has a poor prognosis, although some animals live beyond 5 years of age.
   A. They are affected mainly by pelvic limb weakness during exercise.
   B. They require management of PH and polycythemia.

Monitoring of Animal

I. Early therapeutic intervention can slow or eliminate irreversible myocardial damage and prevent CHF.
II. The prognosis following closure of a PDA is excellent.
   A. A normal lifespan can be anticipated, and most cases do not require any cardiac follow-up.
   B. Exceptions include dogs with marked LV systolic dysfunction, prior CHF, or atrial fibrillation.
III. Monitor clinical signs and PCV in reversed PDA cases.

VENTRICULAR SEPTAL DEFECT

Definition

I. A VSD is a communication between the left and right ventricles, and shunting usually proceeds from the LV to RV.
II. Based on location, a VSD can be classified as para(peri)-membranous, inlet, muscular (trabecular), or subarterial (subpulmonic, supracristal, doubly committed).
III. Large defects are sometimes associated with malalignment of the aorta and are likely to cause aortic root prolapse and valvular regurgitation.
IV. A large VSD is also a component of the tetralogy of Fallot.

Causes

I. VSD is probably caused by genetic factors in some breeds (see Table 8-1).
II. Experimentally, VSD (various species) has been associated with a number of drugs, infections, or environmental factors.

Pathophysiology

I. Most cases of uncomplicated VSD in dogs are well tolerated, as long as the defect is "restrictive."
   A. Most defects that are <50% of the aortic root area are restrictive in nature.
   B. Very large defects are likely to cause CHF and death at approximately 1 to 2 months of age as pulmonary vascular resistance drops (before presentation to a veterinarian).
   C. The shunting physiology of VSD is similar to that of PDA, in that a left-to-right shunt causes pulmonary overcirculation and volume overload of the left atrium and LV.
   D. Large defects complicated by aortic regurgitation are likely to cause CHF.
II. The degree of RV overload depends on the size of the defect, presence of RV outflow tract obstruction, location of the defect, and development of PH.
III. Concurrent PS, a double-chambered RV (a midventricular obstruction), or development of Eisenmenger's physiology can lead to reversed shunting.

Clinical Signs

I. Most dogs and cats are asymptomatic, with occasional cases showing signs of CHF or PH.
II. Cyanosis indicates a complicated VSD.

Diagnosis

I. A systolic murmur, generally loudest over the cranial right sternal edge, is typical of the paramembranous VSD.

II. If the defect is located elsewhere in the septum, or if fibrous tissue partially occludes the defect, a systolic murmur that is apical or loudest over the left sternal edge may occur.
III. Results of radiography are variable, but overcirculation of the lungs is common.
  A. Various combinations of left and right heart enlargement are typical.
  B. The main pulmonary artery can be dilated from increased flow or PH.
IV. The ECG can be normal, or LV enlargement and wide or splintered Q-wave in leads I, II, and aVF may be detected.
V. Echocardiography (2D imaging) demonstrates the defect and Doppler studies delineate the direction and velocity of shunting.
  A. Restrictive defects are characterized by high velocity (>4.5 m/sec) shunting, indicating maintenance of the left-to-right ventricular pressure gradient.
  B. Hemodynamically important defects create significant left-sided volume overload.
  C. It is important to scrutinize the RV for obstructive lesions and the aortic root for malalignment or regurgitation.

Differential Diagnosis

I. Other defects can lead to systolic murmurs on the right side of the thorax, especially tricuspid valve dysplasia and aortic stenosis.
II. Mitral regurgitation can create a similar murmur (in terms of timing).
III. Subpulmonic VSDs create left basilar murmurs that can be confused with PS, aortic stenosis, or mitral regurgitation.

Treatment

I. Most dogs and cats with an isolated, uncomplicated VSD (without severe aortic regurgitation or other lesions) that survive to 4 months of age do not require treatment.
II. Surgical closure of septal defects is the definitive treatment but requires cardiopulmonary by-pass and open heart surgery.
III. Palliative pulmonary arterial banding creates a supravalvular PS and reduces the magnitude of left-to-right shunting; banding is recommended only for those animals with rapidly progressive cardiomegaly and overt or impending CHF.
IV. Transcatheter occlusion devices have been developed for closure of VSDs.
V. If CHF develops, medical management is indicated (see Treatment under Overview of Congenital Heart Disease).
VI. Right-to-left shunting can develop in dogs or cats with VSD from PH (Eisenmenger's complex); valvular or subvalvular PS; or progressive, midventricular fibromuscular obstruction (double-chambered RV).
  A. Exercise intolerance and polycythemia can develop.
  B. Treatment is as described previously for polycythemia.

Monitoring of Animal

I. A small restrictive VSD carries an excellent prognosis for longevity.
II. CHF associated with VSD is uncommon in most small animals.
III. CHF is anticipated in dogs with a VSD, aortic root prolapse, and audible aortic regurgitation.
  A. CHF can develop during middle age from LV volume overload.
  B. Empirical treatment with ACE-inhibitors may be considered.
IV. CHF also develops in some cats with VSD, especially when the defect is nonrestrictive.
V. Infrequently, a VSD closes from fibrous tissue proliferation or adherence of the septal leaflet of the tricuspid valve.
  A. This can lead to a septal aneurysm but without significant shunting.
  B. These lesions are functionally closed.
VI. Yearly cardiology examinations with echocardiography are recommended.

ATRIAL SEPTAL DEFECT

Definition

I. An atrial septal defect (ASD) is a communication between the left and right atria, and shunting usually proceeds from left to right.
II. The location of an ASD determines the classification of the defect.
  A. They are defined as a secundum, primum, or sinus venosus defects.
  B. If the two membranes of the foramen ovale do not close, the functional result is an ASD.
III. A defect in the ventrally located AV septum or the embryonic endocardial cushions can lead to a primum (ventral) ASD, VSD, and malformation of the septal leaflets of the AV valves with regurgitation.

Causes

I. ASD is probably caused by genetic factors in some breeds (see Table 8-1).
II. A patent foramen ovale is created when the two atrial septal membranes are either pulled or pushed apart.
  A. Patency can be maintained by either severe left atrial stretching or from higher-than-normal right atrial pressures that push the membranes apart.
  B. The latter is caused by some other form of right-sided disease (e.g., PS, tricuspid valve malformation).

Pathophysiology

I. A left-to-right shunt with volume overload of the right atrium and RV occurs.
II. Pulmonary overcirculation is also present, but the left atrium typically is normal in size (except with an endocardial cushion defect).
III. A large ASD can cause right-sided CHF or lead to pulmonary vascular injury with PH.
IV. An endocardial cushion defect can cause left-sided or biventricular CHF.

V. Right-to-left shunting can occur across an ASD in the presence of PH or from obstructive lesions on the right side of the heart.
VI. Severe tricuspid regurgitation also can cause cyanosis by raising right atrial pressure and causing right-to-left shunting.

Clinical Signs

I. Most dogs and cats with an isolated ASD are asymptomatic or have nonspecific signs.
II. Pressure differences across an ASD are relatively small; therefore the defect does not cause a murmur other than that of increased flow across the pulmonary valve ("relative" PS).
III. Classically the second heart sound is split, owing to a relatively longer duration of RV ejection.
IV. Occasionally, affected animals have signs of CHF (pleural effusion, ascites) or PH.
V. Cyanosis indicates a complicated ASD.

Diagnosis

I. A systolic murmur is suspicious for CHD.
II. Radiography of an animal with a secundum ASD demonstrates right heart enlargement, dilation of the pulmonary artery, and overcirculation of the lungs; however, left atrial size is variable.
III. With an endocardial cushion defect, significant mitral regurgitation can occur, leading to left heart enlargement or evidence of left-sided CHF on radiography.
IV. ECG shows RV and usually right atrial enlargement with right axis deviation; however, a left cranial frontal axis is more typical of a primum ASD or an endocardial cushion defect.
V. Echocardiography is the diagnostic study of choice.
   A. The septal defect can be observed with 2D imaging, and Doppler studies delineate the direction of shunting, which is often bidirectional.
   B. It is important to scrutinize the RV for obstructive lesions and the AV valves for malformation and regurgitation.
   C. Overreliance on color Doppler imaging for the diagnosis is discouraged, because even normal right atrium (RA) flow patterns can be confusing.

Differential Diagnosis

I. Rule out other causes of systolic murmurs in young dogs, including pulmonic and aortic stenosis.
II. Anomalous pulmonary venous drainage can create a similar physiology and may be associated with a sinus venosus ASD.

Treatment

I. Little experience exists in the management of ASD in dogs and cats, as this defect is relatively uncommon.
   A. With a patent foramen ovale, treatment of the related lesion can cause the defect to functionally close.
   B. Transcatheter atrial septal occlusion devices have been applied to dogs.
   C. Open-heart surgery has been used for successful closure of ASDs, but is not readily available.
II. If CHF develops, medical management is indicated.
III. Right-to-left shunting ASDs may cause exercise intolerance and polycythemia that require treatment.

Monitoring of Animal

I. Yearly cardiology examinations with an echocardiogram are recommended.
II. Radiographs are obtained to monitor endocardial cushion defect cases.
III. Late-onset pulmonary vascular disease with PH or reversed shunting can occur.

TETRALOGY OF FALLOT

Definition and Cause

I. Tetralogy of Fallot is defined as a combination of PS, large (unrestrictive) VSD, dextropositioned aorta, and RV hypertrophy.
II. It is one of the most common causes of cyanotic CHD and has a genetic basis in some breeds (see Table 8-1).

Pathophysiology

I. The presence of PS increases RV systolic pressure and allows shunting of blood from right to left.
II. Depending on the severity of RV outflow obstruction and systemic vascular resistance, blood will shunt from right to left, left to right, or (most commonly) in a bidirectional manner.
III. Right-to-left shunting leads to hypoxemia, cyanosis, and secondary polycythemia.

Clinical Signs

I. The history can include exercise intolerance, syncope, or tachypnea.
II. When the PS is not severe, the condition is well tolerated and shunting is predominately left to right ("pink tetralogy").

Diagnosis

I. A systolic murmur of PS is typically detected over the left heart base.
II. Cyanosis is typical.
   A. Pulse oximetry usually identifies clinically significant desaturation ($SpaO_2$ <90%).
   B. Blood gas analysis reveals hypoxemia, often with Po_2 <65 mm Hg.
III. RV hypertrophy is evident on ECG and imaging studies.
IV. Radiographs demonstrate the following:
   A. RV rounding, a small and straight left heart border on the ventrodorsal projection, and pulmonary undercirculation
   B. The ascending aorta, which can be widened ventrally on the lateral projection (overriding aorta)
V. Echocardiography (2D) is diagnostic and demonstrates the four components of the malformation.

A. Doppler studies show low-velocity shunting across the VSD and high-velocity flow (typically 4 to 5 m/sec) across the proximal pulmonary artery.
B. Contrast echocardiography reveals right-to-left ventricular shunting below the aortic root.

VI. PCV may indicate polycythemia in animals with persistent oxygen desaturation.
VII. Cardiac catheterization is rarely needed to establish the diagnosis.

Differential Diagnosis

I. Tricuspid atresia, pulmonary atresia (pseudotruncus arteriosus), PS with an ASD (or patent foramen ovale), and VSD are other causes of cyanotic CHD.
II. Complex malformations, such as double-outlet RV, can also lead to cyanotic CHD.

Treatment

I. Animals with a sedentary lifestyle often tolerate this disease well, especially if the PS is not too severe.
A. Some animals live for 5 years or longer.
B. Exercise creates vasodilation in skeletal muscle and increases tissue oxygen demands, and may lead to worsening of cyanosis, tachypnea, and exercise intolerance.
II. Sudden death is common from progressive hypoxemia, polycythemia, and cardiac arrhythmias.
III. Drugs that cause systemic vasodilation are avoided, as right-to-left shunting can be exacerbated.
IV. Vasopressors may be needed during anesthesia to avoid systemic hypotension that enhances right-to-left shunting.
V. Beta-blockade with propranolol (starting at 0.25 mg/kg PO TID and increased over 4 weeks to 1 mg/kg PO TID) can be beneficial by reducing exercise-induced RV hypercontractility.
VI. Definitive surgery is rarely done and involves cardiopulmonary by-pass.
VII. Palliative surgery involves the creation of an extracardiac shunt between the systemic and pulmonary circulations (e.g., Blalock-Taussig shunt).
A. Such shunts increase pulmonary flow, improve arterial saturation, and can produce significant clinical improvement.
B. The major limitation is the extent to which these shunts remain patent.
C. Aspirin or other drugs that inhibit platelet activation (e.g., clopidogrel) are indicated.
VIII. Balloon valvuloplasty of a stenotic pulmonary valve can reduce RV pressure, but complete resolution of the PS is contraindicated because it allows for marked left-to-right shunting.
IX. Polycythemia is managed as described previously.

Monitoring of Animal

I. Monitor clinical signs, PCV, and arterial oxygen saturation.
II. Yearly reevaluation is indicated for stable cases.
III. If a palliative shunt has been created, Doppler examination is done to evaluate patency of the shunt.

PULMONIC STENOSIS

Definition and Cause

I. Pulmonic stenosis (PS) is a congenital narrowing of the pulmonic valve, subpulmonic region, or immediate supravalvular tissues.
II. The components of valvular PS include valve thickening, fusion along the valvular commissures, and varying degrees of hypoplasia of the valve.
III. Subvalvular obstruction can be fixed (fibrous) or related to dynamic obstruction from infundibular muscular hypertrophy.
IV. An unusual type of subvalvular PS is associated with a single origin (R2A type) of the coronary arteries from the right sinus of Valsalva.
A. It is most common in English bulldogs.
B. The left coronary artery causes an extramural, subvalvular obstruction.
V. PS is rare in cats.
VI. A genetic basis is responsible for most cases in dogs (see Table 8-1).

Pathophysiology

I. Increased resistance to ejection creates a pressure overload of the RV, with compensatory concentric RV hypertrophy.
II. High-velocity ejection of blood across the stenosis is associated with turbulent flow and poststenotic dilatation of the pulmonary artery.
III. If there is a concurrent patent foramen ovale, ASD, or VSD, then right-to-left shunting can develop.
IV. Cardiac output is limited, and right-sided CHF can occur from diastolic and systolic RV dysfunction, tricuspid regurgitation, and, possibly, atrial fibrillation.

Clinical Signs

I. Most affected dogs are asymptomatic, but fatigue, exercise intolerance, and syncope can be observed in severe cases.
II. If right-sided CHF occurs, abdominal distension develops from ascites.
III. Approximately 30% of dogs with severe PS die suddenly.

Diagnosis

I. The typical ejection murmur of PS is systolic and loudest over the pulmonary valve and craniodorsal left heart base.
A. The more severe the defect, the louder and later the murmur peak.
B. An ejection sound can be detected in valvular PS.
C. A loud holosystolic murmur on the right side is suggestive of tricuspid regurgitation from either RV hypertrophy or concurrent tricuspid valve malformation.
II. Mucous membranes are pink, unless there is right-to-left shunting.
III. A prominent jugular pulse can usually be identified.
IV. Right-sided CHF with hepatomegaly and ascites is found in a small percentage of cases.

V. Rarely, pleural effusion or chylothorax is identified in dogs with CHF.
VI. ECG, thoracic radiography, and 2D echocardiography demonstrate RV enlargement and, often, dilation of the RA.
  A. Imaging reveals poststenotic dilation of the pulmonary artery in severe cases.
  B. The pulmonary circulation is normal to reduced.
VII. Doppler echocardiography shows high-velocity, turbulent flow in the RV outflow tract and the pulmonary artery along with pulmonary insufficiency.
VIII. If RV systolic function is normal (and the animal is not heavily sedated or anesthetized), the peak velocity of ejection correlates with the severity of obstruction.
  A. Velocities <3.5 m/sec (peak gradient <50 mm Hg) indicate a relatively mild stenosis and good prognosis.
  B. Peak velocities >5 m/sec are considered severe (100 mm Hg peak pressure gradient), and carry a guarded to poor prognosis.
IX. Careful examination of the atrial and ventricular septa with color Doppler is needed to exclude a right-to-left shunt, and contrast echocardiography is an efficient way to screen for a defect.
X. Concurrent tricuspid regurgitation is a common finding and can develop from RV overload or from tricuspid valve dysplasia.
XI. Cardiac catheterization is performed mainly in preparation for catheter-based intervention.
XII. Angiography may be required for the identification of a single-origin coronary artery or other vascular anomalies.

Differential Diagnosis

I. Another cause of CHD that creates a systolic murmur or right-sided enlargement
II. Tetralogy of Fallot
III. Functional ejection murmur

Treatment

I. Mild to moderate PS (peak pressure gradients <50 and 100 mm Hg, respectively) generally carry a good prognosis (survival of ≥ 8 years).
  A. Some dogs (75 to 100 mm Hg range) benefit from valvuloplasty.
  B. Severe disease (gradient > 100 mmHg) increases the likelihood of sudden death or CHF.
II. Transcatheter balloon valvuloplasty is the treatment of choice for moderate to severe PS when the lesion is characterized by valvular thickening with commissural fusion.
  A. The procedural mortality is low when performed by experienced operators, and the dilation usually results in a ≥50% reduction of RV systolic pressures.
  B. Successful valvuloplasty of severe stenosis reduces by 50% the risk of sudden death.
  C. Therapy should not be delayed as gradients and muscular hypertrophy can progress with time and growth.
  D. Valvuloplasty is contraindicated in dogs with a single origin of the coronary artery.
III. When PS is complicated by severe RV hypertrophy or subvalvular fibromuscular obstruction, balloon valvuloplasty is combined with propranolol or atenolol (1 mg/kg PO BID), sometimes for life.
IV. Surgical techniques include patch grafting, pulmonary valve repair or resection, or surgical dilation.
  A. They are indicated for cases of severe fibromuscular RV obstruction, broad subvalvular fibrous ring, or in dogs in which PS is complicated by marked pulmonary valvular hypoplasia.
  B. An RV to pulmonary artery conduit can be used to bypass a hypoplastic valve or stenosis related to an anomalous coronary artery.
V. In cases that cannot be treated more definitively, atenolol provides empirical cardiac protection.
VI. PS with patent foramen ovale, ASD, or VSD can progress to right-to-left shunting with polycythemia, which requires treatment.

Monitoring of Animal

I. In cases of mild, stable PS, reevaluation may not be necessary in dogs > 1 year of age.
II. Dogs with moderate to severe PS are examined yearly with Doppler echocardiography so that the pressure gradient, competency of the tricuspid valve, and RV systolic and diastolic function can be monitored.

SUBAORTIC STENOSIS

Definition and Cause

I. Aortic stenosis (AS) is a congenital narrowing of the LV outflow tract.
  A. The condition is common in dogs and rare in cats.
  B. The most common location for obstruction is the subvalvular portion of the outflow tract SAS.
II. Valvular AS occurs in some dogs and is characterized by thick or fused aortic valve leaflets or by the presence of fused bicuspid leaflets.
III. Subvalvular obstruction is typically fixed (fibrous).
  A. Dynamic obstruction of the outflow tract can be caused by a malformation of the mitral valve leading to systolic anterior motion of the mitral valve.
  B. This form of SAS is labile and worsens with elevated sympathetic tone.
IV. Intramural coronary arteries are abnormal in SAS and reduce the blood supply to the myocardium.
V. Dogs with AS are at a higher risk for infective endocarditis.
VI. SAS is a genetic disorder in many dogs (see Table 8-1).

Pathophysiology

I. Pressure overload of the LV is created, with increased systolic pressure needed to eject blood across the stenotic zone.
II. This pressure is generated by concentric hypertrophy of the LV.
III. High-velocity ejection is associated with poststenotic turbulence and dilation in the ascending aorta.

IV. Coronary arterial insufficiency can lead to subendocardial ischemia, which predisposes to exercise intolerance and cardiac arrhythmias.
V. Cardiac output is limited, and left-sided CHF can develop from diastolic and systolic LV dysfunction, mitral regurgitation, and, possibly, atrial fibrillation.
VI. Syncope or sudden death can be triggered by exertion, especially from ventricular arrhythmias or from stimulation of ventricular mechanoreceptors (cardiac baroreceptor reflex).

Clinical Signs

I. Most affected dogs are asymptomatic, but fatigue, exercise intolerance, and syncope can be observed in severe cases.
II. If CHF occurs, tachypnea and other respiratory signs arise from pulmonary edema.

Diagnosis

I. The typical ejection murmur of AS is systolic and loudest over the aortic valve and subaortic areas.
   A. In SAS, the more severe the defect, the louder and later peaking of the murmur, and the more likely a prominent right-sided component (along with radiation into the carotid arteries) will be evident.
   B. The murmur of a true valvular AS is often loudest over the right dorsal heart base.
   C. A loud, holosystolic murmur over the apex may be indicative of concurrent mitral regurgitation.
II. The femoral pulse is late-rising and weak with moderate to severe AS.
III. Overt left-sided CHF occurs in a small percentage of cases.
IV. ECG, thoracic radiography, and 2D echocardiography may demonstrate LV enlargement in moderate to severe cases and, less often, dilation of the LA.
   A. Cardiac size may appear normal on thoracic radiographs.
   B. Concentric LV hypertrophy and subendocardial hyperechogenicity consistent with fibrosis is identified by 2D imaging with severe and sometimes moderate SAS.
   C. Imaging often reveals poststenotic dilation of the ascending aorta (on the right of the midline) in severe cases.
   D. The pulmonary circulation is normal to prominent.
   E. The finding of left atrial dilation is a poor prognostic sign and indicates either LV failure, mitral valve disease, or a left-to-right shunt.
V. Doppler echocardiography shows high-velocity, turbulent flow in the LV outflow tract and the ascending aorta, with the most accurate velocities obtained from a subcostal transducer position.
   A. If LV systolic function is normal (and the animal is not heavily sedated or anesthetized), the peak velocity of ejection correlates with the severity of obstruction.
   B. Peak velocities >4.5 to 5 m/sec are considered severe (>80 to 100 mm Hg peak pressure gradient), and carry a guarded to poor prognosis.
   C. Color and spectral Doppler examination reveal aortic regurgitation (generally silent on auscultation).
   D. The diagnosis of trivial AS by Doppler methods only is controversial.

Differential Diagnosis

I. Other causes of CHD that create a systolic murmur or left-sided enlargement: VSD, mitral valve malformation
II. Other causes of a left-sided murmur: PS, ASD
III. Functional ejection murmur

Treatment

I. Transcatheter balloon dilation of the stenotic orifice reduces LV pressure gradients by 40% to 50%, but does not appear to provide any survival benefit over beta-blockade with atenolol.
II. Open surgical resection of the stenotic lesion provides the best long-term reduction of pressure gradients, but clinical results have been disappointing.
III. With atenolol (1 to 2 mg/kg PO BID) a median survival of >4 years has been observed in some dogs, even with severe SAS (gradients >120 mm Hg).
   A. Atenolol is recommended for all dogs with peak gradients >50 mm Hg.
   B. Beta-blockade of a dynamic SAS caused by mitral valve malformation alleviates the obstruction and allows regression of LV hypertrophy.
IV. Dogs with even mild disease are at higher risk for development of infective endocarditis; therefore, prophylactic antibiotics are administered during elective surgical procedures or whenever wound contamination occurs.

Monitoring of Animal

I. In mild, stable SAS, reevaluation may not be necessary.
II. Dogs with moderate to severe SAS are examined annually with Doppler echocardiography, so the pressure gradients, competency of the aortic and mitral valves, and LV systolic and diastolic functions can be monitored.
III. Giant-breed dogs are evaluated just before full maturity, as the severity of the obstruction can increase dramatically during the first year of life.
IV. Severe SAS carries a poor prognosis, owing to premature death.
   A. Sudden death from cardiac arrhythmias and progressive LV dysfunction are typical outcomes.
   B. Mature dogs with mild SAS are more likely to live normal lives, although some still experience sudden death.

ATRIOVENTRICULAR VALVULAR DYSPLASIA

Definition

I. Dysplasia or malformation of the mitral or tricuspid valves includes a number of morphologic abnormalities of the AV valve apparatus, such as malformed papillary muscles; excessively short or long chordae tendineae; abnormal valve leaflets and cusps; and fusion along valve commissures.

II. The functional outcome is valvular regurgitation (most common), valvular stenosis with obstruction to ventricular filling, or both.
   A. Severity can range from trivial to life threatening.
   B. Concurrent defects, such as an ASD or patent foramen ovale, may occur.
   C. Tricuspid dysplasia in Labrador retrievers can be associated with anomalous conduction that predisposes to reentrant supraventricular tachycardias.

Causes

I. AV valve dysplasia is most likely a genetic disorder in dogs (see Table 8-1).
II. The mode of inheritance is likely autosomal dominant with incomplete penetrance in Labrador retrievers with tricuspid dysplasia.

Pathophysiology

I. AV valve regurgitation causes volume overload of the affected side of the heart.
   A. Chronic, severe regurgitation leads to CHF.
   B. Atrial dilatation predisposes to atrial arrhythmias, including atrial fibrillation.
II. The pathophysiology of AV valve stenosis is more complicated.
   A. The outcome of severe dysplasia may include CHF of the affected side.
      1. Atrial arrhythmias are also very common.
      2. If the stenotic valve is competent, ventricular function is relatively normal.
   B. Acute pulmonary capillary hypertension can lead to acute edema and hemoptysis.
   C. In cases of mitral stenosis, reactive changes in the pulmonary vasculature can lead to significant PH with RV hypertrophy and limited exercise capacity (most common in cats).
   D. In tricuspid stenosis (or severe regurgitation) there is a high potential for continued patency of the foramen ovale, which can lead to right-to-left shunting, arterial hypoxemia, and cyanotic heart disease.

Clinical Signs

I. Clinical signs can be absent until the onset of CHF or atrial fibrillation.
II. Astute clients generally recognize some exercise intolerance.
III. With trivial or mild malformations, the dog is normal.
IV. With tricuspid dysplasia and a patent foramen ovale, fatigue and obvious cyanosis may be noted.

Diagnosis

I. The most common finding is a systolic murmur of AV valvular regurgitation over the affected valve area; however, a mild AV valve malformation may not cause an obvious murmur.
II. Diastolic murmurs of AV valve stenosis are usually very soft and easily missed.
III. Mucous membranes are pink, unless there is right-to-left shunting.
IV. Definitive diagnosis requires careful 2D echocardiographic imaging of the affected valve, combined with Doppler studies.
   A. Diagnosis of subtle AV valvular malformations is often difficult and controversial.
   B. Characteristic Doppler flow patterns can be identified for valvular stenosis and regurgitation.
   C. The severity of the disease can be gauged with noninvasive ultrasound studies.
V. With mitral valve dysplasias changes are most evident on the left side of the heart.
   A. With mitral regurgitation, radiography, ECG, and 2D echocardiography demonstrate LV and LA dilatation.
   B. With mitral stenosis, marked left atrial dilation and possibly PH with secondary RV hypertrophy are evident.
   C. Atrial fibrillation is common and can precipitate clinical signs.
   D. CHF with pulmonary edema is a common finding.
VI. With tricuspid valve dysplasia, right-sided atrial and ventricular enlargement is typical.
   A. Right-sided CHF with hepatomegaly and ascites is found in advanced cases.
      1. Atrial fibrillation is common.
      2. Rarely, pleural effusion or chylothorax is identified in dogs.
   B. A prominent jugular pulse can usually be identified.
   C. Notched or "splintered" R-waves are observed on ECG in dogs, along with occasional reentrant supraventricular tachycardias or ventricular preexcitation.
   D. Cyanosis, arterial hypoxemia, and polycythemia are common when severe dysplasia is complicated by an ASD.
VII. Cardiac catheterization is rarely needed to establish the diagnosis.

Differential Diagnosis

I. Dogs can survive for many years with AV valvular malformation, so acquired disorders, such as myxomatous valvular degeneration (endocardiosis), dilated cardiomyopathy, and infective endocarditis, may also develop.
II. Endocardiosis, PH, and right-sided cardiomyopathies can lead to tricuspid regurgitation and must be distinguished from tricuspid dysplasia.
III. For cyanotic animals, the differential diagnosis is similar to that for tetralogy of Fallot.
IV. AV stenosis can also arise from an obstructive fibrous or fibromuscular ring situated above the mitral or tricuspid valve (called *supravalvular mitral/tricuspid ring*).
V. Tricuspid stenosis can be confused (or occur along) with an obstructive partitioning of the RA, termed *cor triatriatum dexter.*
   A. In this malformation, the caudal RA is separated from the tricuspid orifice by a persistent membrane with a small orifice.
   B. Vena caval blood flow is obstructed and leads to hepatomegaly and ascites.

C. A similar condition can rarely occur in the LA (cor triatriatum sinister), leading to pulmonary venous obstruction.

Treatment

I. Balloon valvuloplasty has been variably successful in dogs with tricuspid and mitral valvular or supravalvular stenosis.
II. Surgical repair or annular support of affected valves can be attempted.
III. Replacement or repair of dysplastic valves has been performed successfully with cardiopulmonary by-pass.
IV. Most cases are treated medically when signs of CHF or atrial fibrillation develop.
   A. Use of an ACE-inhibitor (enalapril) and a beta-blocker (carvedilol, metoprolol) may be considered for dogs with severe mitral regurgitation and associated cardiomegaly.
   B. Heart rate control and avoidance of tachycardia is important to improve ventricular filling in animals with stenotic AV valves.
      1. Beta-blockers may be beneficial in preventing sinus tachycardia.
      2. Diltiazem may be useful for atrial fibrillation.
   C. Animals with stenotic AV valves may be sensitive to diuretic therapy, as ventricular filling depends on higher atrial pressures; however, such therapy may be life saving for peracute pulmonary edema with hemoptysis.
V. Tricuspid malformation associated with an ASD can lead to right-to-left shunting, so manage any secondary polycythemia (discussed previously).
VI. Mild mitral or tricuspid valvular dysplasia is often well tolerated; however, severe lesions lead to CHF and arrhythmias.
   A. Dogs with severe mitral disease usually develop CHF in early to middle age, particularly when the valve is both stenotic and incompetent.
   B. Many dogs with relatively severe tricuspid regurgitation survive for 7 to 8 years before CHF ensues.

Monitoring of Animal

I. The course of disease can be relatively long, especially with tricuspid dysplasia.
II. Severe AV valvular stenosis often causes signs within the first 1 to 2 years of life.
III. For asymptomatic dogs and cats with moderate to severe disease, a cardiology evaluation and echocardiography are preformed at least yearly.

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CHAPTER 9

Acquired Atrioventricular Valvular Disease

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DEGENERATIVE DISORDERS

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Atrioventricular Valvular Degeneration

Definition

I. Pathologic degeneration of the atrioventricular (AV) valves is characterized by the accumulation of glycosaminoglycans (myxomatous proliferation) and fibrosis of the valve leaflets and tendinous chordae.
II. Valvular degeneration leads to insufficient coaptation of the valve leaflet, valvular regurgitation, and eventually congestive heart failure (CHF) in some animals.
III. The degeneration most commonly involves the mitral valve, with or without involvement of the tricuspid valve.
IV. Isolated tricuspid degeneration occurs but is less common.
V. It has been given many names, including endocardiosis, chronic degenerative valvular disease, chronic valvular disease, chronic valvular fibrosis, and acquired mitral or tricuspid regurgitation or insufficiency.

Causes

I. The primary (inciting) cause of myxomatous degeneration is currently unknown.
II. The primary factor may be a defect in the quality of connective tissue (ground substance) within the valve.
III. There is no scientific evidence of any association between the disease and vaccination routines or hematological spread of bacteria from the oral cavity.
IV. AV valvular disease is the most common cardiac disease in dogs, and accounts for the highest cardiac-related mortality (Egenvall et al., 2006).
    A. The disease occurs in all breeds, but is most common in small- to medium-sized dogs, such as the papillon, poodle, Chihuahua, dachshund, and Cavalier King Charles spaniel (Egenvall et al., 2006).
    B. The condition is common in older dogs.
        1. Age of onset is inherited as a polygenetic trait (Swenson et al., 1996; Olsen et al., 1999).
        2. Males have an earlier onset and progress more rapidly than females (Häggström et al., 2004; Egenvall et al., 2006).
    C. The major role played by genetic factors suggests that other factors (level of exercise, degree of obesity, diet) play only a small role.
    D. The prevalence of acquired mitral valve disease in cats without primary myocardial disease is unknown, but it is low and rarely clinically important.

Pathophysiology

I. Myxomatous degeneration
    A. The primary defect leads to abnormal valve motion with prolapse of the leaflets, which in turn increases the shear stress imposed on the leaflets, both directly (abnormal leaflet apposition) and indirectly (increased regurgitant flow).
    B. Regurgitation and valve stress leads to endothelial damage and subsequent activation of fibroblasts in the valve (Black et al., 2005).
    C. This activation causes subendothelial deposition of glycosaminoglycans and fibrosis, leading to further distortion of valve morphology and regurgitation (Black et al., 2005).
II. Valve regurgitation and heart failure
    A. With progression, the valvular lesions cause insufficient coaptation of the leaflets, leading to regurgitation into the atrium.
    B. Severity and progression of AV valve regurgitation depends on the severity and progression of the valvular lesions (Olsen et al., 1999; Pedersen et al., 1999b).
    C. Ventricular dilatation further increases the regurgitation by causing secondary valvular insufficiency.
    D. Compensatory mechanisms include cardiac dilatation, eccentric hypertrophy, increased force and rate of contraction, increased heart rate, increased pulmonary lymphatic drainage (left-sided AV valve regurgitation), fluid retention, and neurohormonal modulation of cardiovascular function (Häggström et al., 2005).
    E. With progression, compensation is no longer possible and leads to reduced cardiac output and increased venous pressures with subsequent pulmonary edema (left-sided CHF) or ascites (right-sided CHF).

Clinical Signs

I. Chief complaints
   A. A murmur may be an incidental finding, with no clinical signs of disease caused by the valvular regurgitation.
   B. Valvular regurgitation may cause cardiac compression of the main stem bronchi.
      1. Cough
      2. Tachypnea, dyspnea
      3. Syncope in conjunction with paroxysms of coughing, often triggered by excitement or exercise
   C. Syncope may occur as a consequence of intermittent supraventricular tachycardia.
   D. Valvular regurgitation may cause clinical signs of CHF (most commonly left-sided).
      1. Cough: often worse in the morning or evening hours
      2. Tachypnea, dyspnea, orthopnea
      3. Lethargy, anorexia
      4. Reduced exercise tolerance
      5. Syncope
      6. Weight loss
      7. Ascites (right-sided CHF)
   E. Sudden death may occur as a consequence of an acute complication (see Monitoring of Animal), but is uncommon, especially in the absence of clinical signs of CHF.

II. Physical examination findings in asymptomatic animals
   A. A systolic click (early stage) is a high-pitched, sharp sound between S1 and S2 heart sounds.
   B. An apical systolic heart murmur is present with mitral or tricuspid regurgitation.
   C. A soft early, late, or holosystolic murmur (grade I-II/VI) is consistent with mild regurgitation.
   D. A loud murmur (grade IV-VI/VI) is consistent with moderate to severe regurgitation (Häggström et al., 1994).

III. Physical examination findings in symptomatic animals
   A. Loud heart murmur (grade IV-VI/VI) and loud first heart sound, unless there is significant myocardial failure
   B. Tachycardia and loss of respiratory sinus arrhythmia
   C. ± Arrhythmia, most commonly supraventricular, premature beats or atrial fibrillation
   D. Weak femoral pulses, pulse deficits
   E. Prolonged capillary refill time, pale mucous membranes
   F. Tachypnea, dyspnea, orthopnea
   G. ± Respiratory crackles (rales) from pulmonary edema
   H. Pink froth in the nostrils and oropharynx from pulmonary edema (fulminant CHF)
   I. Ascites and jugular venous distension with right-sided CHF

Diagnosis

I. Auscultatory findings of a systolic click and/or a left apical systolic murmur compatible with mitral regurgitation (MR) in a geriatric dog of a typical breed are highly suggestive of myxomatous valve disease.
   A. A low-intensity murmur (grade I-II), with or without a systolic click in an otherwise healthy dog, usually indicates low disease severity.
   B. A high-intensity murmur (grade IV-VI) and increased intensity of S1 indicates a more advanced stage of disease.

II. Echocardiographic findings include thickening or prolapse of the AV valve and identification of a regurgitant jet on spectral or color flow Doppler (Box 9-1).
   A. Determination of severity of MR involves assessment of the magnitude of left atrial (LA) dilation and left ventricular (LV) eccentric hypertrophy.
   B. Size of the regurgitant jet on color Doppler may be used to semiquantify the severity of MR (Kittleson et al., 1998; Kittleson et al., 2003).
   C. Unlike small breed dogs, large breed dogs less commonly have severe valve prolapse and thickening.

III. Presence of tachyarrhythmias, such as atrial fibrillation or ventricular ectopy on electrocardiography usually indicates severe disease, presence of complications (acute chordal rupture or myocardial infarction), or other concurrent cardiac disease.

IV. Supraventricular premature complexes are the most common arrhythmia.

V. Radiographic findings include left-sided cardiomegaly and LA dilation in dogs, with moderate or severe MR.

Box 9-1

Echocardiographic Findings in Dogs with Myxomatous Mitral Valvular Disease

Abnormality	Echocardiographic Finding
Severe valvular disease (poor prognosis)	Severe prolapse (>2 mm), valvular thickening, ruptured chordae tendineae, valve flailing
Size and velocity of regurgitant jet	Color Doppler semiquantitative Jet size <30% of LA size = mild MR Jet size >50% of LA size = severe MR Large jet with velocity <5-6 m/sec indicative of increased LA pressure
Left atrial dilation in mild MR	LA:Ao >1.5 = mild LA dilation
Severe LA dilation, high likelihood of CHF	LA:Ao >2 = severe LA dilation
LV volume overload in moderate or severe MR	↑ LV internal diastolic diameter ↑ Fractional shortening (>40%) Hyperdynamic contractions
LV systolic failure in large dogs with mild MR or in small dogs with chronic severe MR	↑ End systolic diameter Normalized or ↓ fractional shortening ↑ EPSS (>6 mm)
Pulmonary hypertension (uncommon)	Right atrial and ventricular enlargement, tricuspid regurgitation TR velocity >2.8 m/sec PI velocity >2.2 m/sec (Johnson et al., 1999)

LA, Left atrium; *MR,* mitral regurgitation; *CHF,* congestive heart failure; *LA:Ao,* left atrial to aortic root diameter; *LV,* left ventricle; *EPSS,* E point to septal separation; *TR,* tricuspid regurgitation; *PI,* pulmonic insufficiency

A. Vertebral heart score of >10.5 is indicative of cardiac enlargement (Buchanan and Bücheler, 1995).
B. Left-sided CHF causes perihilar to caudodorsal pulmonary infiltrates (interstitial, mixed, or alveolar pattern) and pulmonary venous distention.
C. Compression of the left mainstem bronchus causes widening of the left bronchial angle at the body of the LA on dorsoventral and ventrodorsal views and splitting of the bronchi on the lateral view.

VI. Blood pressure (BP) is measured to identify dogs with hypertension (>160 mmHg), because MR is worsened by increased afterload.
VII. Hematology and biochemistry panels are usually unremarkable in mild cases, but more serious cases may have mildly increased liver enzymes and evidence of prerenal azotemia.
VIII. Serum troponin I levels are normal (usually <0.07 ng/mL) in mild cases.
A. Levels are mildly to moderately increased with moderate to severe disease.
B. Severe elevations indicate myocardial ischemia, myocarditis, or infarction (Oyama et al., 2004).
IX. Measurement of natriuretic peptides is often unremarkable in mild cases.
A. Moderate to severe disease is associated with increased levels (Häggström et al., 2000).
B. Plasma concentration of brain natriuretic peptide may be useful to differentiate dogs with CHF-related dyspnea from other causes.

Differential Diagnosis

I. Other causes of systolic heart murmurs
A. Secondary MR from dilated or hypertrophic cardiomyopathy
B. Congenital heart diseases, especially mitral valve dysplasia
C. Infective endocarditis of the AV valve
D. Anemia
E. Physiological flow (innocent) murmur
1. Soft (grade I-II/VI) early systolic murmur
2. Localized to the basilar region or poorly localized to the left side

II. Other causes of respiratory distress
A. Primary respiratory diseases: bronchitis, pneumonia, tracheal/bronchial collapse, neoplasia, others
B. Pleural effusion
C. Noncardiogenic pulmonary edema
D. Anemia

III. Other causes of reduced exercise capacity, lethargy, and muscle wasting
A. Musculoskeletal diseases: chronic degenerative joint disease, intervertebral disc disease, neuromuscular disease, others
B. Other systemic diseases: renal or hepatic failure, neoplasia, anemia

IV. Other causes of episodic weakness and/or syncopal-like signs
A. Seizures
B. Primary arrhythmias

Treatment

I. Asymptomatic disease
A. Treatment is not indicated in the absence of clinical signs.
B. Surgical repair or valve replacement is usually not technically or economically feasible.
C. No treatment has been shown to slow or halt disease progression (Kvart et al., 2002; Häggström et al., 2004).

II. Symptomatic disease
A. Goal is to alleviate clinical signs and improve quality of life and life expectancy.
B. Treatment involves eliminating pulmonary edema and/or ascites, improving hemodynamic flow, controlling heart rate, reducing aortic impedance, providing inotropic support, and protecting the heart from detrimental exposure to neurohormones.

III. Treatment of dogs with compression of mainstem bronchus and no evidence of CHF on radiographs
A. Cough suppressants
1. Hydrocodone bitartrate 2.5 to 10 mg/dog PO BID to QID
2. Butorphanol 0.55 to 1.1 mg/kg PO BID to QID
B. Arterial vasodilators to reduce afterload, regurgitant fraction, and LA size
1. The goal is to reduce the systolic blood pressure by 10 to 20 mm Hg compared with baseline in normotensive dogs.
2. Goal in hypertensive dogs is to reduce the systolic blood pressure to <140 mm Hg (Kittleson MD et al., 1983).
3. Hydralazine is given at 1 to 2 mg/kg PO BID; gastrointestinal side effects are common.
4. Amlodipine is given at 0.1 to 0.3 mg/kg PO SID to BID.

IV. Treatment of acute heart failure
A. Diuresis with furosemide
1. Dose for moderate CHF: 2 to 4 mg/kg IV, IM, SC, PO BID to TID
2. Dose for severe or fulminant CHF: 4 to 8 mg/kg IV, IM, SC every 2 to 6 hours
B. Oxygen supplementation and cage rest with 60% oxygen, then decreased to <50% after 12 hours
C. Nitroglycerine ointment 4 to 12 mg topically BID to TID
1. Apply inside the pinna while wearing gloves.
2. Whether it actually causes venodilation in dogs is controversial (Parameswaran et al., 1999).
D. Arterial vasodilators
1. In animals with severe CHF that do not respond to aggressive diuresis with furosemide, an arterial vasodilator is used to reduce afterload.
2. Hydralazine (1 to 3 mg/kg PO BID) causes acute vasodilation within 30 minutes.
a. Monitor BP every 1 hour initially.

b. Repeat dose if BP has not decreased by 15 to 20 mm Hg.
c. If no change in BP occurs, increase to maximum cumulative dose of 3 mg/kg.
d. Total cumulative dose is then given BID.
e. Reduce dose by 50% in dogs on angiotensin converting enzyme (ACE) inhibitors (Kittleson, 1985).

3. Amlodipine (0.1 to 0.3 mg/kg PO SID to BID) causes vasodilation in 4 to 6 hours, so is not used for fulminant CHF.
4. Sodium nitroprusside (1 to 5 μg/kg/min IV as a constant rate infusion; maximum 10 μg/kg/min IV) is a potent vasodilator that acts within minutes and must be carefully monitored with BP measurements (preferably direct arterial BP).

E. Pimobendan 0.3 to 0.5 mg/kg PO BID
F. Abdominal paracentesis for moderate or severe ascites

V. Treatment of chronic heart failure
A. Choice of drug(s) depends on disease severity and clinical signs.
B. Diuretics are used when there is evidence of CHF on thoracic radiographs or as a preventative in dogs with previous episodes of CHF.
1. Furosemide
a. Dose for mild to moderate CHF: 1 to 3 mg/kg PO SID to BID
b. Dose for moderate to severe CHF: 2 to 4 mg/kg PO BID to TID
c. Doses incrementally increased as needed
d. Maximum effective dose: 4 mg/kg PO TID
2. Spironolactone 2 mg/kg PO SID to BID
a. It is a weak diuretic and is used as adjunctive therapy with furosemide.
b. It may reduce potassium loss in animals receiving furosemide.
3. Hydrochlorothiazide (2 to 4 mg/kg PO BID) for animals with refractory CHF already receiving high furosemide doses

C. ACE inhibitors are indicated once CHF develops.
1. They may improve quality of life, cause minimal to mild reductions in BP, and are not used primarily as vasodilators.
2. They exert modest, positive effects over weeks to months and are not used in acute CHF.
3. They may cause significant azotemia if given to a dehydrated animal that has been treated aggressively with diuretics.
4. Functional azotemia may be seen in a small percentage of dogs and is reversible once the ACE inhibitor is stopped.
5. A renal panel is indicated prior to starting ACE inhibitors, and repeated in 1 to 2 weeks, with discontinuation if moderate or severe azotemia is detected.
6. Doses are as follows:
a. Enalapril 0.5 mg/kg PO BID
b. Benazepril 0.25 to 0.5 mg/kg PO SID
c. Ramipril 0.25 to 0.5 mg/kg PO SID

D. Pimobendan is a phosphodiesterase III inhibitor that acts as a vasodilator and a positive inotrope.
1. Pimobendan is approved in Canada and most European countries, but not in the United States.
a. It may be imported on a compassionate use basis, with permission from the Food and Drug Administration.
b. The approval process takes at least 4 weeks.
2. Hemodynamic effects include reduction in systemic and pulmonary vascular resistance, positive lusitropic (improves diastolic function) and inotropic activity, reduction in LV filling and LA pressure, and improvement in myocardial contractile efficiency without increasing oxygen consumption.
3. It significantly reduces mortality and improves the quality of life in dogs with CHF (Smith et al., 2005; Lombard et al., 2006).
4. Dosage is 0.3 to 0.5 mg/kg PO BID; the presence of food reduces absorption.
5. Side effects include tachycardia and gastrointestinal upset, which are dose related.
6. Contraindications are hypertrophic cardiomyopathy or conditions in which increased stroke volume is not possible owing to functional or anatomical obstructions (e.g., aortic stenosis).
7. It should not be combined with a calcium-channel blocker.

E. Digoxin (0.005 to 0.01 mg/kg or 0.22 mg/m^2 PO BID) is administered to control heart rate if a tachyarrhythmia, such as atrial fibrillation, is present, and may be used in dogs with moderate or severe myocardial failure and MR.
F. Tachyarrhythmias, such as atrial fibrillation, may require therapy with beta blockers or calcium channel blockers, but these drugs must be used with caution because they are negative inotropes (see Chapter 6).
G. Avoid food with high sodium content, such as salty table foods, cured meats and cheeses, and salty dog treats (sausage or bacon flavor).
H. Low-salt, cardiovascular diets (0.15 to 0.2 g Na/1000 kcal) can be used in animals receiving high diuretic doses for refractory, chronic CHF.
1. Such diets help limit sodium and water retention and are used in conjunction with standard medical therapy.
2. Some dogs find these diets less palatable (Rush et al., 2000).

I. Affected dogs are allowed walks, but strenuous exercise is avoided.

Monitoring of Animal

I. Frequency of recheck examinations depends on the severity of valvular insufficiency and clinical signs.
II. Asymptomatic dogs with slight to moderate regurgitation are rechecked every 6 to 12 months, and those with

moderate to severe regurgitation are rechecked every 3 months.

III. After control of acute CHF and discharge from the hospital, reexamination is scheduled in 1 to 2 weeks.
   A. Monitor for resolution of clinical signs, level of hydration, electrolytes, renal function, thoracic radiographic evidence of CHF, and the presence of complications.
   B. If the dog is stable, rechecks are scheduled every 3 to 6 months thereafter, with more severe cases requiring more frequent monitoring.

IV. Complications to monitor for include the following:
   A. Asymptomatic dogs may develop CHF.
   B. Dogs stabilized by medical therapy often develop recurrent CHF.
   C. Dogs with initially left-sided CHF may develop biventricular CHF, with pulmonary hypertension and ascites.
   D. Arrhythmias, especially atrial fibrillation, may occur and may worsen CHF.
   E. Rupture of the chordae tendinae may cause life-threatening pulmonary edema or sudden death.
   F. An atrial tear may lead to an acquired atrial septal defect or pericardial effusion and cardiac tamponade.
   G. Formation of an intracardiac thrombus or large myocardial infarction are rare events.
   H. Small infarcts caused by arteriosclerotic changes are common, but their clinical significance is currently unknown (Häggström et al., 2005).

V. Prognosis and outcome are highly variable.
   A. Dogs without signs of CHF may remain asymptomatic for several years.
      1. Risk factors for progression from mild to severe disease include the severity of valvular lesions, increasing age, and male gender.
      2. Risk factors for the onset of CHF include regurgitation severity, LA size, and elevations of natriuretic peptides (Häggström et al., 2000).
   B. The prognosis for dogs with CHF (acute or stabilized) is dependent on age, severity of failure, and presence of other diseases (e.g., renal failure).
   C. Clinical trials have shown a mean survival time after onset of CHF of 8 to 10 months, but survival time may vary from days to years (Ettinger et al., 1998; BENCH Study Group, 1999).

INFECTIOUS DISORDERS

Kristin MacDonald

Endocarditis

Definition

I. Infective endocarditis is caused by invasion of a microbe into the endothelium of the valves of the heart, resulting in proliferative or erosive lesions, and, consequently, valvular insufficiency.

II. Endocarditis has a low incidence in dogs, and is extremely rare in cats.

III. The mitral and aortic valves are almost exclusively infected.

Causes

I. Predisposing factors
   A. Bacteremia from diskospondylitis, prostatitis, pneumonia, urinary tract infections, pyoderma, periodontal disease, and long-term, indwelling central venous catheters
   B. Subaortic stenosis (SAS) (Sisson and Thomas, 1984)
   C. Possible increased risk associated with corticosteroid use (Calvert, 1982)

II. Etiologic agents
   A. The most common bacterial isolates are *Staphylococcal* spp. (*S. aureus, S. intermedius,* coagulase positive, and coagulase negative), *Streptococcus* spp. (*S. canis, S. bovis*, and beta-hemolytic), and *Escherichia coli*.
   B. Other less common bacteria include *Pseudomonas* spp., *Erysipelothrix rhusiopathiae, Enterobacter* spp., *Pasteurella* spp., *Corynebacterium* spp., and *Proteus* spp.
   C. Since many dogs are currently receiving antibiotics at the time of blood culture, most cases (60% to 70%) are culture negative (MacDonald et al., 2004; Sisson and Thomas, 1984).
   D. *Bartonella* spp. is a fastidious, intracellular bacteria that has emerged as an important cause of endocarditis in dogs.
      1. *Bartonella* spp. were identified in 28% of affected dogs and 45% of dogs with negative blood cultures (MacDonald et al., 2004).
      2. *Bartonella vinsonii berkhoffii* is the most common species isolated, followed by *B. henselae, B. clarridgeiae, B. clarridgeiae*-like, and *B. washoensis* (MacDonald et al., 2004).

Pathophysiology

I. The inciting event is bacterial adherence to the valve.
   A. Disruption of the endothelial surface may occur secondary to inflammatory or mechanical (SAS) causes.
   B. A coagulum of fibrinogen, fibrin, platelet proteins, and fibronectin forms and avidly binds bacteria, and shields them from host defense and antibiotics.
   C. Bacteria may secrete destructive enzymes that erode the valve.

II. Severe mitral or aortic valvular insufficiency leads to elevated LV end-diastolic pressure, LA pressure, and pulmonary capillary wedge pressure, with subsequent left heart failure.

III. Affected animals may develop high titers of antibodies against the offending bacteria.
   A. Immune complexes form, and consist of immunoglobulin (Ig) M, IgG, and complement.
   B. Rheumatoid factor may also be increased, which impairs the ability to solubilize immune complexes.
   C. Immune complexes are deposited in the basement membrane and cause further complement activation and tissue destruction.

D. Immune-mediated glomerulonephritis, polyarthritis, and skin diseases are common sequelae.

IV. Septic or aseptic thromboembolism frequently occurs to the kidney, spleen, heart, brain, systemic arteries, and other organs.

Clinical Signs

I. Medium to large breed, middle-aged to older male dogs are most commonly affected.

II. The most common clinical sign is lameness (44%), followed by lethargy, anorexia, respiratory abnormalities, weakness, and collapse (MacDonald et al., 2004).

III. Cardiovascular abnormalities are commonly found.
   A. A murmur is present in most (89% to 96%) dogs (MacDonald et al., 2004; Calvert, 1982).
      1. A left apical holosystolic murmur occurs with MR.
      2. A left basilar diastolic murmur and bounding femoral arterial pulses are highly suggestive of aortic valve involvement.
   B. Many dogs (4% to 70%) have arrhythmias, including (in order of incidence) ventricular arrhythmias, supraventricular tachycardia, third-degree AV block, and atrial fibrillation (MacDonald et al., 2004; Sisson and Thomas, 1984; Calvert, 1982).
   C. Dyspnea, cough, or rales may be present in animals with CHF.

IV. Fever is present in 70% of dogs, and joint effusion and lameness are also common (MacDonald et al., 2004).

Diagnosis

I. The criteria for diagnosis are presented in Table 9-1.

II. Positive blood cultures help confirm the disease.
   A. Blood samples (three or four) are aseptically collected from different venous sites, 30 to 60 minutes apart, and submitted for aerobic and anaerobic bacterial culture.
   B. Lysis centrifugation tubes (Isolator, Isostat microbial system, Wampole Laboratories, Cranbury, NJ) may increase yield of bacteria.

III. Serum is submitted for measurement of antibody titers to *Bartonella vinsonii berkhoffii*, *Bartonella clarridgeiae*, and *Bartonella henselae*.
   A. A titer ≥1:1024 is strongly suggestive of Bartonellosis.
   B. There is strong cross reactivity among the *Bartonella* spp.
   C. *Bartonella* spp. are rarely cultured despite long-term incubation in enriched medium, so culture is not recommended.

IV. Echocardiographic identification of a hyperechoic, oscillating, vegetative lesion on the valve is the principal method of diagnosing endocarditis.
   A. Erosive lesions may be more difficult to identify.
   B. Color flow Doppler is used to assess the presence and severity of valvular insufficiency.
   C. LA enlargement may be present in chronic endocarditis of the mitral valve, but LA size is most often normal in acute disease.
   D. LV eccentric hypertrophy (increased LV diastolic diameter) occurs in response to chronic aortic and mitral endocarditis.
   E. End-systolic diameter and E-point to septal separation may be increased and fractional shortening decreased in animals with systolic failure secondary to chronic aortic insufficiency.
   F. Transesophageal echocardiography may be needed if visualization of the valves is poor with transthoracic echocardiography and a high clinical suspicion of endocarditis exists.

TABLE 9-1

Criteria for Diagnosis of Infective Endocarditis in Small Animals

MAJOR CRITERIA	MINOR CRITERIA	DIAGNOSIS
Positive echocardiogram: vegetative or erosive lesion, or abscess	Fever Medium to large dog (>15 kg) Subaortic stenosis	Definite Histopathology of valve 2 major criteria present 1 major and 2 minor criteria present
New valvular insufficiency: mild aortic insufficiency without subaortic stenosis or annuloaortic ectasia	Thromboembolic disease Immune mediated disease: polyarthritis, glomerulonephritis	Possible 1 major and 1 minor criteria present 3 minor criteria present
Positive blood culture: ≥2 positive blood cultures ≥3 if isolate is common skin contaminant	Positive blood culture not meeting major criteria *Bartonella* spp. serology ≥ 1:1024*	Rejected Other disease diagnosed Resolution of regurgitation or valvular abnormality within 4 days of treatment No pathologic evidence of endocarditis on postmortem examination

Criteria are modified from Baddour LM, Wilson WR, Bayer AS et al: Infective endocarditis: diagnosis, antimicrobial therapy, and management complications. Circulation. 111:e394, 2005.

*Not officially accepted yet as a criterion in dogs.

V. Thoracic radiographs are obtained to evaluate for CHF, which is seen in approximately 50% of affected dogs (MacDonald et al., 2004).
   A. Perihilar to caudodorsal interstitial to alveolar pulmonary infiltrates and pulmonary venous distension are characteristics of left-sided CHF.
   B. Often there is no evidence of LA enlargement because of the acute nature.

VI. Other diagnostic tests include a complete blood count, serum biochemistry panel, urinalysis, urine protein:creatinine ratio (if proteinuria is present), and urine culture.
   A. Most animals (78%) have leukocytosis, with mature neutrophilia and monocytosis (MacDonald et al., 2004).
   B. A mild, nonregenerative anemia is also common.
   C. Serum biochemistries often reveal azotemia (prerenal or renal), metabolic acidosis, hypoalbuminemia, and elevated liver enzymes.
   D. Hemoglobinuria, hematuria, cystitis, and proteinuria may also be seen.

Differential Diagnosis

I. MR from myxomatous mitral valve degeneration or mitral valve dysplasia
II. Aortic insufficiency secondary to aortic valve degeneration or a large ventricular septal defect
III. Lameness from immune-mediated polyarthritis, septic arthritis, tick-borne diseases, or degenerative arthritis
IV. Fever from other systemic diseases, such as sepsis, pneumonia, neoplasia, or immune-mediated diseases

Treatment

I. Long-term, bactericidal antibiotic treatment is necessary for 3 to 4 months.
   A. Selection of the appropriate antibiotic is based upon culture and sensitivity.
   B. While the culture results are pending, or if there is no microbe cultured, empirical treatment with broad-spectrum antibiotics (aminoglycosides, beta-lactams) is recommended.
   C. Initially, antibiotics are administered for 1 to 2 weeks IV, followed by PO forms.
   D. IV fluids are necessary for animals treated with aminoglycosides, and concurrent furosemide is avoided because it worsens aminoglycoside-induced nephrotoxicity.
   E. Aminoglycosides are contraindicated in CHF for these reasons.

II. Specific antibiotic combinations include the following:
   A. Acute endocarditis
      1. Amikacin 20 mg/kg IV SID and *Timentin* 50 mg/kg IV QID *or*
      2. Amikacin and imipenem 10 mg/kg IV TID for 1 to 2 weeks
   B. Chronic endocarditis
      1. Imipenem 10 mg/kg SC TID *or*
      2. Amoxicillin-clavulanate 20 mg/kg PO TID *or*
      3. Enrofloxacin 5 to 10 mg/kg PO BID for 8 weeks (dogs)
   C. For treatment of Bartonellosis
      1. Acute endocarditis: amikacin (20 mg/kg IV SID) and *Timentin* 50 mg/kg IV QID for 1 to 2 weeks
      2. Chronic endocarditis
         a. Amoxicillin-clavulanate 20 mg/kg PO TID *or*
         b. Doxycycline 5 mg/kg PO SID for 6 to 8 weeks *or*
         c. Azithromycin 5 mg/kg PO SID for 7 days, then QOD for 6 to 8 weeks

III. Treatment of CHF involves the following:
   A. Diuresis with furosemide
      1. Stable mild to moderate CHF: 1 to 4 mg/kg PO BID-TID
      2. Acute fulminant CHF: 5 to 8 mg/kg IV every 2 to 4 hours initially, then reduced
   B. ACE inhibitors
      1. Enalapril 0.5 mg/kg PO BID
      2. Lisinopril 0.5 mg/kg PO SID
      3. Benazepril 0.25 to 0.5 mg/kg SID
      4. Ramipril 0.25 to 0.5 mg/kg PO SID
   C. Positive inotropes if there is myocardial failure: digoxin, pimobendan
   D. Afterload reducers for severe aortic insufficiency: hydralazine, nitroprusside, amlodipine

Monitoring of Animal

I. In animals with positive blood or urine cultures, repeat the culture 1 to 2 weeks after starting antibiotics, and 2 weeks after termination of the antibiotics.
II. An echocardiogram is repeated 1 to 2 weeks after starting therapy, at 4 weeks, and at 2 weeks after stopping therapy to assess vegetative size, chamber sizes, severity of valvular insufficiency, and ventricular function.
III. Repeat antibody titers for *Bartonella* spp. after 1 month of treatment; if they have not decreased, change the antibiotic.
IV. Prophylactic treatment may be considered in animals with increased risk for endocarditis (SAS).
   A. A beta-lactam or cephalosporin is given 1 hour before and 6 hours after surgery or any dental procedure.
   B. No evidence exists that dogs with myxomatous valve degeneration are at increased risk of endocarditis.
V. Prognosis is grave for aortic endocarditis (median survival of 3 days) (MacDonald et al., 2004).
   A. Median survival of mitral endocarditis is 476 days (MacDonald et al., 2004).
   B. CHF or sudden death are the most common causes of death.

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CHAPTER 10

Acquired Myocardial Diseases

Alan Spier | Kristin MacDonald

CANINE CARDIOMYOPATHY

Alan Spier

Definition

I. Idiopathic cardiomyopathy is an intrinsic disorder of cardiac muscle (myocardium) resulting in altered structure/function.
II. Secondary cardiomyopathy includes myocardial abnormalities resulting from other disease processes or etiologies.

Causes

I. By definition, cardiomyopathy implies an idiopathic cause, but genetic and other factors (myocarditis) may be involved.
II. Secondary cardiomyopathies result from other disease processes or conditions.
   A. Chronic volume overload: primary valvular disease, left-to-right shunts
   B. Nutritional deficiencies: carnitine, taurine
   C. Systemic inflammation
   D. Chemotherapy: especially doxorubicin
   E. Tachycardias
   F. Endocrinopathy: hypothyroidism, hypoadrenocorticism, hyperthyroidism

Pathophysiology

I. Cardiomyopathy can affect both mechanical and electrical functioning of the heart.
   A. Mechanical dysfunction
      1. Systolic dysfunction is common in dogs, especially with dilated cardiomyopathy (DCM).
      2. Diastolic dysfunction is rare in dogs but occurs with feline cardiomyopathy.
   B. Electrical dysfunction
      1. Arrhythmogenic right ventricular cardiomyopathy (ARVC) in boxers (boxer cardiomyopathy) is caused by fatty or fibrofatty replacement of the cardiomyocytes of the right and left ventricles (lesser extent).
      2. It can occur as an initial manifestation of DCM.
   C. Both mechanical and electrical dysfunction
      1. DCM in Doberman pinschers
      2. Uncommon manifestation of boxer cardiomyopathy
II. Cardiomyopathy affecting mechanical function ultimately causes decreased stroke volume (SV) and activation of the neuroendocrine system.
   A. Decreased SV causes a decrease in cardiac output (CO).
   B. Decreased CO triggers neurohormonal activation with increased sympathetic tone and activation of the renin-angiotensin-aldosterone system (RAAS).
   C. Sympathetic activation increases heart rate and contractility.
      1. Short-term improvement in hemodynamics and maintenance of blood pressure (BP) occurs, but beta receptor down-regulation begins within 2 days.
      2. Long-term increase in catecholamines exacerbates myocardial fibrosis and dysfunction, thereby worsening cardiac performance.
   D. Neuroendocrine activation is largely responsible for the progression of the heart disease.
      1. Volume overload from RAAS activation increases preload and results in left ventricular (LV) eccentric hypertrophy.
      2. Ventricular filling pressures increase, leading to congestive heart failure (CHF).

Clinical Signs

I. Signs depend on whether a mechanical dysfunction (manifesting as heart failure) or electrical dysfunction (manifesting as syncope or sudden death) is present.
II. With mechanical dysfunction, neuroendocrine activation enables the body to maintain BP and CO, but mechanical dysfunction occurs at the cost of venous pressures.
   A. Increased venous (diastolic) pressure on the left side results in pulmonary edema.
   B. Increased venous (diastolic) pressure on the right side results in ascites and/or pleural effusion.
   C. Retention and extravasation of fluid is usually the first stage of CHF and causes respiratory signs (coughing, tachypnea, dyspnea) and abdominal distension (ascites).
   D. Nonspecific signs, such as loss of energy, appetite, and normal exercise capacity, are often seen at this stage.
III. As heart failure progresses, progressive inability to maintain CO and BP occurs.
   A. Dogs show signs of low output failure, such as exercise intolerance, weakness, and cold extremities.

B. End-stage disease manifests as cardiogenic shock with hypotension and multiple organ dysfunction.

IV. Arrhythmias are a common complication in dogs with mechanical dysfunction (DCM) and exacerbate signs of CHF.
   A. Atrial fibrillation is the most common arrhythmia seen.
   B. Ventricular arrhythmias also are common.

V. For dogs with primarily electrical dysfunction (arrhythmogenic cardiomyopathy), clinical signs are related to episodes of syncope or weakness.
   A. Sudden death may result during syncope.
   B. Syncope in many cases can be considered an aborted sudden death.
   C. Ventricular tachycardia typically causes clinical signs, whereas frequent ventricular premature complexes (VPCs) that occur singly or in pairs are unlikely to cause signs.
   D. Most dogs with arrhythmogenic forms of cardiomyopathy are otherwise normal and show signs only when the arrhythmia is severe, which explains the episodic nature of their signs.

Diagnosis

I. The diagnosis of cardiomyopathy depends on the form of disease.

II. Consider the following in dogs with DCM.
   A. Diagnosis is largely based on signalment, history, and physical examination findings.
      1. Breed disposition is important, with an autosomal dominant mode of inheritance in boxers and Doberman pinschers.
      2. Signs of coughing, exercise intolerance, or overt respiratory difficulty are typical.
      3. Identification of a soft, left apical, systolic murmur indicates mitral regurgitation (MR).
      4. An arrhythmia, especially atrial fibrillation or premature beats, may be present.
   B. Thoracic radiographs are used to identify cardiac enlargement and pulmonary edema or pleural effusion.
   C. Abdominal radiographs and ultrasonography may be used to document ascites.
   D. Electrocardiography (ECG) may identify patterns compatible with chamber enlargement (tall or wide P waves, tall R waves) and confirm the presence of arrhythmias.
   E. Echocardiography is the best method to confirm DCM.
      1. Decreased systolic function and ventricular enlargement are the hallmark findings.
      2. Increased end-systolic ventricular dimension, increased E-point to septal separation, and reduced fractional shortening (FS) are usually detected.
      3. CHF may occur once FS is severely reduced (<15%).
      4. Left atrial (LA) dilation is usually present but is not severe unless there is concurrent myxomatous mitral valvular degeneration.
      5. Annular dilation results in secondary MR.
      6. Implied in the diagnosis is the absence of other conditions that can cause chamber dilation and systolic dysfunction.
      7. Identification of echocardiographic evidence of DCM in an asymptomatic dog is termed *occult dilated cardiomyopathy,* which may be prolonged (4 to 5 years).
   F. Plasma and whole blood taurine are measured in atypical breeds with systolic dysfunction to evaluate for taurine deficiency-induced cardiomyopathy.
      1. Plasma taurine <40 nmol/mL and whole blood taurine <150 nmol/mL are consistent with taurine deficiency.
      2. American cocker spaniels, golden retrievers, and Newfoundlands are overrepresented.
      3. Systolic dysfunction may be reversible with taurine supplementation for several months.
      4. Dose is 500 mg PO BID in small dogs and 1 g PO BID in large dogs.

III. Dogs with arrhythmogenic cardiomyopathy are diagnosed as follows:
   A. Base diagnosis on identification of ventricular arrhythmias via ECG and ambulatory Holter or event monitoring.
   B. Evaluate character of arrhythmia (number, grade, or complexity); however, no criteria for diagnosis of ARVC have been established.
      1. Dogs with VPCs in excess of 500 per day are likely to be affected, but dogs with as few as 50 per day may also be affected.
      2. Dogs with high-grade arrhythmias (couplets, triplets, runs of ventricular tachycardia) are more likely to be affected and may be at increased risk for adverse events.
   C. Other tests are often normal, including thoracic radiography, ECG, and BP.
   D. Boxers may have both mechanical and electrical abnormalities (Harpster, 1983).
   E. Implied in the diagnosis is the exclusion of other causes of ventricular arrhythmias.

Differential Diagnosis

I. For DCM, rule out causes of systolic dysfunction and chamber enlargement.
   A. Chronic volume overload: primary AV valve disease, congenital heart disease
   B. Tachycardia-induced systolic dysfunction: reversible upon resolution of the tachycardia
   C. Myocarditis
   D. Myocardial toxicity: doxorubicin
   E. Systemic illness, metabolic disease

II. For electrical dysfunction, exclude other causes of arrhythmias.
   A. Other forms of heart disease: congenital disease (e.g., subaortic or pulmonic stenosis)
   B. Metabolic, systemic diseases

C. Altered autonomic balance: increased sympathetic tone, pheochromocytoma
D. Drugs and toxicities
E. Associated with surgery and other events: splenic disease and splenectomy, gastric dilatation-volvulus, trauma

Treatment

I. DCM associated with systolic dysfunction and heart failure
  A. Chronic heart failure therapy (see Chapter 9)
    1. Triple therapy with furosemide, angiotensin converting enzyme (ACE) inhibitors, and digoxin
    2. Additional diuretics including spironolactone or thiazides for refractory heart failure
    3. Inodilator therapy with pimobendan 0.25 to 0.3 mg/kg PO BID
    4. Antiarrhythmics for associated arrhythmias (see Chapter 6)
      a. Atrial fibrillation: beta blockers (use with caution in CHF), calcium channel blockers, digoxin
      b. VPCs, ventricular tachycardia: mexiletine, beta blockers, procainamide, amiodarone
    5. Nutritional supplements
      a. Often used, but no evidence to support efficacy
      b. Carnitine 50 mg/kg PO BID to TID
      c. Taurine in dogs 500 mg PO BID and in cats 250 mg PO SID to BID
      d. Coenzyme Q 30 mg PO BID, up to 90 mg PO BID in large dogs
  B. Acute heart failure therapy (see Chapter 9)
    1. Furosemide 1 to 4 mg/kg IV, IM, SC
    2. Supplemental oxygen
    3. Vasodilation
      a. Nitroglycerin $^1/_8$ to $^1/_2$ inch QID topically on pinna of ear or to inguinal area
      b. Sodium nitroprusside starting at 1 µg/kg/min IV as a constant rate infusion (CRI), titrated to desired effect
      c. Hydralazine 1 to 2 mg/kg PO, repeated hourly until BP decreases
    4. Inotropic support
      a. Dobutamine 1 to 5 µg/kg/min IV CRI
      b. Digoxin 0.003 to 0.005 mg/kg PO, IV; increased risk for acute toxicity and exacerbation of arrhythmias with IV use
      c. Pimobendan 0.25 to 0.3 mg/kg PO BID
II. Treatment for occult cardiomyopathy
  A. Systolic dysfunction and/or ventricular dilation with no clinical signs
  B. Therapy not proven to prevent progression
  C. Cardioprotective efforts (possible adverse effects, questionable efficacy)
    1. ACE inhibitors: block adverse effects of angiotensin II on left ventricular hypertrophy and myocardial fibrosis experimentally
    2. Beta blockers: block adverse effects of increased sympathetic tone
    3. Spironolactone: blocks adverse effects of aldosterone on myocardial fibrosis and possibly cardiac hypertrophy experimentally
  D. Digoxin: weak inotrope, not considered cardioprotective, may exacerbate arrhythmias
  E. Beta blockers
    1. Their use in dogs is controversial.
    2. There is no evidence of improved survival in dogs with DCM (Oyama, 2006).
    3. They must be used with caution, because they can make dogs in CHF feel worse.
    4. They must be titrated over 1 to 2 months from a low starting dose.
III. Treatment for arrhythmogenic cardiomyopathy (see Chapter 6)
  A. Adequate studies are lacking to identify if antiarrhythmics reduce the risk of sudden death in dogs; however, arrhythmogenic effects can be seen.
  B. Therapy is more commonly used in animals that are syncopal.
    1. To reduce frequency or severity of episodes
    2. Do not necessarily reduce risk of sudden death
  C. Therapy for asymptomatic animals is very controversial.
  D. Common medications include mexiletine, beta blockers, sotalol, procainamide, and amiodarone.

Monitoring of Animal

I. Screening tests for normal dogs or monitoring the asymptomatic dog for disease progression
  A. Mechanical disease is diagnosed primarily by echocardiography.
  B. ECG (ideally by Holter monitoring) identifies presence of arrhythmogenic disease.
  C. Holter monitor results may have value for predicting onset of overt disease.
II. Monitoring the asymptomatic dog on medication
  A. Echocardiography and ECG/Holter monitoring are useful to evaluate progression of disease.
  B. Echocardiography can be used to monitor for adverse effects of beta-blocker therapy (worsened systolic dysfunction).
  C. ECG identifies exacerbation of arrhythmias with digoxin.
  D. Thoracic radiographs are important to evaluate presence of CHF from disease progression or as an adverse effect of beta-blocker therapy.
  E. BP measurement is important in dogs receiving ACE inhibitors, spironolactone, or beta blockers.
  F. Kidney function and electrolytes are monitored in dogs receiving ACE inhibitors, spironolactone, or digoxin.
  G. For dogs on digoxin, serum levels are measured 7 to 10 days after starting the drug (6 to 8 hours post-pill), with an ideal range of 0.7 to 2 ng/mL.
  H. For dogs receiving antiarrhythmic therapy, monitor ECG for reductions in frequency and severity of arrhythmias (see Chapter 6), and for proarrhythmic effects of antiarrhythmic drugs.

III. Monitoring the dog on therapy for CHF
  A. Monitor for reaccumulation of fluid via thoracic radiography and abdominal ultrasonography.
  B. Echocardiography is generally not as useful once a diagnosis has been made and CHF therapy has been initiated.
  C. Monitor for adverse effects of therapy by evaluating BP, kidney function, electrolytes, and ECG.
IV. Prognosis variable
  A. Dogs with occult DCM may remain asymptomatic for years.
  B. Dogs with DCM and CHF usually succumb in 6 to 12 months.
  C. DCM warrants a worse prognosis (weeks to months) in Doberman pinschers.
  D. Some dogs with arrhythmogenic cardiomyopathy may remain asymptomatic for years and die of unrelated disease.
    1. Dogs are always at risk for sudden death, usually during exercise or excitement.
    2. ARVC and DCM (type III) boxer cardiomyopathy carry a poor prognosis (weeks to months).

FELINE MYOCARDIAL DISEASES

Kristin MacDonald

Hypertrophic Cardiomyopathy

Definition and Causes

I. Concentric hypertrophy (increased muscle thickness) of the LV occurs in the absence of other causes, such as systemic hypertension, aortic stenosis, or hyperthyroidism.
II. Idiopathic forms usually occur in domestic shorthair cats.
III. Autosomal dominant mode of transmission occurs in Maine coon cats from a missense mutation of the sarcomeric protein, myosin-binding protein C.
IV. An autosomal dominant form also occurs in American shorthair cats.
V. There is often a familial basis in other purebred cats.

Pathophysiology

I. A sarcomeric defect of a myocardial muscle protein causes dysfunction of the affected sarcomeres (contractile unit of the muscle cell), which leads to increased myocyte stress, and subsequent development of myocyte hypertrophy, collagen synthesis, and myocyte disarray (malalignment of myofibrils).
II. The end result is abnormal diastolic function consisting of delayed relaxation and increased myocardial stiffness.
III. As diastolic function worsens, the LV diastolic pressure increases, which leads to elevated LA and pulmonary venous pressures.
IV. Left-sided CHF (pulmonary edema ± pleural effusion) occurs when LA pressure exceeds 20 to 25 mm Hg.
V. LA dilation may lead to thrombus formation within the LA or auricle.
VI. Sudden death may occur secondary to a severe ventricular arrhythmia.

Clinical Signs

I. Males are more often diagnosed than females, and the mean age is 6.5 years (range 4 months to elderly (Rush et al., 2002; Atkins et al., 1992).
II. Other predisposed breeds are the ragdoll, British shorthair, Norwegian forest cat, Turkish van, Scottish fold, and Devon rex.
III. A dynamic systolic murmur is ausculted in 80% of cats with hypertrophic cardiomyopathy (HCM).
IV. Other auscultation abnormalities may include a gallop heart sound (S3 or S4) or an arrhythmia (Atkins et al., 1992: Rush et al., 2002).
V. Respiratory abnormalities are often present in cats with CHF, such as tachypnea, dyspnea, rales or crackles, or dampened lung sounds ventrally.
VI. Lameness and absence of arterial pulses are found if arterial thromboembolism has occurred.
VII. Some nonspecific signs (lethargy and anorexia) may occur.
VIII. Many cats have no clinical signs.
IX. Sudden death may be the only abnormality.

Diagnosis

I. Echocardiography
  A. Using two-dimensional (2D) echocardiography, measurement of LV wall or interventricular septal thickness at end-diastole is ≥6mm.
    1. Papillary hypertrophy may be the first abnormality detected.
    2. End-systolic cavity obliteration is also common.
  B. Systolic anterior motion of the mitral valve may be seen using the right parasternal, long-axis, LV outflow tract view.
    1. Color flow Doppler reveals a double jet of turbulent blood flow in the LV outflow tract and MR.
    2. Severity of systolic anterior motion is determined by continuous wave Doppler measurement of the peak systolic aortic blood flow velocity from the left apical 5-chamber view and reveals a dynamic, late-systolic, peaking jet.
  C. LA dilation is assessed by measurement of the LA and aortic (Ao) diameters using 2D echocardiography from the right parasternal, cross-sectional view, with LA defined as LA:Ao ≥ 1.5.
  D. Tissue Doppler imaging is useful to detect diastolic dysfunction, which is reflected by reduced early diastolic myocardial velocity and may be abnormal prior to development of concentric hypertrophy.
  E. Mitral inflow velocity measurements may show a delayed relaxation pattern or a restrictive pattern in more severe diastolic dysfunction.
II. Thoracic radiography
  A. Pulmonary venous distension and interstitial to alveolar pulmonary infiltrates may be seen with left-sided CHF.

B. Although any pattern of edema distribution is possible, infiltrates often occur in the perihilar region and caudal-ventral lung lobes.
C. Pleural effusion may be seen secondary to left- or right-sided CHF.

III. Electrocardiography
A. The most common arrhythmias are VPCs, atrial premature complexes, or atrial fibrillation (in severe cases).
B. Other abnormalities indicating LV hypertrophy include left axis deviation (mean electrical axis 0 to 90 degrees) and QRS amplitudes >1 mv.

Differential Diagnosis

I. Diseases causing compensatory concentric hypertrophy
A. Systemic hypertension
B. Hyperthyroidism
C. Subaortic or valvular aortic stenosis

II. Other cardiac diseases including unclassified cardiomyopathy, restrictive cardiomyopathy, DCM, or acquired AV valvular degeneration

III. Noncardiac causes of pleural effusion (see Chapter 19)

IV. Innocent heart murmurs
A. They may be caused by dynamic, right ventricular outflow tract stenosis.
B. In cats, differentiation of innocent murmurs from murmurs caused by structural heart disease requires echocardiography.

Treatment

I. Treatment of asymptomatic cats with echocardiographic evidence of HCM but no radiographic evidence of CHF is debatable.
A. Antihypertrophic treatment is recommended if there is moderate or severe concentric hypertrophy.
B. No studies have evaluated the effects of diltiazem or beta blockers on survival or time to development of CHF in cats with compensated HCM and no thromboembolism.
C. Ramipril does not reduce LV mass or improve diastolic function in Maine coon cats with mild to severe compensated HCM (MacDonald et al., 2006).
D. Atenolol is used to reduce systolic anterior motion and possibly reduce hypertrophy, and is given at 6.25 to 12.5 mg PO SID to BID.
1. Target heart rate is <160 beats per minute.
2. Atenolel is a selective beta-1 blocker, but may aggravate bronchoconstriction in asthmatic cats.
E. Diltiazem may reduce concentric hypertrophy (Bright et al., 1991).
1. Diltiazem 7.5 mg PO TID
2. *Dilacor XR* 30 mg PO SID to BID (sustained-release formulation)
3. *Cardizem CD* 45 mg or 10 mg/kg PO SID (sustained-release formulation)

II. Reduction of moderate to severe systolic anterior motion of the mitral valve is done with beta blockers to reduce LV pressure overload, which may reduce the concentric hypertrophy.

III. Acute decompensated CHF requires the following:
A. Furosemide 1 to 2 mg/kg SC, IM, IV every 2 to 8 hours
B. Oxygen supplementation
C. ± Nitroglycerin 2% 1/8 to 1/4 inch every 4 to 6 hours topically for 24 hours
D. Therapeutic thoracocentesis for significant pleural effusion

IV. Chronic CHF is treated with the following:
A. Furosemide
1. Mild CHF: 1 mg/kg PO SID to BID
2. Moderate CHF: 2 to 3 mg/kg PO BID
3. Severe CHF: 3 to 4 mg/kg IV, IM, SC, PO BID to TID
B. ACE inhibitors
1. Enalapril 0.5 mg/kg PO BID
2. Ramipril, lisinopril, or benazepril 0.5 mg/kg PO SID
3. After obtaining baseline renal blood work
4. Questionable efficacy (Fox, 2003)

V. For chronic, refractory CHF, add hydrochlorothiazide 1 to 4 mg/kg PO BID and introduce a low-salt diet.

VI. Antiarrhythmic therapy is indicated for significant arrhythmias (see Chapter 6).

Monitoring of Animal

I. In acute CHF, monitor resting respiratory rate and effort.
A. Thoracic radiographs are repeated in 24 hours to assess improvement in pulmonary edema.
B. In stable animals with CHF, repeat thoracic radiographs 1 week after starting therapy.

II. Repeat renal panel and electrolytes 1 week after starting ACE inhibitors and furosemide.
A. If significant azotemia develops after starting ACE inhibitors, discontinue them and reduce the furosemide dose temporarily.
B. Mild azotemia is expected when using ACE inhibitors and diuretics.
C. Moderate hypokalemia may need correction with potassium gluconate PO.

III. In cats with HCM and no LA dilation, repeat an echocardiogram every 4 to 6 months initially, and if stable for >12 months, consider an annual echocardiogram.

IV. Repeat an echocardiogram 1 to 2 weeks after initiating treatment for systolic anterior motion, and measure aortic blood flow velocity.
A. Additionally, monitor murmur intensity and heart rate.
B. Ideally, cats given beta blockers should have heart rates ≤160 beat per minute and murmur intensity should lessen.

V. For cats with LA dilation, repeat an echocardiogram and thoracic radiographs every 3 to 6 months.

VI. In cats with hyperthyroidism or systemic hypertension, echocardiography is repeated 4 months after adequate treatment.
A. Hypertrophy regresses if it is secondary to hyperthyroidism or hypertension.
B. HCM is a concurrent disease if hypertrophy persists despite normal BP and thyroxine levels.

VII. In cats with HCM without CHF or arterial thromboembolism, the prognosis is variable.
  A. Prognosis ranges from good to fair (median survival >5 years) (Atkins et al., 1992).
  B. Young, male purebred cats may develop severe disease by 2 to 4 years of age.
VIII. In cats with CHF or thromboembolism, survival is variable (mean survival of 2 months and 3 months, respectively) (Laste and Harpster, 1995).

Dilated Cardiomyopathy

Definition and Causes

I. DCM is a primary myocardial disease resulting in systolic myocardial failure (decreased contractility).
II. Most cases are idiopathic in origin.
III. Taurine deficiency can induce myocardial failure that is reversible.
  A. Taurine is an essential amino acid in cats, with the highest concentrations occurring in the myocardium, retina, central nervous system, leukocytes, and platelets.
  B. Taurine may help maintain intracellular osmolality, calcium concentration, and ion fluxes in the heart.
  C. Prior to 1988, feline diets were deficient in taurine (Pion et al., 1992a).
  D. Commercial diets are now supplemented with taurine, but cats fed vegetarian diets or exclusively one kind of canned food may develop taurine deficiency (Pion et al., 1992a).

Pathophysiology

I. Decreased contractility results in an increased end-systolic volume and reduced CO, leading to hypotension and activation of the β-adrenergic nervous system and RAAS.
II. The increased end-systolic volume results in increased LV diastolic filling pressure.
III. Increased preload leads to a compensatory, eccentric LV hypertrophy (increased end-diastolic diameter).
IV. Left-sided CHF develops when LV end-diastolic pressure exceeds 20 to 25 mmHg.
V. When there is also right ventricular myocardial failure, right-sided CHF (ascites, hepatomegaly, pleural effusion, jugular venous distension) develops with right ventricular end-diastolic pressures ≥15 mm Hg.

Clinical Signs

I. Respiratory signs may include tachypnea, dyspnea, and, rarely, coughing.
II. Ascites may occur with right-sided CHF.
III. Other nonspecific signs include lethargy or inappetence.
IV. Signs of arterial thromboembolism or syncope may occur.

Diagnosis

I. Thoracic radiography
  A. Pleural effusion is common and may obscure the cardiac silhouette.
  B. Left- and right-sided cardiomegaly, LA dilation, pulmonary venous distension, and pulmonary edema are common findings.
  C. The caudal vena cava may be dilated if there is right-sided CHF.
II. Echocardiography
  A. Systolic myocardial failure is present if increased end-systolic diameter (>10 mm), reduced FS (<28% or <20% with severe DCM), and increased E point to septal separation (>4 mm) are found.
  B. A compensatory increased end-diastolic diameter (>18 mm) may be detected.
  C. LA dilation is commonly present (La:Ao ≤ 1.5).
  D. Right ventricular eccentric hypertrophy and right atrial dilation are common.
  E. Mild secondary MR and tricuspid valve regurgitation may develop from annular dilation.
  F. Tissue Doppler imaging may show reduced systolic myocardial velocity.
III. Plasma and whole blood taurine
  A. They are indicated to rule out taurine deficiency.
  B. Plasma taurine <50 nmol/mL and whole blood taurine <250 nmol/mL are diagnostic.
IV. Systolic BP is often normal unless there is severe DCM and low-output heart failure.

Differential Diagnosis

I. Myocardial failure and eccentric hypertrophy may be caused by other cardiac diseases, such as severe MR, patent ductus arteriosus, or ventricular septal defect.
II. Congestive heart failure may be caused by HCM, unclassified cardiomyopathy, restrictive cardiomyopathy, acquired AV valve disease, or congenital heart diseases.
III. Pleural effusion may be caused by noncardiac diseases (see Chapter 19).
IV. Ascites may be caused by peritonitis, liver disease, neoplasia, or hypoproteinemia.

Treatment

I. Positive inotropic therapy is indicated when there is moderate or severe myocardial failure.
  A. Digoxin 0.031 mg PO QOD in cats <4 kg or SID in cats >4 kg
  B. Pimobendan 0.3 mg/kg PO BID
II. Administer taurine (250 mg PO BID) if the cat is taurine deficient or until results of taurine assays are available.
  A. Myocardial function improves over 2 to 4 months with taurine supplementation.
  B. After recovery of myocardial function, all other medications except taurine may be discontinued.
III. If CHF is present, begin furosemide and an ACE inhibitor, as described for HCM.
IV. Begin anticoagulant therapy if there is moderate or severe LA dilation (see Arterial Thromboembolism).
V. Avoid negative inotropes (beta blockers) in cats with moderate or severe myocardial failure.

Monitoring of Animal

I. Repeat thoracic radiographs following the onset of diuretic therapy and intermittently throughout treatment.
II. Repeat renal panel and electrolytes 1 to 2 weeks after starting an ACE inhibitor.
III. Measure serum digoxin level in 7 to 14 days (6 to 8 hours post-pill), with the ideal level being 0.7 to 2 ng/mL.
IV. Repeat echocardiography 2 months after starting medical therapy to assess myocardial function.
V. The prognosis for idiopathic DCM is grave, and cats with CHF may survive weeks to several months.
VI. Taurine deficiency-induced cardiomyopathy has a good prognosis for cats that survive the first several weeks (Pion et al., 1992b).

Miscellaneous Feline Cardiomyopathies

See Table 10-1.

Arterial Thromboembolism

Definition

I. Embolism of a thrombus (blood clot) occurs to a distal arterial site.
II. The origin of the thrombus in cats with severe cardiac disease is almost always the LA or auricle.

Causes

I. Thromboembolism occurs with severe heart diseases that cause LA dilation.
II. Most cats with arterial thromboembolism (75%) have moderate or severe LA dilation (Smith et al., 2003).

Pathophysiology

I. LA dilation leads to stasis of blood, and a thrombus forms within the dilated LA or auricle.
II. Other contributing factors may include red blood cell and platelet hyperaggregability.
III. Systemic arterial thromboembolism occurs most frequently to the terminal aorta and occasionally to the right brachiocephalic trunk.
IV. Vasogenic amines (serotonin and thromboxane) are released from the thrombus and cause collateral vasoconstriction.
V. Reperfusion injury may occur when the thrombus is lysed and often results in acute, life-threatening acidosis and hyperkalemia.

Clinical Signs

I. Acute paresis, often of the hind limbs
II. Pain with recent (<24 hours) thromboembolism
III. Absent or markedly reduced arterial pulse
IV. Cyanotic nail beds and foot pads
V. Possible muscle contracture in the affected limbs
VI. Murmurs common

Diagnosis

I. Detection of suspicious clinical signs on physical examination
II. Absence of bleeding or oozing of dark blood with trimming of a toenail artery
III. No blood flow detected by Doppler placed over the femoral artery

TABLE 10-1

Miscellaneous Feline Cardiomyopathies

DISORDER	CLINICAL SIGNS	ECHOCARDIOGRAPHIC DIAGNOSIS	TREATMENT/PROGNOSIS
Unclassified cardiomyopathy	Similar to HCM Tachypnea, dyspnea, gallop rhythm, ± murmur	Left atrial ± right atrial dilation ± Mild left ventricular hypertrophy ± Mild ↓ contractility Mild AV insufficiency ± Diastolic dysfunction	Furosemide and ACE inhibitor for CHF Anticoagulant for moderate to severe atrial dilation ± Antiarrhythmic
Restrictive cardiomyopathy*	Similar to HCM Tachypnea, dyspnea, gallop rhythm, ± murmur	Severely hyperechogenic endocardium Severe fibrotic band bridging the left ventricular free wall and septum Severe diastolic dysfunction	Furosemide and ACE inhibitor for CHF High risk (45%) of thromboembolism
Arrhythmogenic right ventricular cardiomyopathy†	Right-sided CHF Ascites, pleural effusion, hepatomegaly Ventricular arrhythmia (75%), gallop rhythm	Severe right atrial and right ventricular dilation Mild tricuspid regurgitation ± Right ventricular aneurysm ± Mild left atrial dilation	Grave prognosis Median survival 30 days Ventricular antiarrhythmic drugs Anticoagulant for moderate to severe atrial dilation

HCM, Hypertrophic cardiomyopathy; *ACE,* angiotensin converting enzyme; *CHF,* congestive heart failure; *AV,* atrioventricular valve.

*Fox PR: Endomyocardial fibrosis and restrictive cardiomyopathy: pathologic and clinical features. J Vet Cardiol 6:25, 2004.

†Fox PR, Maron BJ, Basso C et al: Spontaneously occurring arrythmiogenic right ventricular cardiomyopathy in the domestic cat: a new animal model similar to the human disease. Circulation 102:1863, 2000.

IV. Identification of the thrombus and obstructed flow distal to the thrombus on abdominal ultrasonography
V. Thoracic radiographic findings compatible with CHF
VI. Detection of underlying cardiac disease on echocardiography

Differential Diagnosis

I. Intervertebral disc disease with acute disc herniation
II. Cranial cruciate rupture or other orthopedic diseases

Treatment

I. Supportive care is indicated for all cases.
   A. Many cats autolyse their thromboemboli within 1 to 14 days.
   B. Provide pain medications.
      1. Hydromorphone 0.05 to 0.2 mg/kg SC, IM QID
      2. Butorphanol 0.1 to 0.4 mg/kg SC, IV, IM QID
      3. Buprenorphine 0.01 mg/kg SC, IV, IM TID
   C. Consider low-dose acepromazine (0.05 to 0.1 mg/kg SC, IV, IM) as a sedative and vasodilator.
   D. Assess bladder size and express distended bladders (rarely necessary).
   E. Turn laterally recumbent cats.
   F. Institute range-of-motion exercises after the initial 24 hours.
   G. Consider IV fluids at low rates (half maintenance) if no CHF is detected.
II. Anticoagulation is necessary to prevent further thrombus formation.
   A. Aspirin 6 mg/kg PO every 72 hours has had variable efficacy (Pion, 1988; Smith et al., 2003).
   B. Heparin is given at 50 to 100 units/kg SC QID, with the therapeutic goal of prolonging the activated partial thromboplastin time (APTT) to 1.5 × baseline.
   C. Low–molecular-weight heparins (enoxaparin or dalteparin) may be substituted at 1 mg/kg SC BID to TID, but no controlled studies have evaluated their efficacy in cats.
   D. Warfarin may eventually be started at 0.25 mg PO SID.
      1. Use heparin initially and continue it for a 48-hour overlap period.
      2. Dosage adjustments are needed to maintain international normalized ratio or APTT at 1.5 to 2 × baseline.
   E. Clopidogrel is a platelet inhibitor that has been used in cats at 18.75 mg PO SID (Hogan et al., 2004).
III. Thrombolytic therapy is rarely performed.
   A. Only 40% of cats survived to be discharged from the hospital (Pion, 1988).
   B. The dose of streptokinase is 90,000 units IV over 30 minutes, then 45,000 U/hr for 3 hours.
   C. Tissue plasminogen activator is given at 0.25 to 1 mg/kg/hr IV, with total dose of 1 to 10 mg/kg IV.

Monitoring of Animal

I. Assess the presence and severity of pain, and titrate opioids as needed.
II. Palpate femoral arterial pulses, and inspect the nail beds and foot pads to assess return of blood flow.
III. Inspect the skin of the affected limbs for discoloration, lichenification, or other evidence of impending necrosis.
IV. Monitor renal function and electrolytes.
V. Monitor respiratory rate and effort, and repeat thoracic radiographs in cats treated with furosemide for CHF.
VI. Repeat APTT in cats receiving heparin ± warfarin to achieve a target of 1.5 × baseline.
VII. Prognosis is poor in cats that show no return of blood flow within several days.

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CHAPTER 11

Pericardial Disorders

Anthony H. Tobias

CONGENITAL/DEVELOPMENTAL DISORDERS

Peritoneopericardial Diaphragmatic Hernia

Definition

I. A peritoneopericardial diaphragmatic hernia (PPDH) is a defect in the ventral diaphragm and pericardium that allows abdominal contents to enter the pericardial space.
II. Herniated structures include liver, gall bladder, spleen, stomach, small intestines, omentum, and falciform ligament.
III. PPDH is an uncommon defect.
  A. Incidence in cats is 0.05%.
  B. Incidence in dogs is 0.02%.
  C. Data are from the Veterinary Medical Database at Purdue University from January 1992 to April 2003.
IV. Persian cats and Weimaraners may be predisposed (Evans and Biery, 1980; Neiger, 1996).

Causes and Pathophysiology

I. During embryonic development, the diaphragm forms from the ventrally located septum transversum, the mesoesophagus, a pair of pleuroperitoneal folds, and tissue from the body wall.
II. The liver arises as a large ventral outgrowth from the foregut ectoderm and grows cranioventral to penetrate the septum transversum, and eventually distracts from the septum transversum, to form the ventral mesentery (falciform ligament).
III. If separation between the developing liver and septum transversum is defective, an opening in the ventral part of the diaphragm may occur, allowing the peritoneal and pericardial cavities to communicate.
IV. Abdominal organs may then pass through the defect into the pericardial space resulting in a PPDH (King, 1999; Noden and de Lahunta, 1985).
V. The diaphragm does not form part of the pericardium in small animals, and traumatic PPDH has not been reported in either the dog or cat (Neiger, 1996; Hay et al., 1989).

Clinical Signs

I. Clinical signs vary depending on the herniated organs or tissue.
II. Some affected animals show no clinical signs, and PPDH is an incidental finding.
III. In symptomatic animals, signs referable to the respiratory and gastrointestinal system predominate.
  A. Tachypnea, respiratory distress, vomiting, and anorexia are common.
  B. Other signs include lethargy, weight loss, diarrhea, and coughing.

Diagnosis

I. The following physical examination findings support a diagnosis of PPDH:
  A. The apex beat may be absent or displaced; heart sounds are frequently muffled.
  B. Some animals have a fever.
  C. Commonly associated abnormalities in dogs include sternal malformations (incomplete xiphoid; pectus excavatum; and absent, deformed, and fused sternebrae), cranioventral abdominal hernias, and other congenital heart defects (pulmonic stenosis, ventricular septal defect).
  D. Associated abnormalities in cats are less common and are usually limited to sternal malformations and cranioventral abdominal hernias.
II. Radiographic findings that support a diagnosis of PPDH include the following:
  A. Enlargement of the cardiac silhouette with dorsal displacement of trachea, overlapping of the diaphragmatic and caudal cardiac silhouette borders, and sternal malformations may be seen.
  B. The cardiac silhouette often contains gas-filled bowel loops and structures of differing radiolucencies (Figure 11-1, *A*).
  C. The hepatic silhouette may be small or absent in the anterior abdomen.
  D. Various other organs (e.g., small intestines, spleen) may be absent from the abdomen (Figure 11-1, *B*).
  E. In cats, a dorsal peritoneopericardial mesothelial remnant, which represents the dorsal border of the hernia, may be recognized in the lateral view as a curvilinear opacity between the cardiac silhouette and the diaphragm, either ventral to or superimposed over, the caudal vena cava (Berry et al., 1990).
  F. Positive and negative contrast peritoneography and gastrointestinal contrast studies are occasionally necessary to confirm the diagnosis.

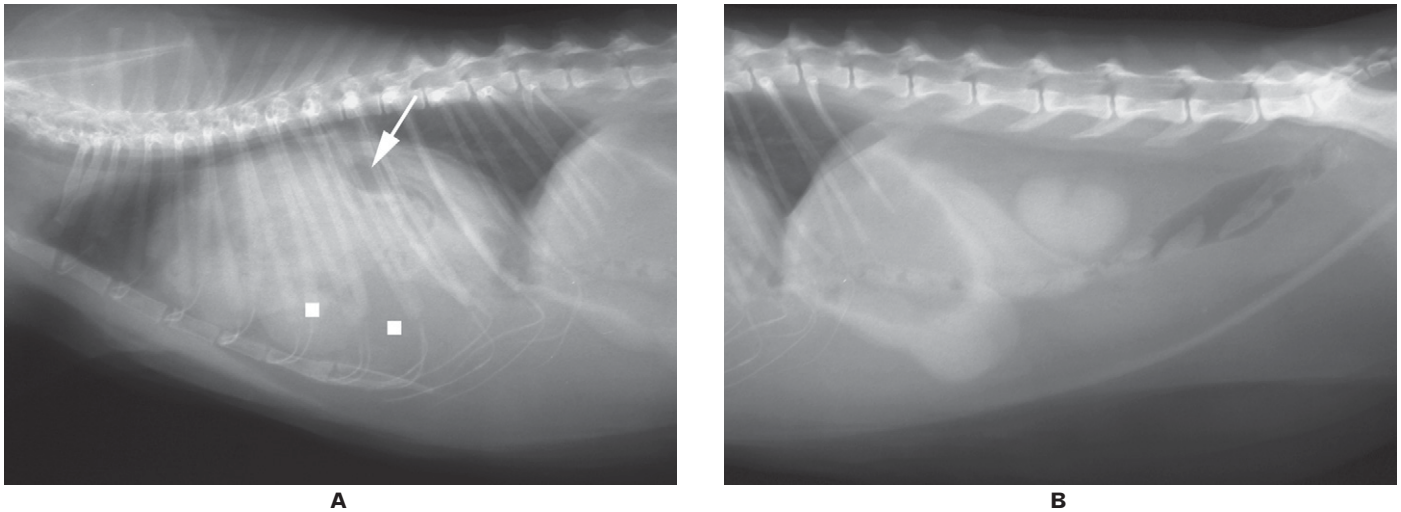

FIGURE 11-1 Lateral thoracic (**A**) and abdominal radiographs (**B**) from a cat with a peritoneopericardial diaphragmatic hernia. **A,** A markedly enlarged cardiac silhouette contains gas-filled bowel loops *(arrow)* and structures of differing radiolucencies *(squares)*. **B,** Most of the abdominal contents are displaced into the pericardial space, leaving the abdomen fairly empty. *Modified from Tobias AH: Pericardial disorders. p. 1104. In Ettinger SJ, Feldman EC (eds): Textbook of Veterinary Internal Medicine. 6th ed. Elsevier, St. Louis, 2005; with permission.*

III. Electrocardiograms (ECGs) may be normal or show low-voltage complexes and abnormal orientation of the mean electrical axis.
IV. Echocardiography reveals abdominal viscera within the pericardial space.
    A. Pericardial effusion is present in some cases.
    B. In cats the liver is the most commonly herniated organ, and focal hyperechoic areas (myelolipomas) are frequently seen within the herniated lobe(s) (Tobias, 2005).

Differential Diagnosis

I. Pericardial effusion
II. Primary cardiac disease
III. Diaphragmatic hernia

Treatment and Monitoring

I. Surgical PPDH reduction and repair are necessary for all cases that have clinical signs ascribable to the defect and are strongly recommended for all young animals with PPDH (symptomatic or not).
II. Prognosis with surgery is excellent.
III. In older animals, adhesions between herniated organs and the pericardium may complicate or preclude PPDH reduction.
IV. Consequently, in an asymptomatic older animal where PPDH is an incidental finding, it may be prudent to recommend continued observation rather than surgical repair.

Benign Intrapericardial Cysts

Definition and Causes

I. Benign intrapericardial cysts are large, fluid-filled masses within the pericardial space that occur occasionally in small animals.
II. In virtually all cases, histopathology discloses that the cysts are encapsulated adipose tissue, with extensive hemorrhage and necrosis, or organizing cystic hematomas.
III. In some cases, the benign intrapericardial cyst is associated with a small PPDH.
IV. In other cases, the cyst is attached by a pedicle to the apex of the pericardium as a result of prenatal herniation of omentum or falciform fat from the peritoneum into the pericardium and subsequent closure of a PPDH.
V. Cyst formation probably results from vascular obstruction of the herniated tissue, or repeated trauma from the beating heart (Simpson et al., 1999; Sisson et al., 1993).
VI. Intrapericardial hepatic cysts have been described in cats with PPDH as a result of incarceration of portions of the liver (Less et al., 2000; Liptak et al., 2002).
VII. True congenital intrapericardial cysts in humans are endothelium-, epithelium-, or mesothelium-lined (depending on their origin) and are rare in small animals (Labadie, 1993; Sisson et al., 1993).

Clinical Signs and Diagnosis

I. Intrapericardial cysts cause cardiac tamponade (significant compression of the heart from accumulating pericardial contents) by direct cardiac compression and associated pericardial effusion.
II. The pathophysiology, clinical signs, and diagnosis for pericardial effusion and cardiac tamponade are discussed later in this chapter.

Treatment

Surgical removal of the cyst and its associated pedicle, pericardectomy, and repair of the PPDH.

Pericardial Defects

I. Pericardial defects are communications between the pericardial and pleural space that may be single or multiple

and range in size from small, round or oval holes to total absence of one side of the pericardium.

II. They are rare in dogs and are usually found incidentally on postmortem examination.

III. Some are thought to be congenital (Gagg and Luer, 1977).

IV. Herniation with incarceration of cardiac chambers through pericardial defects has been reported in dogs (Gagg and Luer, 1977; Sisson and Thomas, 1999; Van den Ingh, 1977).

ACQUIRED DISORDERS

Pericardial Effusion

Definition

I. Accumulation of an abnormal amount of pericardial fluid within the pericardial space

II. Data from the University of Minnesota Veterinary Medical Center (UMVMC) from January 1999 to December 2001
   A. The incidence in dogs was 0.43%.
   B. Average age was 9.7 ± 2.2 years.
   C. Average weight was 31.2 ± 12.6 kg.
   D. There was no sex predisposition, and golden retrievers were overrepresented (Tobias, 2005).

Causes

I. Infections
   A. Bacterial
      1. Bacterial infections are uncommon causes.
      2. Most bacterial infections are thought to arise from intrapericardial foreign body penetration, especially by migrating grass awns (foxtails or *Hordeum* spp.) (Aronson and Gregory, 1995).
   B. Fungal
      1. Systemic *Coccidioides immitis* is an occasional cause in dogs (Heinritz et al., 2005; Shubitz et al., 2001; Thomas et al., 1984).
      2. *Aspergillus niger* has also been reported in a dog (Carpenter et al., 2001).
      3. In most cases, fungal infections result in effusive-constrictive or constrictive pericarditis.
   C. Viral: occasionally feline infectious peritonitis
   D. Protozoal: rarely visceral leishmaniasis in dogs (Font et al., 1993)

II. Idiopathic forms
   A. Pericardial effusions are idiopathic in origin in 19% to 23% of affected dogs (Berg and Wingfield, 1983; Tobias, 2005).
   B. Signalment is typical of pericardial effusion in general.

III. Metabolic and/or toxic forms (uncommon)
   A. Secondary to uremia (Berg and Wingfield, 1983; Rush et al., 1990)
   B. Cholesterol-based effusion with hypothyroidism (MacGregor et al., 2004)
   C. Coagulation disorders
      1. Dogs: anticoagulant rodenticide toxicity (Petrus and Henik, 1999)
      2. Cats: secondary to disseminated intravascular coagulation, warfarin toxicity, other coagulopathies (Rush et al., 1990)

IV. Cardiovascular disorders
   A. Pericardial effusion is frequently detected in dogs and cats with congestive heart failure (CHF), but seldom in sufficient quantity to cause significant hemodynamic compromise.
   B. Left atrial perforation is an uncommon cause in small-breed dogs with severe mitral regurgitation from chronic degenerative valvular disease.

V. Neoplasia
   A. Cardiac hemangiosarcoma
      1. It is a highly malignant neoplasm of vascular endothelium that usually involves the wall of the right atrium (RA) or auricle.
      2. It is the most common cause of pericardial effusion in dogs (61% of dogs in UMVMC data) (Tobias, 2005).
      3. Signalment is typical of pericardial effusion in general.
      4. Primary cardiac hemangiosarcoma of the RA has been reported in a cat (Merlo et al., 2002).
   B. Heart base tumors
      1. The term is used to designate any mass located at the base of the heart in association with the ascending aorta and main pulmonary artery.
      2. Most are aortic body tumors in dogs, although 5% to 10% are ectopic thyroid tumors (Capen, 1978).
      3. Despite being the second most common cardiac tumor in dogs (7% of dogs in UMVMC data), incidence is approximately tenfold lower than cardiac hemangiosarcoma (Ware and Hopper, 1999).
      4. English bulldogs, boxers, and Boston terriers are predisposed.
         a. These tumors also occur in nonbrachycephalic breeds.
         b. Chronic hypoxia-induced hyperplasia and neoplasia of chemoreceptors may explain the predisposition of brachycephalic dogs to aortic body tumors (Hayes and Sass, 1988).
      5. Age range at time of diagnosis is 6 to 15 years (average 10 years) (Owen et al., 1996).
      6. Both male and no gender predispositions have been reported.
      7. They occasionally occur in cats.
   C. Mesothelioma
      1. Mesothelioma, a diffuse neoplasm of the pericardium and other serosal surfaces, was confirmed in 5% of dogs in UMVMC data (Tobias, 2005).
      2. No sex or breed predisposition has been reported.
      3. It has rarely been described in cats.
   D. Other uncommon cardiac tumors: lymphosarcoma, rhabdomyosarcoma, fibrosarcoma

VI. Trauma
   A. Pericardial effusions associated with intrapericardial foreign bodies occur occasionally.
   B. In UMVMC data, one dog (1%) had pericardial effusion associated with an intrapericardial pellet.

Pathophysiology

I. Pericardial effusion increases intrapericardial pressure and causes cardiac tamponade.
II. Cardiac tamponade results in depressed cardiac output (CO), elevation and equilibration of right and left ventricular diastolic pressure and pericardial pressure, and pulsus paradoxus.
III. Increased intrapericardial pressure impairs ventricular filling in diastole, which results in diminished stroke volume.
IV. Pericardial effusion also causes decreased systolic function because the compressed and underfilled cardiac chambers operate at the lower ends of their respective Frank-Starling curves (Spodick, 2001).
V. Acute accumulations of relatively small amounts of pericardial effusion can cause profound hemodynamic compromise and clinical signs of low CO.
VI. With more chronic accumulations, the volume of the pericardial sac expands (Kardon et al., 2000).
    A. Compensatory mechanisms (increased sympathetic tone, activation of the rennin-angiotensin-aldosterone system) increase heart rate and preload or filling pressure in an effort to restore CO.
    B. Atrial natriuretic peptide does not increase, because atrial distention (the primary stimulus for atrial natriuretic peptide secretion) does not occur owing to external compression of the heart (Koller et al., 1987, Spodick, 1989).
    C. Signs of increased systemic venous pressure predominate and manifest as right-sided CHF (hepatomegaly, ascites, jugular distention, pleural effusion).
VII. Pulsus paradoxus is defined as ≥10 mmHg decrease in systolic arterial blood pressure (BP) with inspiration during normal breathing (Spodick, 2001).
    A. Left ventricular stroke volume and systemic arterial BP normally decrease slightly with inspiration.
    B. This phenomenon is accentuated with cardiac tamponade and may be recognized clinically as phasic variations in pulse quality associated with respiration.

Clinical Signs

I. Clinical complaints and histories are most commonly acute and nonspecific.
II. Presenting signs from UMVMC data are as follows:
    A. Lethargy (53%)
    B. Respiratory difficulty (44%)
    C. Collapse (40%)
    D. Reduced appetite (38%)
    E. Vomiting (30%)
    F. Abdominal distention (23%)
    G. Less common: polydipsia, weakness, coughing

Diagnosis

I. Physical examination findings range from vague and subtle to hemodynamic collapse.
    A. Muffled heart sounds are most common.
    B. Other findings include depression, weak pulses, and abdominal distention with a fluid wave (ascites).
    C. Jugular distention and pulsus paradoxus may be identified.
II. Thoracic radiographic features that support a diagnosis of pericardial effusion are as follows:
    A. An enlarged and globoid cardiac silhouette, with tracheal elevation and widening of the caudal vena cava
    B. Overlap of the cardiac silhouette and diaphragm and bilateral contact between the pericardium and the chest wall
    C. A sharply delineated edge to the cardiac silhouette, because the distended pericardium has little or no motion during systole and diastole
    D. Lung fields that show no evidence of left-sided CHF (no cardiogenic pulmonary edema)
    E. Typical radiographic findings with chronic, large-volume effusions
        1. With smaller effusions, the cardiac silhouette is variably enlarged and it is not necessarily globoid.
        2. Pleural effusion may obscure the cardiac silhouette.
    F. Other possible abnormalities: pulmonary metastases, radiopaque intrapericardial foreign bodies
III. Electrocardiographic findings may include the following:
    A. Most dogs with pericardial effusions have either a normal sinus rhythm or a sinus tachycardia.
    B. Ventricular arrhythmias are fairly common, and supraventricular arrhythmias occasionally occur.
    C. Low-voltage QRS complexes (R waves <1 mV in all limb leads) are present in approximately half the cases.
    D. Electrical alternans (beat-to-beat variations in the contour and amplitude of the QRS complex, ST segment, and T wave) strongly suggests the presence of pericardial effusion (Bonagura, 1981) (Figure 11-2).
IV. Hematology and biochemistry tests may reveal the following:
    A. Dogs with hemangiosarcoma are frequently anemic and may have nucleated red blood cells (RBCs), schistocytes, acanthocytes, and thrombocytopenia.
    B. Mild-to-moderate liver enzyme elevations often occur from hepatic congestion.
    C. Mild prerenal azotemia may be present.
    D. Cats with feline infectious peritonitis may have neutrophilia, lymphocytopenia, and hyperglobulinemia.
    E. Ascitic fluid analysis discloses a modified or high-protein transudate.
    F. *C. immitis* serology is indicated in dogs from endemic areas.
    G. Assessment of coagulation is recommended prior to pericardiocentesis if a coagulopathy is suspected clinically.
    H. Serum cardiac troponin I assays may be useful in dogs to distinguish between cardiac hemangiosarcoma and idiopathic pericardial effusion, with higher concentrations usually present with cardiac hemangiosarcoma (Shaw et al., 2004).
V. Pericardial effusions in dogs, irrespective of cause, are almost always sanguinous or serosanguineous, sterile in-

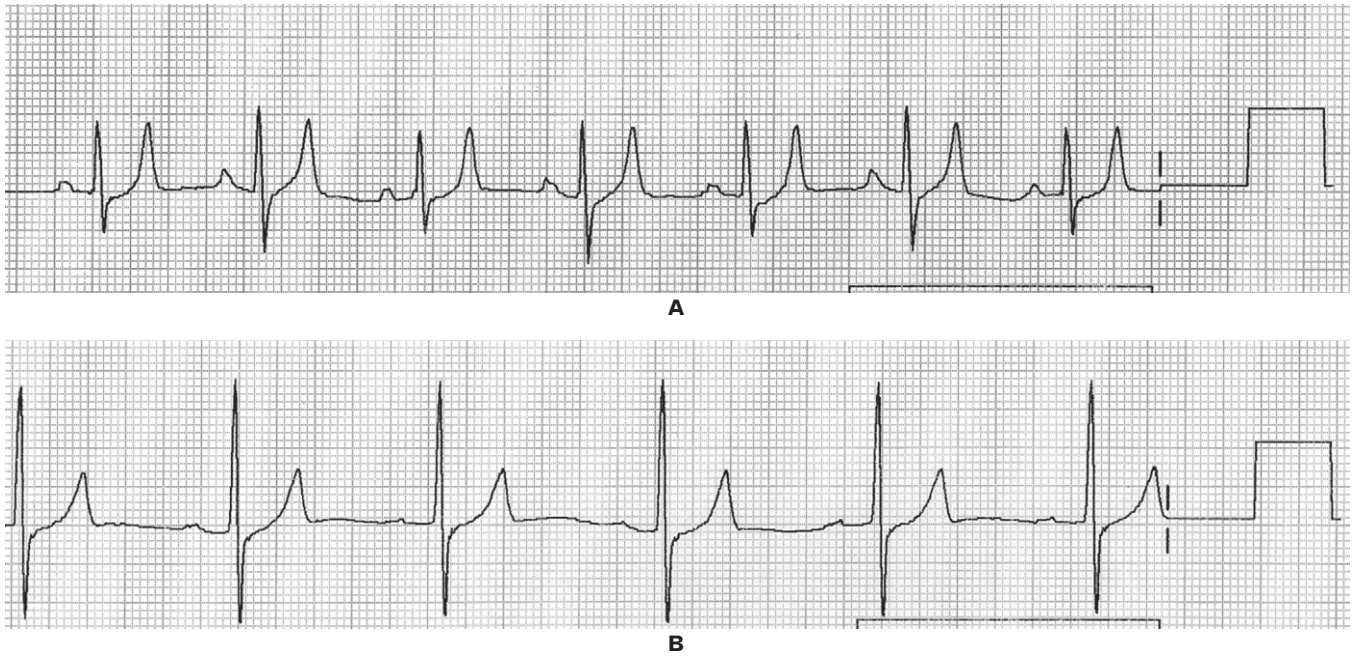

FIGURE 11-2 Lead II electrocardiograms from a dog with pericardial effusion. **A,** Before pericardiocentesis, the complexes are low-voltage (R wave amplitude approximately 1 mV), the QRS complexes show beat-to-beat variations in contour and amplitude (electrical alternans), and heart rate is 140 beats per minute (bpm). **B,** After pericardiocentesis, R wave amplitude is almost 2 mV, electrical alternans is no longer present, and heart rate is 110 bpm. Calibration square is 1 mV in amplitude.

flammatory exudates and similar in gross appearance to blood, but they do not clot.

A. Cytologic evaluation does not differentiate between neoplastic and nonneoplastic causes in most cases.
B. Total nucleated cell counts, RBC counts, protein concentrations, pericardial fluid pH, and other biochemistries overlap extensively between causes (de Laforcade et al., 2005; Fine et al., 2003; Sisson et al., 1984).
C. Hemangiosarcoma and aortic body tumors are rarely identified on cytological evaluation.
D. Pericardial diseases that lead to effusion result in dramatic mesothelial proliferation; exfoliated mesothelial cells often have characteristics that mimic malignancy (Alleman, 2003).
E. Despite its generally low diagnostic yield, pericardial fluid cytology (and culture when appropriate) is crucial for the diagnosis of some of the less common causes of pericardial effusion, such as bacterial and protozoal pericarditis, and lymphoma.

VI. Echocardiography is the most sensitive and specific noninvasive method to confirm the presence of pericardial effusion.
   A. With two-dimensional (2D) echocardiography, pericardial effusion appears as an echolucent zone surrounding the heart.
   B. In cases with concurrent pleural effusion, the pericardium is well visualized with fluid on either side.
   C. The heart may show swinging motions within the pericardial fluid.
   D. Cardiac chambers may appear small, and the walls may show thickening or pseudohypertrophy from external compression.
   E. The right atrial free wall is normally rounded throughout the cardiac cycle, reflecting positive right atrial transmural pressure.
      1. Any inversion or collapse of the right atrial free wall provides indirect evidence of elevated intrapericardial pressure and transient reversal of transmural pressure.
      2. Right atrial inversion occurs in late diastole and continues into ventricular systole (Figure 11-3, *A*).
   F. Right ventricular diastolic collapse is characterized by inward motion of the right ventricular free wall that may range from a transient and localized concavity to virtual complete right ventricular chamber obliteration throughout diastole.

VII. Echocardiography also detects intrapericardial masses.
   A. Findings consistent with cardiac hemangiosarcoma
      1. Hemangiosarcoma most commonly arises from the wall of the RA or auricle, protrudes into the pericardial space, and moves with the RA or auricle.
      2. It may also protrude into the right atrial chamber, and involve other areas of the heart base, pericardium, and right atrioventricular groove.
      3. Typically small hypoechoic spaces (mottled or cavitary appearance) and occasionally cystic lesions are seen.
      4. It is usually demonstrated in the right parasternal long- and short-axis views.

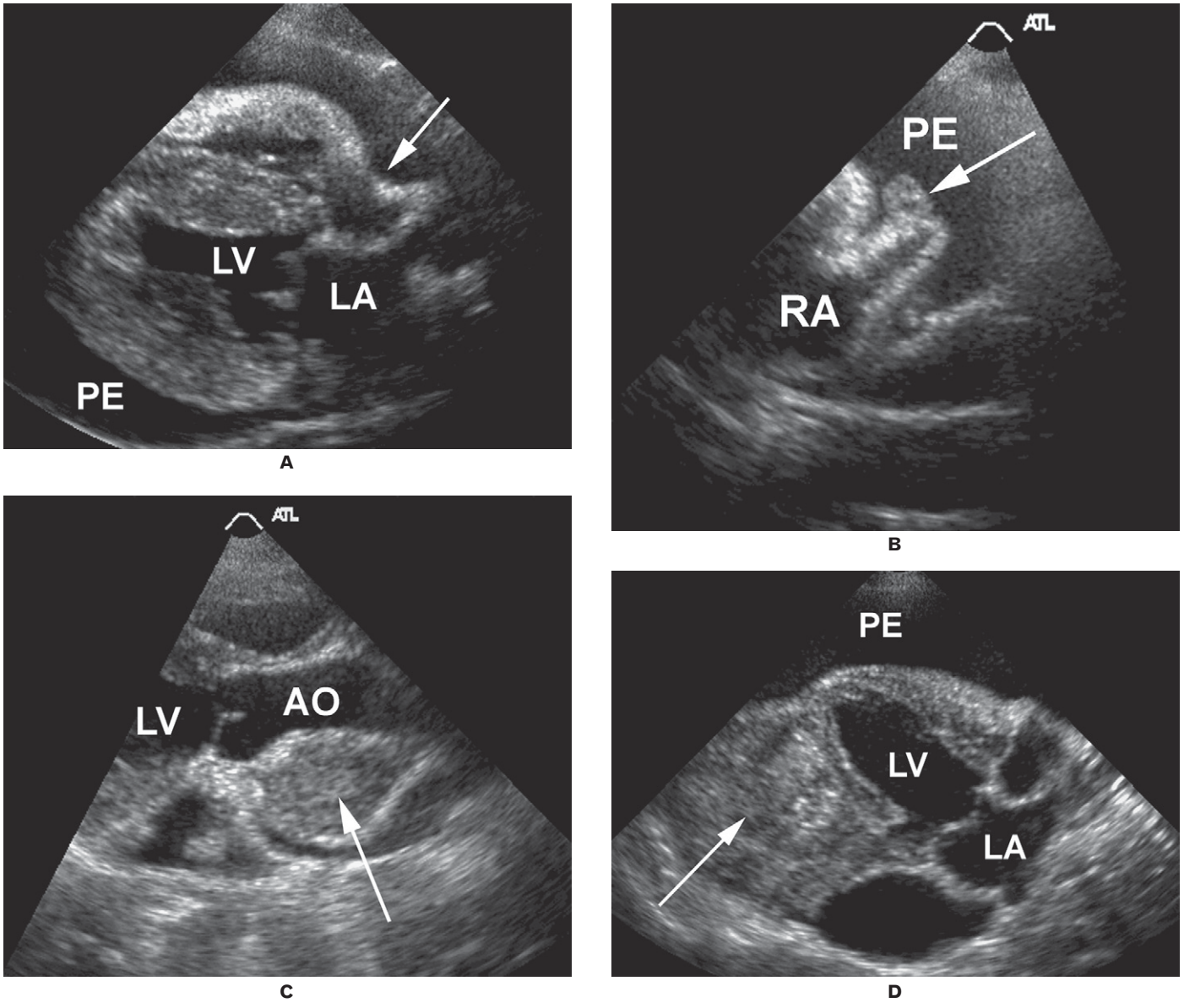

FIGURE 11-3 Echocardiograms from dogs with pericardial effusion. **A,** The effusion forms an echolucent zone around the heart. Inversion of the right atrial free wall *(arrow)* indicates cardiac tamponade. **B,** Imaging from the left cranial location demonstrates a small cavitated hemangiosarcoma *(arrow)* protruding from the wall of the right auricle. **C,** A large tumor *(arrow)* associated with the ascending aorta is characteristic of a heart base tumor. **D,** A large tumor *(arrow)* is arising from the wall of the left ventricle and was a confirmed fibrosarcoma. *LV,* Left ventricle; *LA,* left atrium; *PE,* pericardial effusion; *RA,* right atrium; *AO,* aorta.

5. Occasionally the mass is identified best in left parasternal views (see Figure 11-3, *B*).

B. Features characteristic for heart base tumors
   1. Heart base tumors are associated with the ascending aorta (see Figure 11-3, *C*).
   2. They vary from small, oval structures to extensive masses that surround the aorta and main pulmonary artery.
   3. Indentation or invasion of the atria and major blood vessels may be seen.
   4. They tend to have a more homogenous echogenicity than hemangiosarcoma.

C. Other echocardiographic findings
   1. Other cardiac tumors (see Figure 11-3, *D*)
   2. Abdominal viscera within the pericardial space with PPDH
   3. Benign intrapericardial cysts
   4. Intrapericardial thrombi associated with left atrial perforation

VIII. Whenever the clinical condition permits, pericardiocentesis is deferred until a thorough echocardiographic examination has been completed.
   A. Pericardial fluid forms an echolucent zone around the right atrium and auricle, and the ascending aorta.
   B. Consequently, the presence of pericardial fluid greatly facilitates the detection of intrapericardial masses,

especially cardiac hemangiosarcoma and heart base tumors.

IX. Idiopathic pericardial effusion is a diagnosis of exclusion that is made when no intrapericardial masses are identified and ancillary tests do not disclose a cause.

X. Mesothelioma rarely forms discrete masses detectable by echocardiography.
   A. It is extremely difficult to distinguish from idiopathic effusion, even with pericardial histopathology and immunohistochemistry (Churg et al., 2000; Stepien et al., 2000).
   B. In many cases, the diagnosis is only confirmed on postmortem examination.
   C. A clinical course that includes accumulation of significant amounts of pleural effusion within 4 to 6 months of pericardectomy suggests mesothelioma.
   D. The chronic inflammatory process of idiopathic effusion may predispose golden retrievers to pericardial mesothelioma (Machida et al., 2004).

Differential Diagnosis

I. Other causes of right-sided CHF (e.g., dilated cardiomyopathy, tricuspid dysplasia) and ascites (e.g., hepatic disease, abdominal neoplasia)

II. Other causes of muffled heart sounds: pleural effusion, thoracic masses, diaphragmatic hernia

III. Other causes of low-voltage complexes on ECG: pleural effusion, obesity, hypothyroidism

IV. Other causes of prominent enlargement of the cardiac silhouette on thoracic radiography: dilated cardiomyopathy, tricuspid dysplasia, PPDH

Treatment and Monitoring

I. Pericardiocentesis for removal of fluid is necessary for any animal with significant hemodynamic compromise.

II. Following pericardiocentesis and appropriate supportive care, treatment is directed towards the specific cause.

III. Dogs with bacterial pericarditis are treated with pericardectomy, removal of any foreign bodies, chest drainage, and antibiotics for up to 6 months.
   A. Many recover without complications.
   B. Prognosis is good when treated aggressively with a combination of surgical and medical therapy (Aronson and Gregory, 1995).

IV. Treatment and prognosis for *C. immitis*–related pericardial disease is discussed under Constrictive/Effusive-Constrictive Pericarditis.

V. There is no effective treatment for feline infectious peritonitis and the disease is invariably fatal, but pericardiocentesis may provide temporary palliation with clinically significant pericardial effusion.

VI. First episodes of idiopathic pericardial effusion may sometimes be treated by pericardiocentesis alone, followed by pericardectomy in recurrent cases.
   A. Cardiac tamponade often recurs within 1 to 2 months of pericardiocentesis and is often fatal.
   B. Recurrent tamponade with effusive-constrictive pericarditis may also develop (Tobias, 2005).
   C. Complete cure is uncommon, but long-term survival has been reported with repeated pericardiocentesis (Mellanby and Herrtage, 2005).
   D. Surgical or minimally invasive thoracoscopic pericardectomy is recommended with the initial episode of idiopathic pericardial effusion to avoid the risk of recurrent, potentially fatal cardiac tamponade.
   E. Surgical pericardectomy also permits examination of thoracic and intrapericardial structures for causes of pericardial effusion.
   F. Pericardectomy is usually curative for idiopathic pericardial effusion.

VII. Left atrial perforation may require only medical therapy for CHF.
   A. Episodes of weakness or collapse may be transient.
   B. Relatively little pericardial fluid and only mild echocardiographic evidence of cardiac tamponade may be present.
   C. Echocardiograms repeated 7 to 10 days later may demonstrate resolution of both the pericardial effusion and intrapericardial thrombi.
   D. These cases have severe underlying heart disease and survival beyond 6 months after the acute episode is uncommon.
   E. Pericardiocentesis is required for cases that are hemodynamically compromised from cardiac tamponade.
      1. Continued hemorrhaging may necessitate blood transfusion, and thoracotomy to remove large clots from the pericardial space and repair the left atrial perforation.
      2. The prognosis in such cases is grave (Prosek et al., 2003; Sadanaga et al., 1990).

VIII. Treatment for cardiac hemangiosarcoma is challenging, and the prognosis is extremely poor.
   A. By the time of diagnosis, it usually has metastasized and should be considered a systemic disease.
   B. Palliative pericardiocentesis is usually associated with marked clinical improvement, but cardiac tamponade typically recurs within a few days, often resulting in death or euthanasia (median survival time of 11 days, range 0 to 208 days from UMVMC data) (Tobias, 2005).
   C. More aggressive treatment of cardiac hemangiosarcoma includes various combinations of tumor resection, pericardectomy, chemotherapy, and splenectomy (for splenic metastases).
      1. Despite these therapies, median survival time is short (56 days, range 0 to 229 days).
      2. Chemotherapy, especially with doxorubicin, after tumor resection may prolong survival, but the benefit appears to be small (Weisse et al., 2005).

IX. Most aortic body tumors are benign and expansive, although they may be locally invasive and/or metastasize in dogs and cats.
   A. The biological behavior of ectopic thyroid tumors at the heart base is not well described, although both

adenomas and adenocarcinomas with metastases have been reported.
B. Complete surgical resection of heart base tumors is seldom possible because they are highly vascular, associated with major blood vessels, and usually extensive by the time of diagnosis.
C. In a retrospective study of dogs with aortic body tumors, palliative pericardectomy often prolonged survival, with excellent quality of life.
1. Median survival time following pericardectomy was 730 days.
2. Median survival time without pericardectomy was 42 days (Ehrhart et al., 2002).

X. Pericardial mesothelioma is difficult to treat.
A. Long-term survival has been reported in a dog treated with pericardectomy, intracavitary cisplatin and intravenous doxorubicin (Closa et al., 1999).
B. Following a presumptive diagnosis (accumulation of significant amounts of pleural effusion within 4 to 6 months of pericardectomy), repeated thoracocentesis is necessary and adjunctive chemotherapy (intracavitary cisplatin, intravenous doxorubicin) should be considered.

XI. Cardiac lymphosarcoma is classified as stage V, substage b.
A. Dogs with stage III lymphosarcoma or higher and clinical signs (substage b) have a poor prognosis for remission and survival.
B. In a retrospective study of 12 dogs treated with various combinations of pericardiocentesis, pericardectomy, and chemotherapy, median survival time was 41 days.
C. Three dogs were alive 328 days after initial diagnosis, suggesting that cardiac lymphosarcoma may not always warrant a poor prognosis (MacGregor et al., 2005).

Constrictive/Effusive-Constrictive Pericarditis

Definition

I. Constrictive pericarditis is fusion of the visceral and parietal layers, with the heart encased within a stiff, fibrotic pericardium.
II. Effusive-constrictive pericarditis may be defined as a combination of a relatively small amount of a tense pericardial effusion enclosed within an unyielding, fibrous, parietal pericardium (Spodick, 2001).

Causes and Pathophysiology

I. Effusive-constrictive pericarditis occurs occasionally in dogs.
A. Many causes are idiopathic, or develop months or years after an episode of idiopathic pericardial effusion.
B. Other causes include metallic foreign bodies, *C. immitis*, *Aspergillus niger*, actinomycosis, and osseus metaplasia of the pericardium.

II. Constrictive pericarditis in dogs is uncommon.
A. It may develop as a consequence of any form of chronic pericarditis.
B. It may be a severe complication of systemic *C. immitis*.

III. Pathophysiology is similar to other causes of cardiac tamponade, except that the nondistensible, thickened, fibrotic pericardium contributes substantially (effusive-constrictive pericarditis) or entirely (constrictive pericarditis) to compression of the heart.

Clinical Signs and Diagnosis

I. Effusive-constrictive pericarditis
A. Dogs typically have signs of right-sided CHF.
B. Common complaints are abdominal distention and muscle wasting.
C. Findings on physical examination include abdominal distention with a fluid wave (ascites), jugular distention, and muffled heart sounds.
D. On ECG, a normal sinus rhythm or sinus tachycardia and low-voltage QRS complexes are commonly found.
E. The cardiac silhouette on thoracic radiography ranges from normal to moderately enlarged and rounded, and the caudal vena cava may appear wide.
1. The presence of pleural effusion may complicate evaluation of the size and shape of the cardiac silhouette.
2. Radiopaque intrapericardial foreign bodies may be detected.
F. Echocardiography shows pericardial effusion that separates the myocardium and pericardium by just a few millimeters.
1. Echocardiographic signs of cardiac tamponade (late diastolic to systolic inversion of the right atrium, and diastolic collapse of the right ventricle) are usually present.
2. Pericardial thickness cannot be accurately assessed except in extreme cases.
G. *C. immitis* serology is indicated in dogs from endemic areas.

II. Constrictive pericarditis
A. Clinical signs, thoracic radiographs, and electrocardiographic findings are similar to other causes of chronic cardiac tamponade and effusive-constrictive pericarditis.
B. In contrast to most other forms of pericardial disease, echocardiography demonstrates neither pericardial effusion nor right atrial and ventricular collapse, but may include the following:
1. Abrupt flattening of the left ventricular posterior wall on M-mode echocardiography in mid to late diastole
2. Rapid early closure of the mitral valve, as well as premature pulmonary valve opening
3. A diastolic septal bounce, mild atrial enlargement, vena cava and hepatic vein dilation, and ascites
4. Alterations in the flow characteristics in pulmonary veins, vena cava, hepatic vein, and across the mitral valve
5. Thickened pericardium in severe cases (Myers and Spodick, 1999)
C. Cardiac catheterization is generally necessary to establish the diagnosis, and hemodynamic findings include the following:

1. Elevation and equilibration or near equilibration of the diastolic pressures of all cardiac chambers
2. A right atrial pressure trace with an M or W pattern
3. A ventricular pressure trace that shows a dip-and-plateau pattern or "square-root" sign in diastole
4. Rapid IV fluid infusion possibly necessary to fully reveal characteristic hemodynamic features (Myers and Spodick, 1999; Sisson and Thomas, 1999; Thomas et al, 1984)

D. *C. immitis* serology is indicated in dogs from endemic areas.

Differential Diagnosis

Similar to pericardial effusion

Treatment and Monitoring

I. Treatment for idiopathic effusive-constrictive pericarditis involves pericardectomy, and the prognosis is excellent.
   A. Slight epicardial fibrosis and roughness that does not require epicardial excision is present in most cases.
   B. Adhesions between the visceral and parietal pericardium are uncommon.

II. Severe involvement of the epicardium and adhesions between the parietal and visceral pericardium confer a less favorable prognosis.
   A. Dogs with fungal pericarditis from *C. immitis* are particularly prone to extensive involvement of both the visceral and parietal pericardium.
   B. In such cases, pericardectomy and excision of the constricting epicardium from the underlying myocardium are necessary, along with long-term antifungal therapy and monitoring.
      1. In a retrospective study of 17 dogs with effusive-constrictive pericarditis from *C. immitis*, perioperative mortality was high (23.5%).
      2. Surgery was successful in relieving right-sided CHF in some dogs, with longevity >2 years (Heinritz et al., 2005).

III. The treatment, monitoring, and prognosis for cases of constrictive pericarditis are similar to effusive-constrictive pericarditis with severe involvement of the epicardium and adhesions between the parietal and visceral pericardium.

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CHAPTER 12

Heartworm Disease

Ray Dillon

CANINE HEARTWORM DISEASE

Definition

I. Heartworm disease (HWD): inflammatory disease of pulmonary vasculature and lung parenchyma
II. Distribution
  A. It occurs in temperate and tropical climates where suitable mosquito vectors and reservoir animals exist.
  B. It is endemic in most parts of the world, including southern Canada, Central America, South America, Australia, Japan, western and southern Africa, and southern Europe.
  C. In the United States, canine HWD has been detected in every state.
III. Primary hosts and principal reservoirs of infection
  A. Domestic dogs: almost 100% of dogs infected with third-stage larvae develop adult heartworm (HW) infections
  B. Wild canines, wolves, foxes, and coyotes
IV. Other susceptible hosts
  A. Domestic and captive wild cats (e.g., African lion)
  B. Ferret: more susceptible than cats
  C. California sea lion
V. Aberrant hosts
  A. Other mammals, including humans
  B. May be infected but do not become microfilaremic, so do not serve as reservoirs of infection

Causes

I. *Dirofilaria immitis* with mosquitoes as an obligatory intermediate host
II. Lifecycle of *D. immitis* (Figure 12-1)
  A. Microfilaria (MF)/embryo stage (L1)
    1. MF may circulate in the blood of an infected canine host for >2 years after being released by a gravid female.
    2. Live MF actively navigate capillaries.
    3. MF are ingested by a suitable mosquito vector.
  B. Third stage (L3)
    1. MF molt twice (L1→L2, L2→L3) in the mosquito to reach the infective L3, with maturation occurring in the midgut region.
    2. MF migrate (only mature L3) to the proboscis of the infected mosquito within 12 to 40 days, depending on ambient temperature.
    3. Requirements for the mosquito to develop infective larvae are 130 heat units (1 heat unit is a mosquito environment of 1° C of temperature >14° C each day).
    4. MF are deposited on the skin and enter the definitive host through a mosquito bite wound.
  C. Tissue migratory stages
    1. L3 infective larvae molt (within 2 weeks) to the fourth stage (L4) and migrate toward the heart.
    2. Maturation to the fifth stage (juvenile to adult, L5) occurs about 50 to 70 days after infection.
  D. Adult stage
    1. Fifth-stage larvae penetrate systemic veins between 70 and 85 days and arrive in the right ventricle as immature L5.

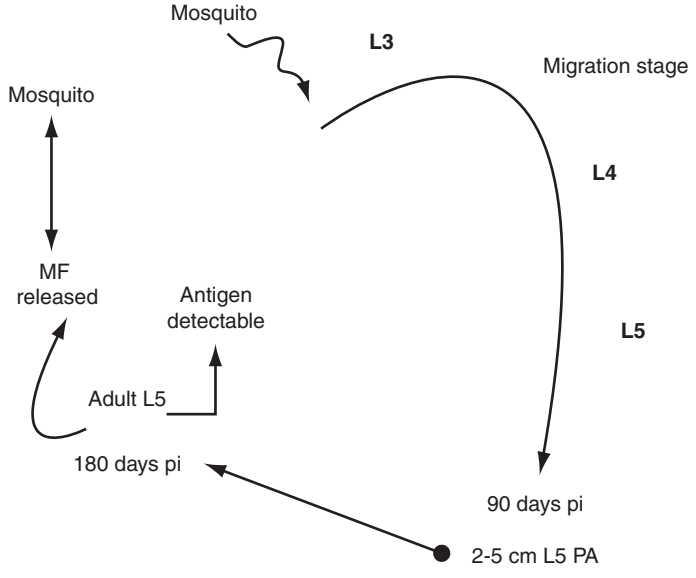

FIGURE 12-1 Life cycle of *Dirofilaria immitis*. Third-stage larvae (L3) are deposited on the skin and enter the host during mosquito feeding. After molting into fourth stage (L4) and migration, fifth stage (L5) arrive in the pulmonary arteries (PAs) 75 to 90 days postinfection (pi). Immature L5 stages are in distal pulmonary arteries for 3 months before antigen or microfilaria can be detected. Worms grow to full size and patency occurs by 180 days after infection. If males and females are present, microfilaria (MF) are eventually released into the circulation making L1 stages available for ingestion by feeding mosquitoes.

2. L5 locate in the distal pulmonary arteries as 1.5-cm worms, usually in left and right caudal pulmonary arteries.
3. L5 mature over the next 90 days and become adults by 180 days postinfection.
4. Adult worms may survive up to 5 years.

III. Pathogenic lifecycle stages
- A. The L5 (immature and mature) HW is responsible for most pathologic changes.
- B. Renal glomerular changes have been attributed to deposition and immunological destruction of MF but are of limited clinical significance.
- C. Death of MF cause significant inflammation in any tissue that can persist months after death.
- D. Cardiopulmonary changes are associated with the following:
  1. Arrival of immature L5 (90 days postinfection) in the lungs
  2. Physical presence of live adult HWs
  3. Death of immature L5 and adult HWs
  4. Release of substances from adult HWs, with local and systemic effects

IV. Variability of host responses to parasite infection
- A. *Wolbachia* spp. role in *D. immitis*
  1. It is an intracellular endosymbiotic bacteria with vertical transmission that is present in all stages of the HW life cycle (L1 to L5)
  2. Highest concentrations are in the reproductive tract of female HWs.
  3. Absence of bacteria results in infertility and decreased MF production.
  4. Association of bacteria and inflammation secondary to HWD is unclear.
- B. Killing bacteria with tetracyclines before adulticides may be associated with less pathology, but clinical significance is unknown.

Pathophysiology

I. Pulmonary vascular disease
- A. Vascular lesions are related to severity of inflammation and shear stress on endothelium associated with high cardiac output.
- B. Endothelial injury and myointimal proliferation is associated with local trauma and platelet activation by live and dead (especially) HWs.
- C. Cor pulmonale is a consequence of the activity pattern of the dog and not HW numbers (e.g., active dogs with low worm burden may have severe cardiovascular disease).
- D. Myointimal proliferation may be reversible after removal of HWs, but capillary bed fibrosis and increased pulmonary vascular resistance associated with small vessel disease may be irreversible.
- E. Embolization and obstruction of flow are rarely the cause of pulmonary hypertension.
- F. Acute lung injury is the most life-threatening aspect of HWD.

II. Cardiac disease
- A. High cardiac outputs with exercise, together with lung pathology in active dogs cause the following:
  1. Right ventricular hypertrophy (RVH): classic cor pulmonale
  2. Right-sided congestive heart failure (CHF) and ascites
  3. Pulmonary hypertension
- B. Tricuspid valve regurgitation may develop.
  1. Dilatation of tricuspid annulus from right ventricular enlargement
  2. Mechanical interference by HWs (caval syndrome)

III. Pulmonary parenchymal disease
- A. Diffuse interstitial infiltration
  1. Initial arrival of immature L5s at 70 to 90 days postinfection results in intense eosinophilic inflammation.
  2. Parenchymal lesions and loss of type I alveolar cells are especially significant during death of HWs.
  3. Pulmonary fibrosis of capillary beds occurs in active dogs.
- B. Pulmonary granulomas
  1. Develop after HW death and thrombosis
  2. Associated with immunological destruction of MF and most severe in occult HWD (no circulating MF)

IV. Caval syndrome
- A. Heavy adult worm infections (typically >75 HWs)
- B. Displacement of worms to the right atrium, caudal vena cava, and hepatic veins
- C. Presence of the worms within the tricuspid valve annulus causing tricuspid insufficiency
- D. Tricuspid insufficiency and hepatic congestion resulting in red blood cell fragility and lysis

V. Glomerulonephritis
- A. Deposition of immune complexes containing worm antigen in the glomerular basement membrane
- B. Physical damage to glomerulus by viable MF
- C. Rarely significant proteinuria

Clinical Signs

I. General trends
- A. Although HW infection can cause devastating disease, dogs often remain asymptomatic indefinitely.
- B. Signs may develop as early as 3 to 6 months after infection from the pulmonary reaction to arriving L5s.
- C. Pulmonary hypertension and significant cardiac changes may never occur or may be delayed in the inactive dog.
- D. Significant disease may develop in the athletic dog regardless of worm numbers.
- E. Death of HWs is associated with acute clinical signs.

II. Signs associated with chronic cardiopulmonary disease
- A. Nonproductive cough
- B. Respiratory distress
- C. Exercise intolerance, lethargy
- D. Syncope triggered by sudden exercise
- E. Weight loss: cardiac cachexia
- F. Ascites
- G. Hemoptysis: uncommon except with HW death

III. Acute signs associated with caval syndrome

A. Anorexia, lethargy, weakness, fever
B. Hemolytic crisis: icterus, hemoglobinuria, bilirubinuria, pale mucous membranes
C. Tachycardia, bounding pulses
D. Acute, intermittent, or chronic (weeks) duration

Diagnosis

I. Physical examination findings
   A. Heart murmur (inconsistent finding)
      1. Systolic murmur of tricuspid regurgitation may develop secondary to tricuspid insufficiency.
      2. A murmur of tricuspid regurgitation is common in dogs with caval syndrome.
      3. A diastolic murmur of pulmonary valve insufficiency is uncommon.
      4. Splitting of the second heart sound from asynchrony of closure of the aortic and pulmonic valve is associated with pulmonary hypertension and severe HWD.
   B. Lung sounds: harsh rales possible
   C. Evidence of right-sided CHF
      1. Jugular venous pulsation, distention
      2. Hepatomegaly, ascites
      3. Chronic weight loss
      4. Gallop rhythm: accentuated third heart sound
   D. Normal examination in most dogs with HWD
II. Thoracic radiography
   A. Diffuse interstitial pattern initially develops in caudal lung lobes 90 days after infection (HW haze).
   B. The earliest vascular changes are linear opacification of peripheral pulmonary arteries in the caudal lung lobes on the ventrodorsal (VD) view.
   C. Pulmonary artery tortuosity, loss of uniform tapering, and truncation develop over time.
   D. If the dog is active and increased cardiac output is generated over time, the result is right heart hypertrophy, with increased sternal contact on the lateral view and a "reverse D-shaped" heart on the VD view.
   E. Diffuse interstitial patterns and loss of detail can be associated with eosinophilic pneumonitis and acute lung injury.
   F. Nodular pulmonary parenchymal densities are indicative of focal granulomas and major arterial thrombosis.
   G. Large eosinophilic granulomas with clearly defined borders are uncommon.
   H. Minimal changes may occur even with significant worm burdens.
III. Electrocardiography (ECG)
   A. ECG evidence of RVH may occur and result in right axis deviation and deep S waves.
   B. Arrhythmias are very uncommon, even with severe disease.
IV. Echocardiography
   A. Hypertrophy of the right ventricular wall
   B. Right atrial enlargement and tricuspid insufficiency in severe HWD
   C. Paradoxical motion of the interventricular septum in some cases of pulmonary hypertension
   D. Pulmonary artery dilation with pulmonary hypertension
   E. HWs in cross-section: short parallel, echodense lines in the pulmonary artery (right peristernal view) and right heart
   F. Pulmonary hypertension: tricuspid regurgitation velocity >3 m/sec, pulmonic insufficiency velocity >2.7 m/sec
V. Clinical laboratory findings
   A. Hematology: possible eosinophilia and basophilia early in the infection
   B. Serum biochemical profile
      1. Hypergammaglobulinemia
      2. ± Elevation of hepatic enzymes
      3. Elevated serum creatinine and blood urea nitrogen (BUN) with coexisting disease or caval syndrome
   C. Urinalysis
      1. Albuminuria: rarely associated with HWD
      2. Hemoglobinuria, hyperbilirubinuria: post-caval syndrome
VI. Definitive diagnostic tests
   A. Species identification of circulating MF
      1. MF of *D. immitis* and *D. reconditum* must be differentiated.
      2. Rarely, other MF are identified in dogs from Europe.
      3. Although routine tests for MF have become less common, they are still important.
         a. MF are reservoirs of infection.
         b. Some microfilaremic dogs do not have detectable amounts of circulating HW antigen (Ag).
         c. MF-positive dogs with large numbers of MF may have adverse reactions to microfilaricidal medications.
      4. Concentration techniques (Knott test and filter method) are far superior to fresh blood smears as screening tests because MF numbers vary with temperature and activity of the dog.
      5. MF detection is negative in 40% to 50% of spontaneous HW cases and higher in dogs on preventative medications.
      6. False-positive results can occur with poor laboratory technique, failure to kill MF after adulticidal therapy, and in puppies from transplacental transfer of MF before birth if the bitch was MF positive.
      7. Only 1% to 3% of dogs with circulating MF do not have adult HWs in the heart.
   B. Serological testing
      1. Some infected dogs do not have circulating MF for one of the following reasons:
         a. Prepatent infection, with L5s in heart and lungs that are not mature enough to produce MF
         b. Host hypersensitivity to MF (immune occult)
         c. Unisex infection: >30% of MF-negative dogs
         d. Microfilaricide (chemoprophylaxis) suppression of MF
         e. Infertile HWs
      2. Regardless of testing method, all commercially available Ag assays test for the same glycoprotein.

a. The Ag measured is released in quantities high enough to be detected only from fully mature female HWs.
b. Microwell titer methods detect the lowest Ag loads (higher sensitivity).
c. There is a general relationship between the number of fully mature, female HWs and the amount of Ag.
d. False-negative results are caused by low antigenemia.
(1) Immature infections
(2) Low numbers of females
(3) Unisex (male) infections
(4) Test method with low sensitivity (whole blood tests)
e. False-positive results are rare.
(1) Technical errors: inadequate wash techniques in microwell titer methods
(2) Nonspecific binding to sample debris

C. Application of MF and HWAg testing
1. A positive MF test does not assure the presence of adult HWs.
2. A positive HWAg test indicates a current or recent infection with adult HWs.
3. A negative HWAg test does not indicate the dog is HW negative.
4. A dog can have immature adult HWs (3 to 6 months postinfection) in the heart and be negative on both MF and HWAg testing.
5. After initial testing of any dog >6 months of age, retest 3 months later to ensure HW status.
6. When screening in areas where prevalence of infection is low, the predictive value of a positive test result depends more on the specificity of the test than its sensitivity.

D. Direct visualization of adult HWs via two-dimensional echocardiography
1. The right cardiac chambers, main pulmonary artery, and caudal vena cava can be adequately imaged for adult HWs.
2. Findings can be negative in large dogs when worms reside in distal pulmonary vessels that cannot be imaged.
3. Negative results do not rule out the disease.
4. A cluster of worms surging back and forth through the tricuspid valve is a classic feature of caval syndrome.

Differential Diagnosis

I. Pulmonary thromboses
A. Hyperadrenocorticism
B. Glomerulonephritis with low antithrombin III levels
C. Idiopathic pulmonary thrombosis
D. Autoimmune hemolytic anemia
E. Primary pulmonary hypertension
F. Previously resolved HWD

II. Pulmonary neoplasia

III. Primary chronic respiratory disease
A. Chronic bronchitis
B. Bacterial and fungal pneumonia
C. Tracheal collapse

IV. Heart failure
A. Dilated cardiomyopathy
B. Pericardial disease
C. Valvular heart disease

V. Pleural cavity diseases

Treatment

I. Pretreatment evaluation
A. Perform a thorough physical examination with particular attention to coexisting diseases that might complicate therapy.
B. Counsel the owner of working dogs that exercise intolerance may continue postadulticidal therapy.
C. Thoracic radiography assesses the degree of cardiac and pulmonary arterial changes but cannot predict postadulticidal complications.
D. Initial laboratory tests include a complete blood count, serum biochemical profile, urinalysis, and semiquantitative HWAg assay.
E. Additional studies include ECG and echocardiography.

II. General sequence of therapy
A. Confirm positive results and determine Ag load with microwell testing methods.
B. Perform pretherapy screening for subclinical disease.
C. Initiate an HW preventative medication that has no acute microfilaricidal activity (NOTE: Milbemycin is microfilaricidal at the preventative dose.)
D. Administer melarsomine in split doses (see following discussion).
E. Restrict exercise during and for 6 weeks after last administration of adulticide.
F. Check for MF and treat (if present) with microfilaricide 4 weeks after melarsomine.
G. Recheck HWAg 3 to 4 months after melarsomine.

III. Patient classification (Table 12-1)
A. Classification of dogs can be useful in considering the reversibility of the disease and ability of the dog to regain activity.
B. It is not useful in predicting complications of adulticidal therapy.
C. There is a strong relationship between the number of worms killed (which cannot be predicted) and postherapeutic complications.

IV. Elimination of adult HWs
A. Melarsomine HCl (Immiticide)
1. Treat dogs with class 1 and class 2 disease with two injections of 2.5 mg/kg IM, 24 hours apart.
a. This standard dose may be used in areas where the HW burden is consistently low.
b. Regardless of classification, in endemic areas all dogs should be treated with the split-dosing regimen (see following discussion).
2. Give dogs with class 3 disease in endemic areas one injection of 2.5 mg/kg IM; wait at least 30 days, then give two injections of 2.5 mg/kg IM, 24 hours apart (split-dosing regimen).

TABLE 12-1

Classification of Heartworm Disease in Dogs

CLASS	CRITERIA
Class 1: subclinical disease	1. Weakly positive HWAg test (low worm burden) 2. No clinical signs 3. Normal physical examination 4. Thoracic radiographs normal or mild evidence of pulmonary arterial or parenchymal changes 5. Laboratory tests normal
Class 2: moderate disease	1. Moderately positive HWAg test (moderate worm burden) 2. Moderate exercise intolerance and/or an occasional cough 3. Good to fair general condition 4. Moderate right ventricular and/or main pulmonary artery enlargement, moderate enlargement of the pulmonary arteries with truncation, diffuse perivascular pulmonary parenchymal infiltrates on radiography 5. Possibly mild anemia, circulating eosinophilia
Class 3: severe disease	1. Strongly positive HWAg test (high worm burden) 2. Obvious clinical signs: significant exercise intolerance, respiratory distress, persistent cough, ascites, anorexia, weight loss 3. Poor to fair general condition, increased respiratory sounds, easily elicited cough, jugular venous distention, ascites, prolonged capillary refill time, pale mucous membranes 4. Right ventricular and atrial enlargement, enlarged pulmonary arteries with pruning, truncation and loss of arterial arborization, diffuse pulmonary parenchymal infiltrates with evidence of pulmonary thromboembolism 5. Elevated levels of blood urea nitrogen, creatinine, and hepatic enzymes

HW, Heartworm; *Ag,* Antigen

3. Even with careful attention to needle handling and injection techniques (medication must be given by deep-lumbar IM injection), local inflammation occurs.
4. Reactions to one injection may not consistently be followed by reactions to subsequent injections.
5. Efficacy against adult HWs is significantly higher than that of thiacetarsamide, and incidence of acute hepatic and renal toxicities is rare.
6. Minimize physical activity during and for 4 to 6 weeks after treatment.
7. Death of HWs (typically 2 to 3 weeks after injections) is associated with acute lung injury and platelet activation.
8. Efficacy is related to the age and sex of the worm, and a single injection can result in significant, acute lung injury if older worms are present.

B. Slow-kill methods
1. Ivermectin (Heartgard Plus) administered at the preventative dose (6 μg/kg PO once monthly) for >18 months has been associated with an incomplete, slow kill of adult HWs.
2. Monthly dosing with selamectin *(Revolution)* has less adulticidal effect than with ivermectin *(Heartgard Plus)*.
3. Moxidectin and milbemycin have very limited adulticidal effects at the preventative doses.
4. The killing of HWs (regardless of cause) is associated with acute lung injury and increased lung pathology.
5. Dogs not confined and treated with slow-kill methods have increased risk of thromboembolic disease and acute respiratory distress.
6. Slow-kill methods are not considered an effective alternative to adulticidal therapy unless other significant medical problems exist.

C. Surgical extraction of adult HWs
1. Straight alligator forceps are used for worms in the right atrium or caudal vena cava.
2. Venotomy is indicated only in caval syndrome.
3. Pulmonary arteriotomy can be performed but is usually confined to heavy worm burdens where adulticides are considered too risky.
4. Flexible grasping forceps can be introduced with fluoroscopy into the pulmonary artery via a venotomy for worm removal.

V. Elimination of MF

A. Ivermectin
1. Dose is 50 μg/kg PO, repeated in 2 weeks if MF persist.
2. The cattle parasiticide may be diluted 1:9 with propylene glycol and given at 0.5 mL/10 kg PO.
3. Dosage in collies and other ivermectin-sensitive dogs must be precise, because adverse reactions may occur at the 200 μg/kg dose.
4. Microfilaricidal reactions may occur within 2 hours in dogs with high MF numbers, so hospitalization and monitoring are prudent.
5. Prophylactic dosing of avermectins also eliminates MF by embryostasis and results in the elimination of circulating MF within 6 to 12 months, even when adults are present.

B. Milbemycin oxime
1. The prophylactic dose (500 μg/kg PO) is microfilaricidal and eliminates MF quickly.
2. Microfilaricidal reactions may occur within 2 hours in dogs with high MF numbers, so hospitalization and monitoring are prudent.

3. Inadvertent administration to dogs of unknown MF status should be avoided.

VI. Chemoprophylaxis of HW infection
   A. Ivermectin
      1. Dosage is 6 to 12 μg/kg PO once monthly.
      2. Protection is provided for an exposure period of at least 45 days preceding administration.
      3. If administered for 12 consecutive months, it kills all stages up to 4 months postinfection.
      4. At 4 months postinfection, the HWs are already in the pulmonary arteries and death of the worms is associated with lung injury, thus the terms *reach-back effect* and *prevention of infection* when administered to dogs with immature HW infections.
      5. Long-term administration to dogs with prepatent or patent infections results in suppression of MF.
      6. This dose is safe in all breeds of dogs.
   B. Milbemycin oxime
      1. Dose is 500 μg/kg PO once monthly.
      2. It also controls roundworm, hookworm, and whipworm infections.
      3. If administered for 12 consecutive months, it kills all stages up to 3 months postinfection.
      4. At 3 months postinfection, the HWs are already in the pulmonary arteries and death of the worms is associated with lung injury, thus the terms *reach-back effect* and *prevention of infection* when administered to dogs with immature HW infections.
      5. Long-term administration to dogs with prepatent or patent infections results in suppression of MF.
      6. This dose is safe in all breeds of dogs.
   C. Selamectin
      1. Dosage is 6 mg/kg applied topically every 30 days.
      2. It kills adult fleas and prevents flea eggs from hatching.
      3. This dose is safe in all breeds tested.
   D. Moxidectin
      1. Dose is 0.17 mg/kg SC every 6 months.
      2. It reduces circulating MF numbers and is not associated with adverse effects.
      3. Currently, the repositol injection formula is not commercially available.
   E. Diethylcarbamazine citrate (DEC)
      1. Dosage is 6.6 mg/kg PO SID preceding infection and for 60 days following last exposure to mosquitos.
      2. In dogs with MF, acute reactions can occur.
      3. It may be continued in dogs that subsequently become microfilaremic, as long as daily administration is not interrupted for >3 days.
      4. It may be used immediately in occult (MF-negative) infections.
   F. Reports of lack of efficacy of chemoprophylaxis
      1. Lack of client compliance is the most common cause of poor efficacy.
      2. An initial HWAg test will be negative when immature HWs are present, and if preventatives are dispensed, the dog may become positive on assay repeated 6 to 12 months later.

VII. Ancillary treatments
   A. Prednisolone
      1. Dosage is 1 to 2 mg/kg PO BID for acute lung injury associated with adulticidal therapy.
      2. It can be administered in decreasing doses over 2 weeks for suspected eosinophilic pneumonitis and pulmonary granulomas.
      3. Routine administration is not recommended with adulticidal therapy.
   B. Supplemental oxygen: induces pulmonary vasodilation and oxygenation during postadulticidal complications
   C. Therapy for right-sided CHF
      1. Strict exercise limitation
      2. Diuretics in modest doses
      3. Dietary sodium restriction
      4. Supplemental oxygen

Monitoring of Animal

I. Complications of therapy are numerous (Table 12-2).
II. Assess the efficiency of adulticide treatment by the following:
   A. Clinical signs of efficacy
      1. Development or worsening of respiratory signs 5 to 10 days after treatment from death of HW
      2. Eventual improvement in respiratory signs
      3. Nonprogression of postadulticidal signs after 8 weeks
   B. HW antigenemia
      1. Persistence beyond 12 to 20 weeks after treatment is indicative of a residual or new infection.
      2. Disappearance within 12 to 20 weeks indicates complete eradication or survival of very few worms.
   C. Microfilaremia: disappearance of MF does not guarantee all adults have been killed, because preventatives suppress MF production.
III. Assessing efficacy of microfilaricides requires timing of reexaminations.
   A. Ivermectin usually eliminates MF within 2 weeks (often within 72 hours).
   B. MF may persist in some cases.
      1. Occasionally postadulticide MF-negative status is not achieved.
         a. Persistent, dual-sex infection
         b. Inadequate dose of microfilaricide
      2. A postadulticide return of MF may occur within weeks of an initially successful microfilaricide treatment.
         a. Persistent, dual-sex infection
         b. Unisex infection with female continuing to release MF
      3. A postadulticide return of MF may occur 2 to 3 months after successful microfilaricide treatment because of reinfection with a new generation of HWs.
         a. Inadequate dose or duration of chemoprophylactic agent
         b. Noncompliance with chemoprophylactic administration

TABLE 12-2

Complications of Heartworm Therapy

THERAPIES	COMPLICATIONS AND TREATMENT
Adulticide	
Melarsomine	Deep muscle pain and swelling at injection site Use separate needle for injection Deeply inject in the muscle with digital pressure afterward Consider antiinflammatory drugs for muscle pain Subsequent injections may not follow same reaction Systemic effects Minimal complications compared to thiacetarsamide Efficacy is highly dose related, and accurate dosing by weight is critical to efficacy Pulmonary thromboembolism Fever, tachypnea, cough, and sometimes hemoptysis are evident Clinical signs usually manifest as the worms die (5 to 14 days after treatment) Disseminated intravascular coagulation may develop owing to rapidity and number of worms dying Prednisolone and oxygen are useful Bacterial pneumonia is a very rare complication of heartworm therapy Exercise restriction is essential
Microfilaricides	
Ivermectin	Overdosing in a sensitive dog may produce dose-dependent side effects Minor signs (within 10 to 12 hours) include salivation, vomiting, mydriasis, tachypnea, disorientation, stupor, mild ataxia, and tremors Severe signs (may begin within 4 to 6 hours) are marked ataxia, tremors, seizures, recumbency, coma, and death Therapy for toxicosis involves supportive care with fluid therapy Rapid reduction in MF may be confused with toxicosis Onset within 2 to 8 hours: listlessness, fever, anorexia, vomiting, diarrhea, cough, shock Therapy: supportive care with fluid therapy and corticosteroids
Milbemycin oxime	No adverse reactions attributed when administered at preventative doses Rapid reduction in MF may cause clinical signs Onset within 2 to 8 hours: listlessness, fever, anorexia, vomiting, diarrhea, cough, shock Therapy: supportive care with fluid therapy and corticosteroids
Chemoprophylactic Agents	
Ivermectin	There are no confirmed reports of adverse reactions at the prophylactic dose It is safe in all breeds at this dose
Milbemycin oxime	There are no confirmed adverse reactions to date In dogs with high MF numbers, acute reactions are related to microfilaricidal activity
Selamectin	There are no confirmed reports of adverse reactions at the prophylactic dose It is safe in all breeds
Moxidectin	Localized reactions at injection sites Repositol formula is not currently available No adverse reactions are reported from oral administration
Diethylcarbamazine	Systemic reactions occur in *Dirofilaria immitis* MF-positive dogs within 20 minutes of receiving the drug: Emesis, diarrhea, salivation Depression, lethargy, incoordination, collapse Hypovolemic shock Disseminated intravascular coagulation Reaction peaks within 1 to 2 hours, with recovery in most dogs by 6 hours Supportive therapy consists primarily of fluid therapy and administration of corticosteroids

MF, Microfilaria.

FELINE HEARTWORM DISEASE

Definition

I. An inflammatory disease of pulmonary vasculature and lung parenchyma
II. Distribution
  A. In temperate and tropical climates in which suitable mosquito vectors and reservoir animals exist
  B. Endemic in most parts of the world and in every location where dog HWD reported
III. Primary hosts and principal reservoirs: canine species
  A. Domestic and captive wild cats (e.g., African lion) are susceptible.
  B. Ferrets are more susceptible than cats.
  C. Because the infected cat rarely produces MF, a mosquito must feed on a dog and then after L3s develop, the mosquito must feed on a cat in order for the cat to get HWD.
  D. The different feeding preferences of mosquito species for cats and dogs influence the transmission of HWD from dogs to cats.

Causes

I. Caused by parasite *D. immitis,* with the mosquito as an obligatory intermediate host
II. Lifecycle of *D. immitis* (see Figure 12-1)
  A. The mortality rate of immature L5s is higher in cats than dogs, which results in more lung inflammation associated with some early worm death (80 to 160 days after infection).
  B. Adult worms may survive 1 to 3 years in cats.
III. Pathogenic lifecycle stages
  A. The L5 (immature and mature) HW is responsible for nearly all pathologic changes.
  B. The arrival and death of some immature L5 stages as early as 70 days after infection account for the early, acute respiratory disease that occurs in cats.
  C. No renal glomerular changes have been attributed to HWD in cats.
  D. Death of MF causes significant inflammation in any tissue.
  E. Cardiopulmonary changes are associated with the following:
    1. Arrival of immature L5s: intense eosinophilic reaction in cats
    2. Physical presence of live, adult HWs
    3. Death of immature L5 and adult HWs causing acute lung injury as early as 3 months after infection
    4. Release of substances from adult HWs with local and systemic effects
    5. Continued inflammatory lung disease after HW death

Clinical Signs

I. Clinical signs are respiratory, not cardiac in nature.
II. Signs can include the following:
  A. Coughing
  B. Intermittent dyspnea
  C. Sporadic vomiting: rarely associated with eating but not always associated with respiratory signs
  D. Lethargy, weight loss
  E. Hemoptysis: uncommon
  F. Nonspecific neurological signs: aberrant migration or location
III. Sudden death may result.

Diagnosis

I. Physical examination findings
  A. Heart murmurs: rare
  B. Lung sounds: harsh rales, increased bronchovesicular sounds
  C. Rarely signs associated with right-sided CHF
    1. Jugular venous pulsation, distention
    2. Pleural effusion: muffled heart and lung sounds
II. Thoracic radiography
  A. Pulmonary radiographic features are first recognizable in the caudal lung lobes and best appreciated in the VD projection.
  B. The first radiographic signs are bronchointerstitial and associated with arrival of immature L5s.
  C. Indistinct widening of the caudal pulmonary arteries may occur and can be obscured by lung parenchymal densities.
  D. Peribronchial and interstitial pulmonary lesions are often independent of tortuosity and truncation of peripheral pulmonary arteries, and the caudal lung lobes are typically the most affected.
  E. Enlargement of the caudal pulmonary arteries (ratio >1.6:1 when compared with the 9th rib in the dorsoventral or VD projection) is a transient lesion that may abate even with persistent HWD.
  F. Pleural effusion has been documented but is uncommon.
III. ECG
  A. ECG evidence of RVH is rare in cats, because pulmonary hypertension is uncommon.
  B. Hemodynamically significant arrhythmias are rare.
IV. Echocardiography
  A. The RV is typically normal.
  B. Dilatation of the main pulmonary artery and visualization of adult worms may be detected in the right parasternal view.
V. Clinical laboratory findings
  A. Eosinophilia and basophilia are highly suggestive.
  B. Biochemistry profiles and urinalysis are typically normal.
VI. Definitive diagnosis of infection
  A. Serological and MF testing
    1. Cats with HWD typically do not have circulating MF because of the following:
      a. Prepatent infections
      b. Host hypersensitivity to MF (immune occult)
      c. Unisex infection
      d. Infertility of female HW
    2. When present, MF are very transient.

3. Commercially available HWAg detection kits are applicable for all host species, with the exception of the bifunctional antibody/hemagglutination test.
   a. False-negative results are caused by low antigenemia.
      (1) Prepatent (immature) infections
      (2) Light infections with <3 worms
      (3) Unisex (male) infections
   b. False-positive results are uncommon.
      (1) Technical errors: related to inadequate wash cycles
      (2) Nonspecific binding to sample debris
4. Feline HW antibody (Ab) tests are sensitive and specific for Ab response to developing larvae and adults.
   a. Most commercial HWAb tests become positive 2 to 3 months after the infection.
   b. Cats with adult HWs may be HWAb negative.
   c. Because each commercial test evaluates different Ab responses to different Ags, discordant results between testing methods are common when examining the same cat at different times during the HW lifecycle.

B. Interpretation of results
   1. A positive HWAg test is indicative of a current or recent infection with adult female HWs.
   2. A negative HWAg test does not eliminate the disease.
   3. A negative HWAb test does not eliminate HWD.
   4. A positive HWAb test documents that the cat has been successfully infected and the L3 stage has molted and lived at least 2 to 3 months.
      a. Results may or may not reflect immature HWs in the pulmonary arteries.
      b. Results do not establish a diagnosis of an adult infestation.
      c. Ab titers or concentrations indicate a recent infection but are also frequently associated with death of immature and adult HWs.

C. Direct visualization of adult HWs with two-dimensional echocardiography
   1. The right cardiac chambers, the main pulmonary artery and right branch, and the caudal vena cava can be adequately imaged to identify adult HWs.
   2. Findings may be positive even when all other tests are negative.
   3. Failure to visualize HWs does not rule out the disease as immature worms may reside in distal pulmonary arteries.

Differential Diagnosis

I. Feline bronchial disease (asthma)
II. Pulmonary neoplasia
III. Inflammatory respiratory disease: feline infectious peritonitis, pneumonia, lung worms, lung flukes
IV. Heart failure: cardiomyopathy, pericardial disease, valvular heart disease

Treatment

I. Because of the severity of postadulticide complications in cats, adulticides are rarely administered.
II. Clinical evaluation involves the following:
   A. Thorough physical examination
   B. Thoracic radiography
      1. Assesses degree of cardiac and pulmonary arterial and parenchymal changes
      2. May help differentiate feline HWD from other potential diagnoses
   C. Selective laboratory tests
      1. Complete blood count, serum biochemical profile, urinalysis
      2. Semiquantitative HWAg assessment using a microwell technique to determine low antigenemia
      3. HWAb assay
   D. Additional special studies depending on the clinical circumstances
      1. ECG: seldom diagnostic
      2. Echocardiography
         a. Sensitivity is much greater in cats than in dogs.
         b. The bifurcation of the pulmonary artery must be imaged.
         c. Worms appear as short, hyperechoic, parallel lines.
      3. Nonselective pulmonary angiography
         a. Allows for critical evaluation of pulmonary vascular size and tortuosity, even in the presence of pulmonary parenchymal infiltrate
         b. May detect intraluminal filling defects
         c. May help rule out important differential diagnoses
III. Most investigators recommend *against* the use of adulticide therapy in cats.
   A. Melarsomine HCl (Immiticide)
      1. Limited safety or efficacy studies in cats.
      2. Single dose of 2.5 mg/kg IM resulted in 35% worm kill with no significant adverse effects, but adulticide efficacy was not significantly different from placebo (McCall, 2005).
   B. Surgical extraction of adult HWs
      1. Horsehair brush or endoscopic basket retrieval device via venotomy or pulmonary arteriotomy
      2. Indicated only in symptomatic cats in which HWs can be visualized with echocardiography or that are Ag positive
IV. Elimination of MF is rarely needed in cats.
   A. Ivermectin
      1. The prophylactic dose (24 μg/kg PO) is almost microfilaricidal.
      2. MF often disappear spontaneously.
   B. Milbemycin oxime
      1. Prophylactic dose (500 μg/kg PO) is also microfilaricidal.
      2. Microfilaricidal reactions may occur within 8 hours in cats with high MF numbers (very uncommon).

V. Chemoprophylaxis for HWD is as follows:
   A. Ivermectin
      1. Dosage is 24 µg/kg PO once monthly (4 × the canine dose).
      2. Protection is provided for an exposure period of at least 45 days preceding administration.
   B. Milbemycin oxime
      1. Dosage is 500 µg/kg PO once monthly (same as the canine dose).
      2. Provides protection for the prior 45 days, if administered at 60 and 90 days after exposure.
   C. Selamectin
      1. Dosage is 6 mg/kg applied topically every 30 days.
      2. It kills adult fleas and prevents flea eggs from hatching.
      3. It also controls internal parasites.

VI. Supportive therapy for chronic disease includes the following:
   A. Prednisolone
      1. Dosage is 1 to 2 mg/kg PO BID, then tapered over 7 to 14 days.
      2. It decreases pulmonary parenchymal inflammation caused by immature L5 stages and acute lung injury.
   B. Bronchodilators
      1. They are used to control bronchoconstriction associated with eosinophilic parenchymal inflammation.
      2. Theophylline 25 mg/kg PO has had mixed results.
   C. Antileukotrienes
      1. Empirically decrease the life-threatening respiratory crisis
      2. Montelukast sodium *(Singular)* 5 mg PO SID

Monitoring of Animal

I. Complications of therapy
   A. Adulticide administration or spontaneous death of HWs can be fatal.
      1. Acute lung injury
      2. Pulmonary thromboembolism with severe lung injury
         a. Prednisolone is useful, as for dogs (see earlier).
         b. Antibiotics are not necessary because pneumonia is rare.
         c. Exercise restriction for 4 weeks is essential.
   B. Complications associated with the use of microfilaricides are uncommon because these drugs are infrequently used in cats.
   C. All prophylactic HW prevention can be administered to HW-positive cats.
      1. Ivermectin
         a. No confirmed reports of adverse reactions at prophylactic doses
         b. Safe in all breeds at this dose
      2. Milbemycin oxime
         a. No confirmed adverse reactions to date
         b. Has unlikely but potential side effects in cats, with high MF numbers related to its microfilaricidal activity
      3. Selamectin: no confirmed adverse reactions to date

II. Long-term prognosis of HW-positive cats
   A. Cats with respiratory and cardiac disease
      1. They are radiographed every 3 months after a positive diagnosis.
      2. Clinical signs often do not correlate with radiographic lesions.
      3. Medication is continued to decrease parenchymal inflammation, even in asymptomatic cats.
      4. Cats rarely develop cardiac changes, and CHF is uncommon.
      5. Death of HWs is unpredictable and typically associated with exacerbation of respiratory signs.
   B. Prognosis in cats with HWD
      1. HW-positive cats are placed on preventatives to avoid additional infections.
      2. HWAb titers do not reflect status of adult HWs.
      3. Conversion of a cat from HWAg positive to negative does not consistently reflect status of adult HWs.
      4. Most cats with HWs eventually survive the infection but may continue to have chronic respiratory disease.
      5. Lifelong treatment for chronic bronchial disease may be necessary, even after death of all HWs in cats.

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CHAPTER 13

Introduction

J. David Fowler

FUNCTIONAL ANATOMY OF THE RESPIRATORY SYSTEM

I. Nasal cavity and sinuses
   A. They extend from external nares to nasopharynx.
   B. Nasal turbinates are lined by ciliated columnar epithelium and mucus-producing goblet cells.
      1. Larger particles (≥6 μm) in inspired air are trapped via turbulent precipitation.
      2. Inspired air is warmed and humidified.
      3. Mucus contains factors responsible for local immunity, such as interferon, lysozyme, and protease inhibitors.
      4. A reflex sneeze follows stimulation.

II. Nasopharynx and pharynx
   A. Coordinated pharyngeal muscle contractions are necessary for normal swallowing.
   B. A reflex induced by irritation stimulates reverse sneezing.
   C. Lymphocytic aggregates are involved in immunological response to inhaled antigens.

III. Larynx
   A. Complex of articulated cartilages: arytenoids, thyroid, cricoid, and epiglottis
   B. Intrinsic musculature of larynx
      1. Abduction during inspiration reduces airway resistance.
      2. Adduction during swallowing prevents aspiration.
      3. Cough reflex is induced by laryngeal stimulation.

IV. Trachea
   A. It is lined by ciliated columnar epithelium.
      1. Mucociliary action moves sedimented particulate matter toward the pharynx, where the matter is coughed and swallowed.
      2. Local factors in mucus are responsible for mucosal immunity.
   B. Stimulation results in cough.

V. Small airways: bronchi and bronchioles
   A. Distribution of inspired air into lungs
   B. Immunoglobulin A: predominant immunoglobulin
   C. Smooth muscle within bronchioles involved in bronchial constriction

VI. Pulmonary parenchyma
   A. Alveoli
   B. Pulmonary interstitium
   C. Pulmonary capillaries
   D. Area of diffusion of gases

VII. Pleural space and mediastinum
   A. Mediastinum contains major vasculature, trachea, esophagus, thymus, and heart.
   B. Pleural space is defined as a potential space between the lungs and chest wall.
   C. Pleural space is lined by mesothelium and normally contains a small volume of fluid.

VIII. Chest wall
   A. Protects intrathoracic structures
   B. Actively contributes to inspiration via external intercostal muscles

RESPIRATORY PHYSIOLOGY

I. Ventilation
   A. Inspiration is an active process.
      1. Contraction of diaphragm
      2. Contraction of external intercostal muscles
   B. Expiration is normally passive.
      1. Elastic recoil of diaphragm, chest wall, and lung
      2. Active expiration by abdominal contraction during exertion
   C. Work of breathing is determined by three factors:
      1. Compliance work is determined by lung and chest wall elastic forces.
      2. Tissue resistance work is determined by the viscosity of the lung and chest wall structures.

3. Airway resistance work is determined by the integrity and dynamics of the nares, larynx, trachea, bronchi, and bronchioles.
   a. Compliance and tissue resistance are affected by pulmonary parenchymal diseases.
   b. Airway resistance is affected by airway disease.

D. Alveolar ventilation is defined as the rate at which new air reaches the alveoli.
1. Normal tidal volume is a small percentage of total lung capacity.
   a. Insufficient volume to reach alveoli
   b. Gases exchanged via diffusion from small airways to alveoli
2. Dead space is defined as air volume within the airways where gas exchange does not occur.
   a. Anatomical dead space is normal.
   b. Physiologic dead space consists of alveoli that are nonfunctional owing to decreased blood flow.

II. Perfusion

A. Efficient gas exchange depends on physiological distribution of pulmonary blood flow.

B. Distribution is affected by alveolar oxygen concentration.
1. Decreased alveolar oxygen concentration (<70% of normal) causes vascular constriction.
2. Vascular constriction results in increases in vascular resistance up to five times normal.
3. Increased vascular resistance shunts blood away from hypoxic alveoli.
   a. Opposite effect from that in systemic vasculature
   b. Termed *physiologic shunt*

C. Pulmonary vasculature accommodates increased flow during exercise.
1. There is an increase in the number of open capillaries.
2. Existing capillaries distend to accommodate greater flow.
3. Pulmonary artery pressure increases.

III. Gas exchange

A. Gas exchange occurs in the respiratory unit.
1. Respiratory bronchioles
2. Alveolar ducts
3. Atria
4. Alveoli

B. Respiratory units are lined by a membrane.
1. Thin layer of fluid and surfactant
2. Alveolar epithelium
3. Basement membrane of alveolar epithelium
4. Interstitial space
5. Capillary basement membrane
6. Capillary endothelium

C. Rate of gas exchange through the respiratory membrane is a function of several factors.
1. Thickness of the respiratory membrane
   a. Average: 0.6 μm
   b. Increased with edema, pulmonary fibrosis
2. Surface area: decreased with emphysema
3. Diffusion coefficient of gases
   a. CO_2 is 20 times greater than O_2.
   b. O_2 is two times greater than nitrogen.
4. Differences in partial pressure of gases across the respiratory membrane

D. Ventilation/perfusion (V_A/Q) ratio determines the efficiency of gas exchange.
1. Abnormal ratio of ventilation to perfusion leads to inefficient gas exchange.
   a. Ventilation approaches zero, blood flow normal ($V_A/Q = 0$): no gas exchange
   b. Ventilation normal, blood flow approaches zero (V_A/Q = infinity): no gas exchange
2. Decreased V_A/Q arises with inadequate ventilation relative to perfusion and results in shunted blood that does not become oxygenated.
3. Increased V_A/Q occurs with poor perfusion of normally ventilated alveoli and is termed *physiologic dead space*.
4. Both increased V_A/Q and decreased V_A/Q occur simultaneously in many respiratory disease processes.
   a. Bronchial obstruction: decreased V_A/Q
   b. Alveolar disruption: increased V_A/Q

LOCALIZING RESPIRATORY DISEASE

I. History and signalment

A. Signalment can be helpful because many respiratory diseases are breed associated.
1. Tracheal collapse in small-breed dogs
2. Idiopathic laryngeal paralysis in large-breed dogs

B. Dyspnea is defined as pathologically increased respiratory effort.

C. Excessive respiratory reflexes are common presenting complaints.
1. Reverse sneezing is consistent with nasal or nasopharyngeal disease.
2. Cough indicates irritation of the trachea or airways.
   a. Dry cough is consistent with tracheobronchial irritation.
   b. Moist cough is seen with exudative processes, such as pneumonia.
3. Sneezing localizes a disease to the nasal passages.

II. Observation of respiratory pattern

A. Increased inspiratory effort and duration are typical of extrathoracic obstructive disease.
1. Laryngeal paralysis
2. Laryngeal stenosis
3. Tracheal stenosis or collapse

B. Increased expiratory effort and duration are typical of intrathoracic obstructive diseases, such as chronic bronchitis.

C. Marked inspiratory intercostal effort with rapid effortless expiration is consistent with pleural space-occupying disease.

D. Noise associated with respiration can be helpful in identifying the site of disease.

1. Whistling or raspy with nasal obstruction
2. Stertor with pharyngeal obstruction
3. Stridor with dynamic laryngeal obstruction
4. Expiratory wheezes with bronchial obstruction

III. Auscultation and percussion
   A. Normal lung sounds
      1. Bronchial sounds are heard best on expiration and over the trachea, and are quieter in peripheral lung fields.
      2. Vesicular sounds are normally very quiet and are best heard in peripheral lung fields during deep inspiration.
   B. Abnormal lung sounds
      1. Wheezes are usually heard on expiration and indicate obstruction or narrowing of small airways.
      2. Crackles are caused by the opening of small airways during inspiration and are heard with bronchial inflammation and pneumonia.
      3. Bronchial sounds referred to the peripheral lung fields may indicate lung consolidation.
      4. Loss of normal vesicular sounds ventrally in a standing animal is consistent with pleural effusion.
      5. Bowel sounds on thoracic auscultation are consistent with possible diaphragmatic hernia.
   C. Percussion
      1. Thorax is normally resonant on percussion.
      2. Areas of decreased resonance indicate lung consolidation or pleural fluid accumulation.
      3. Increased resonance is difficult to appreciate, but may be heard with emphysema or pneumothorax.

IV. Palpation
   A. Chest wall
      1. Intrathoracic extension of chest wall tumors is typically greater than extrathoracic expansion.
      2. Flail chest is caused by multiple fractures of adjacent ribs and causes paradoxical chest wall motion.
   B. Cervical region
      1. Flattening of tracheal rings is noted with tracheal collapse.
      2. Cervical tumors can cause compression of the trachea, larynx, or recurrent laryngeal nerves.

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CHAPTER 14

Diseases of the Nasal Cavity and Paranasal Sinuses

Stacey Nicoll Madden

INFECTIOUS/INFLAMMATORY DISEASES

Rhinitis/Sinusitis

Definition

I. Rhinitis is inflammation of the nasal cavity, and sinusitis is inflammation of the nasal sinuses.
II. Rhinitis and sinusitis often occur together and can be acute or chronic.

Causes

I. Bacterial infections
  A. Primary bacterial infections are rare, although secondary infections are common.
  B. They are most often a secondary complication of viral, parasitic, or fungal rhinitis; nasal foreign bodies; trauma; dental disease; or neoplasia (Van Pelt and McKiernan, 1994).
  C. Anaerobic bacteria and mycoplasma species were detected in nasal biopsy samples more commonly in cats with chronic rhinosinusitis (Johnson et al., 2005).
II. Viral infections
  A. In the dog, canine distemper virus is the most common cause of rhinitis.
    1. The incidence is low in vaccinated dogs, but it does occur in puppies 3 to 6 months of age as maternal antibodies are decreasing (Van Pelt and McKiernan, 1994).
    2. In unvaccinated and/or overcrowded populations, the virus may affect animals of any age.
  B. Other causes include parainfluenza virus, herpesvirus, and adenovirus (Clark and Carothers, 1992).
  C. Most infections in cats arise from feline herpesvirsus (rhinotracheitis) or calicivirus, especially in kittens 6 to 12 weeks of age (Morse, 1985).
  D. Recurrent rhinitis is common with feline leukemia virus or feline immunodeficiency virus (Beck et al., 1986).
III. Fungal infections
  A. The most common organism in the dog is *Aspergillus* spp.
  B. Also seen are *Penicillium*, *Cryptococcus*, and *Rhinosporidium* spp. (Gartrell et al., 1995).
  C. The most common organism in the cat is *Cryptococcus* spp., whereas *Aspergillus* spp. occurs rarely.
  D. Dogs with cryptococcosis have a greater propensity to develop secondary central nervous system (CNS) involvement and disseminated disease than do cats (O'Brien et al., 2004).
IV. Parasitic infections
  A. Although uncommon, examples in the dog include the nasal mite, *Pneumonyssoides caninum*, and a nasal nematode, *Capillaria aerophila* (King et al., 1990).
  B. In the cat, parasitic infections include *C. aerophila* and the gapeworm, *Mammomonogamus iere* (Cape, 1992).
V. Allergic conditions
  A. Allergic (immune-mediated) rhinitis is an uncommon condition in dogs (Burgener et al., 1987).
  B. There is little evidence that feline allergic rhinitis exists.
VI. Dental disease
  A. Both periodontal disease and endodontic disease can lead to a chronic rhinitis (Marreta, 1992).
  B. Oronasal fistula is also a cause of rhinitis.
VII. Foreign bodies
  A. Although an uncommon cause, foreign bodies may enter the nasal cavity by inhalation or be thrust into the nasopharynx and choanae as an animal chews (Van Pelt and McKiernan, 1994).
  B. Common foreign bodies include grass awns, twigs, and rocks.
VIII. Trauma
  A. Blunt trauma can give rise to epistaxis.
  B. Depressed facial bone fracture fragments may develop into sequestra with secondary rhinitis.
IX. Idiopathic cases (Sharp, 1990; Cape 1992)
  A. Rhinitis is idiopathic when clinical signs persist without a definitive cause.
  B. Chronic inflammatory rhinitis is commonly found in dogs with chronic nasal disease and is characterized by lymphoplasmacytic infiltrates in the nasal mucosa in the absence of an obvious etiologic process (Windsor and Johnson, 2006).
  C. Detection of high levels of fungal DNA in nasal biopsies of dogs with lymphoplasmacytic rhinitis suggests that fungal organisms may be causally associated with the inflammation (Windsor et al., 2006).

D. Some cases may actually be allergic in nature (McCarthy and McDermaid, 1990).

Pathophysiology

I. The nasal cavity responds initially to most insults by increasing glandular activity, giving rise to a serous nasal discharge.
II. Mucoid or mucopurulent discharge is seen as the disease becomes chronic or if secondary bacterial infection develops (Van Pelt and McKiernan, 1994).
III. As the disease progresses, mucosal erosion and ulceration can develop.
IV. Lysis of bone and loss of normal turbinate structure are common with more aggressive etiologies.

Clinical Signs

I. Signalment
  A. Dolichocephalic and mesocephalic breeds are more susceptible to fungal infection, whereas brachycephalics are rarely affected (Sharp, 1990).
  B. Neoplasia is more common in older dogs and is relatively rare in cats.
II. Sneezing
  A. Acute onset of paroxysmal sneezing may indicate inhalation of a foreign body.
  B. Chronic, intermittent sneezing is associated with many different causes.
  C. Gagging may also be observed as discharge pools in the nasopharynx.
III. Nasal discharge
  A. It is the primary clinical sign with nasal disease.
    1. Note whether discharge is acute or chronic, uni- or bilateral.
    2. Note character (mucoid vs hemorrhagic) of discharge.
  B. Serous nasal discharge is common early in the course of many diseases.
  C. Mucoid or mucopurulent discharge occurs with viral, bacterial, and fungal infections, as well as chronic allergy.
  D. Hemorrhagic discharge occurs with trauma, coagulation abnormalities, and fungal disease, particularly aspergillosis.
  E. Unilateral discharge is usually found with foreign bodies, dental disease, and fungal disease.
  F. Unilateral nasal discharge may be seen in animals with bilateral disease.
  G. Bilateral discharge is consistent with infectious diseases, allergy, and coagulopathies.
IV. Ulceration of the nares
  A. Occurs with many causes of rhinitis
  B. Most consistently seen with mycotic infections (Sharp, 1990)
V. Facial asymmetry
  A. Facial symmetry may be lost owing to bony or soft tissue changes.
  B. It is associated with fungal disease, trauma, or secondary inflammation.
VI. Ocular discharge
  A. It may indicate blockage of the nasolacrimal duct.
  B. Exophthalmia or inability to retropulse the eye suggests extension of disease behind the globe.
VII. Loss of airway patency
  A. Indicates severe airway compromise
  B. May be bilateral or unilateral

Diagnosis

I. Physical examination techniques and findings
  A. Palpate nasal region carefully for pain or soft-tissue swelling.
  B. Focal swelling with or without drainage may indicate a tooth root abscess.
  C. Facial deformity often reflects a destructive process, such as neoplasia or fungal infection (Rudd and Richardson, 1985).
  D. Ulceration at the external nares is consistent with fungal infection.
  E. Evaluate patency of the nasal passages.
  F. Evaluate eyes for epiphora, exophthalmos, or inability to retropulse the globes (Rudd and Richardson, 1985).
  G. Perform a complete oral examination.
    1. This may require heavy sedation or general anesthesia.
    2. Evaluate and palpate the hard and soft palates, tonsils, and oral mucosa.
      a. Nasopharyngeal masses may produce a ventral bulge in the soft palate.
      b. Tumors of the nasal cavity may cause a palpable deviation of the hard palate.
II. Clinical pathology
  A. Obtain a routine database to evaluate general health status and as a preliminary assessment for general anesthesia.
  B. Assess a coagulation panel if epistaxis is present.
III. Cytology
  A. Nasal cytology is often nonspecific; however, it occasionally provides or confirms the diagnosis.
  B. Cytological specimens are obtained after radiographs.
  C. Cytology does not appear to be a reliable means for detection of chronic rhinitis in cats (Michiels et al., 2003).
  D. Cytology of tissue samples obtained and collected under direct endoscopic visualization in dogs with aspergillosis has high diagnostic accuracy (DeLorenzi et al., 2006).
  E. Specimens are obtained via nasal swab, flush, or biopsy.
    1. Nasal swabs: poor diagnostic value
    2. Nasal flushing: rigid catheter is inserted aggressively into the nasal cavity with intermittent flushing and suction to obtain fluid and tissue.
    3. Biopsy samples: evaluation of impression smears, histopathology
IV. Culture and sensitivity testing

A. Nasal swab cultures are of little diagnostic value because of the diversity of normal flora present.
B. Tissue samples are cultured for both bacteriological and fungal analysis.
C. Positive fungal cultures are reliable if they are consistent with radiographic and rhinoscopic findings, or with serological testing (Harvey, 1984).

V. Fungal serology
A. Use agar gel double diffusion (AGDD), counterimmunoelectrophoresis (CIE), and enzyme-linked immunosorbent assay techniques to detect serum antibodies against *Aspergillus* spp. (Sharp et al., 1991b).
B. Use some caution when interpreting positive results because false-positive rates for AGDD and CIE are between 5% and 15% (Sharp et al., 1991b).
C. Serological tests must be interpreted in light of the clinical findings and diagnostic test results.
D. The latex cryptococcal antigen test (LCAT) is considered diagnostically accurate.

VI. Plain radiography
A. The dorsoventral, intraoral view of the nasal cavity and the rostrocaudal view of the frontal sinus are most useful.
B. Other useful projections are the lateral and ventral 20-degree rostral-dorsocaudal oblique views (Russo et al., 2000).
C. The signs with the highest predictive value for rhinitis in dogs are lack of ipsilateral sinus lesions, lucent foci, focal or multifocal loss of turbinate detail, and focal soft-tissue opacification (Gibbs et al., 1979).
D. Changes in cats include opacification of one or both nasal passages and frontal sinuses, nasal septum erosion, loss of turbinate structure, soft-tissue opacification, and erosion of the lateral bones (O'Brien et al., 1996).
E. Signs of fungal infection are nasal turbinate destruction, punctate lysis of the frontal and vomer bones, and increased density in the caudal nasal cavity and frontal sinuses (Sullivan et al., 1986).

VII. Computed tomography (CT) and magnetic resonance imaging (MRI)
A. Both CT and MRI are considered superior to radiography in defining the extent of the disease process and in differentiating infectious rhinitis from neoplasia (Codner et al., 1993).
B. CT is the best technique for detection of cortical bone lesions associated with nasal disease (Saunders et al., 2004).
C. CT and MRI are also useful in determining the degree of CNS involvement (Park et al., 1992).
D. Diagnostic imaging is best performed before biopsy or surgery.

VIII. Rhinoscopy
A. Rhinoscopy allows gross visualization of intranasal contents and identification of intranasal parasites, foreign bodies, oronasal fistulas, mass lesions, inflammatory or erosive processes, and mycotic plaques (Lent and Hawkins, 1992).
B. The diagnostic success of rhinoscopy alone is 8% and of rhinoscopy-assisted biopsy is 83% (Lent and Hawkins, 1992).
C. There is poor correlation between rhinoscopic appearance and inflammation severity in nasal biopsy specimens in cats with upper respiratory tract disease (Johnson et al., 2004).
D. Rhinoscopy is performed with an otoscope, flexible endoscope, or rigid arthroscope (Gartrell, 1995).
E. Anterograde rhinoscopy and retroflexed endoscopy have higher specificity and sensitivity than radiology for the diagnosis of neoplasia, inflammatory rhinitis, aspergillosis, and foreign bodies (Tasker et al., 1999).
F. Rhinoscopy is not as useful as CT and MRI for defining the extent of lesions and cannot assess bone involvement (Saunders et al., 2004).

IX. Tissue sampling methods
A. Obtain biopsy samples for histopathologic analysis in a blind fashion with rhinoscopic guidance or via rhinotomy.
B. Use radiography, CT, and MRI to help guide the biopsy.
C. Rhinoscopy-assisted biopsy provides a definitive diagnosis in 83% of cases (Lent and Hawkins, 1992).
D. Perform rhinotomy if previous nonsurgical methods fail or if it may have therapeutic potential or diagnostic benefits.

Treatment

I. Bacterial infections
A. Treatment of the underlying cause is vital in achieving resolution; otherwise, antimicrobial therapy provides only temporary resolution of clinical signs.
B. Antimicrobial selection is based on culture results.
1. Heavy growth of a single organism is clinically important.
2. If culture results are not available, or if a mixed flora is cultured, administer broad-spectrum antibiotics for a minimum of 4 to 6 weeks.
C. Medical management of cats with chronic, recurrent bacterial rhinitis/sinusitis offers temporary improvement, but clinical signs often return once treatment is completed.
1. Extension of the bacterial infection into the frontal sinus establishes a nidus not amenable to medical therapy (O'Brien and Harvey, 1976).
2. Such cases may be helped by surgical ablation of the frontal sinuses, followed by implantation of autogenous fat grafts and curettage of the ethmoid conchae (Anderson, 1987).
D. Supportive therapy is also important in the treatment of secondary bacterial rhinitis.
1. Adequate hydration and nutrition must be maintained.
2. The external nares are cleaned of debris, as needed.
3. Nebulization may aid in the movement of secretions and help relieve obstructed nasal passages.

4. Topical administration of decongestants may improve airflow, increase drainage, and decrease secretions (Ford, 1983).
   a. Phenylephrine (1.25%) applied as nose drops BID to TID
   b. Pseudoephedrine 15 to 50 mg PO BID to TID (dogs) and 2 to 4 mg/kg PO BID to TID (cats)
   c. Diphenhydramine 2 to 4 mg/kg PO TID

II. Viral infections
   A. Treatment is mainly supportive.
   B. Maintain adequate nutrition and hydration.
   C. Because secondary bacterial infections are common, treatment with broad-spectrum antibiotics is indicated.

III. Aspergillosis
   A. Rhinotomy followed by a 1-hour infusion of 2% enilconazole and oral itraconazole resulted in a satisfactory outcome in dogs with severe or recurrent aspergillosis (Clayes et al., 2006).
   B. Frontal sinus trephination, followed by a 5-minute flushing of 1% topical clotrimazole solution and installation of 1% clotrimazole cream resulted in an 86% positive response rate (Sissener et al., 2006).
   C. Topical 1% to 2% enilconazole can be administered through endoscopically or blindly placed tubes (Zonderland et al., 2002; Schuller and Clercx, 2007).
      1. Administer 120 to 200 mL and provide total drug contact time of 45 to 60 minutes.
      2. Two to three treatments are usually necessary, but good clinical results have been observed with 5% enilconazole within days of the initial treatment (McCullough et al., 1998).
   D. Topical administration of 1% clotrimazole is done through blindly placed tubes (Davidson and Pappagianis, 1985).
      1. Use 50 mL per nasal cavity and provide a contact time of 60 minutes.
      2. Multiple treatments may be necessary.
      3. Complete resolution of clinical signs may occur in dogs within 28 months of initiating therapy (Davidson et al., 1992).
      4. Adverse drug reactions have been reported, including pharyngitis, pharyngeal edema, and prolongation of anesthetic recovery (Caulkett et al.,1997).
   E. Ketoconazole at 5 mg/kg PO BID or thiabendazole at 10 mg/kg PO BID, administered for 6 to 8 weeks, can eliminate the disease in up to 50% of dogs (Sharp and Sullivan, 1989).
   F. Fluconazole at 1.25 to 2.5 mg/kg PO BID may provide resolution of clinical signs in 60% of dogs (Sharp et al., 1991a).
   G. Itraconazole at 5 mg/kg PO BID for 2 to 3 months is approximately 70% successful and induces less side effects than ketoconazole (McKiernan, 1997).
   H. Rhinotomy alone is rarely therapeutic in cases of nasal aspergillosis.
   I. Turbinectomy may be of benefit where removal of dense fungal plaque formation aids in topical drug exposure.

IV. Cryptococcosis
   A. The preferred treatment for feline cryptococcosis is fluconazole 2.5 to 5.0 mg/kg PO SID to BID (Malik et al., 1992).
      1. Fluconazole can penetrate the CNS.
      2. It is the treatment of choice for cats with CNS involvement (Perfect et al., 1986).
   B. Other agents include ketoconazole 10 mg/kg PO BID and itraconazole 10 mg/kg PO SID (Van Pelt and Lappin, 1994).
   C. The combination of amphotericin B and flucytosine has also been recommended.
      1. Amphotericin B 0.25 to 0.50 mg/kg IV every 48 to 72 hours, with total cumulative dose of 5.0 mg/kg
      2. Flucytosine 100 mg PO QID until 2 months after the resolution of signs (Ford, 1983)

V. Parasitic infections
   A. Treatments for *P. caninum* include ivermectin 0.2 to 0.4 mg/kg SC (except for ivermectin-sensitive breeds) and milbemycin oxime 0.5 to 1.0 mg/kg PO once a week for 3 weeks (Gunnarson et al., 1999).
   B. Nasal capillariasis in the dog can be treated with ivermectin 0.2 mg/kg PO once(except for ivermectin-sensitive breeds); levamisole 10 mg/kg PO SID for 5 days and repeated in 9 days; and fenbendazole 25 mg/kg PO BID for 10 days (Gartrell, 1995).
   C. In cats, nasal capillariasis is treated with ivermectin 0.2 mg/kg SC, PO once, and repeated in 3 weeks.

VI. Allergic disease: see treatment of allergies in Section 12.

VII. Dental disease
   A. Periodontal pockets and oronasal fistulas are treated by tooth extraction, closure of the defect with a mucoperiosteal flap, and appropriate antimicrobial therapy (Marreta, 1992).
   B. Fractured teeth and associated endodontic disease are treated with either root canal or extraction procedures (Van Pelt and McKiernan, 1994).

VIII. Foreign bodies
   A. If found under endoscopic guidance, attempt removal.
   B. Remove small foreign bodies rostrally with forceps.
   C. Push larger ones into the nasopharynx or pharynx for removal (McCarthy and McDermaid, 1990).
   D. If numerous small foreign bodies are present, or if a single one is tightly lodged in the nasal cavity, rhinotomy is indicated.
   E. Removal is followed by appropriate antimicrobial therapy.

IX. Trauma
   A. If acute, attempt to control epistaxis with sedation and packing the nose with gauze.
   B. If a depressed bone fragment is retained as a sequestrum, it is managed as a foreign body and removed.

X. Idiopathic disease
   A. Medical management of feline idiopathic chronic rhinosinusitis consists of antibiotic therapy, decongestants, supportive care, and, possibly, oral corticosteroids.

B. For dogs with chronic lymphoplasmacytic rhinitis, treatment options include antihistamines, oral and inhalant steroids, nonsteroidal antiinflammatories, antifungal medications and various antibiotics, such as doxycycline and azithromycin (Windsor and Johnson, 2006).
C. Surgical options include sinus trephination and irrigation, rhinotomy and turbinectomy, or ethmoid curettage and frontal sinus ablation with autogenous fat grafts (Cape, 1992).

Monitoring of Animal

I. In most cases, clinical signs resolve within 10 to 14 days of treatment.
II. If chronic destructive rhinitis is present, some degree of nasal discharge may persist.
III. Multiple treatments may be needed in dogs with aspergillosis.
A. Serial CT or MRI examinations can be used to assess response to treatment.
B. Long-term outcome following enilconazole therapy appears to be good (Schuller and Clercx, 2007).
IV. Monitor liver enzymes on a regular basis in animals receiving fluconazole or ketoconazole.
V. LCAT titers can be used to monitor response to therapy in cases of cryptococcosis (McKiernan, 1997).

Nasopharyngeal Stenosis

Definition and Cause

I. Nasopharyngeal stenosis is an unusual form of upper airway obstruction secondary to scar tissue formation across the nasopharynx (Griffon and Tasker, 2000).
II. It is thought to occur in cats following severe upper respiratory infections, particularly those that involve mucosal ulceration, such as that seen with herpesvirus (Novo and Kramek, 1999).
III. Choanal atresia and secondary nasopharyngeal stenosis occurs rarely in the dog (Richardson and Osguthorpe, 1988).
IV. Choanal atresia is failure of the posterior nasal cavity to communicate with the nasopharynx (Richardson and Osguthorpe, 1988).
V. A form of choanal atresia, called *nasopharyngeal dysgenesis,* has been reported in the dachshund (Kirberger et al., 2006).

Clinical Signs

I. Chronic history of nonprogressive upper airway stertor unresponsive to medical management.
II. Signs exacerbated by eating or swallowing
III. Minimal nasal discharge or history of sneezing
IV. Dachshunds with nasopharyngeal dysgenesis
A. Usually young: 1 to 5 years of age
B. Dyspnea, expiratory cheek puff
C. Salivation, dysphagia

Diagnosis

I. Physical examination findings
A. Upper airway stertor is ameliorated by open-mouthed breathing.
B. Lack of airflow through either nostril is noticed.
C. Macroglossia occurs in affected dachshunds.
II. Plain radiography
A. It does not aid in the diagnosis of secondary stenosis, but usually reveals lack of communication between the naso- and laryngopharynx in dachshunds with dysgenesis.
B. Increased soft-tissue opacity in one or both nasal passages may be seen with choanal atresia (Richardson and Osguthorpe, 1988).
III. Rhinoscopy
A. Retroflex the endoscope above the soft palate to view the caudal nasal passage.
B. With stenosis, the caudal opening is markedly reduced by the presence of a web of tissue across the nasopharynx.
C. Evaluate further the degree of stenosis via cannulation of the external nares with a small catheter.
D. Typically, the catheter cannot be advanced into the oropharynx.
E. With choanal atresia, the choanal openings are severely restricted or blocked completely.
IV. Oral examination of dogs with dysgenesis
A. Slitlike intrapharyngeal ostium visible
B. Confirms macroglossia

Differential Diagnosis

I. Other causes of chronic upper respiratory tract disease, including rhinitis, nasopharyngeal polyps, sinusitis, and neoplasia.
II. Pharyngeal or laryngeal disorders

Treatment

I. Secondary stenosis requires surgery.
A. Incise the soft palate to expose the nasopharynx, then resect the stenotic web of tissue.
B. To prevent recurrence, the resultant defect in the dorsal nasopharynx is reconstructed using an advancement flap from mucosa at the nasopharynx and laryngopharynx (Griffon and Tasker, 2000).
C. The use of a Wallstent wire-braided endoprosthesis may also help prevent recurrence (Novo and Kramek, 1999).
D. Bougienage of the stricture has had limited success (Novo and Kramek, 1999).
II. Choanal atresia is managed using a ventral rhinotomy for excision of the choanal membranes.
A. As with acquired stenosis, recurrence is high.
B. Permanent tracheostomy to relieve clinical signs may also be considered (Richardson and Osguthorpe, 1988).
III. Surgery to enlarge the nasopharyngeal opening in dogs with dysgenesis has not been very successful (Kirberger et al., 2006).

Monitoring of Animal

I. Recurrence of clinical signs from stricture recurrence is common.
II. Repeat the rhinoscopy 6 to 8 weeks following surgery to assess patency of the nasopharynx and choanae.

III. Although the inspiratory noise usually resolves following surgery, nasal discharge and congestion may remain.

NEOPLASIA

Nasal and Nasopharyngeal Polyps

Definition

I. Polyps are rare in dogs and relatively uncommon in cats.
II. They are the most common nasopharyngeal disease found in young cats.
III. They are small, benign masses that eventually lead to nasal or nasopharyngeal obstruction.
  A. Nasopharyngeal polyps are believed to grow from the mucosa of either the auditory tube or middle ear (Landsborough, 1994).
  B. Nasal polyps are thought to arise from the ethmoturbinates (Galloway et al., 1997).

Causes and Pathophysiology

I. Nasopharyngeal polyps are often associated with otitis media.
  A. Whether otitis media is a primary or secondary factor in the etiopathogenesis of polyp formation is unknown (Kapatkin et al., 1990).
  B. The proliferative tissue caused by otitis media may grow down the auditory tube to the nasopharynx or out through the tympanum to the external ear canal (Kapatkin et al., 1990).
II. Bacterial and viral infections and congenital lesions may play a role in the development of nasopharyngeal polyps (O'Brien and Harvey, 1976; Parker and Binnington, 1985).
III. It is thought that nasal polyps develop as a sequela to chronic upper respiratory inflammation (Galloway et al., 1997).

Clinical Signs

I. With nasopharyngeal polyps, signs of upper airway obstruction predominate and include stertorous breathing, dyspnea, sneezing, and nasal discharge.
II. Some cats with nasopharyngeal polyps present with Horner's syndrome (see Chapters 105 and 108).
III. Animals with nasal polyps present with sneezing, stertorous breathing, and inspiratory dyspnea.

Diagnosis

I. Physical assessment
  A. Evaluate for signs of upper airway obstruction, Horner's syndrome, and otic disease.
  B. Under heavy sedation or general anesthesia, perform an oropharyngeal examination, including palpation of the soft palate.
II. Skull radiography
  A. Evaluate lateral, oblique, open-mouth, and ventrodorsal views.
  B. Pay special attention to the osseous and tympanic bullae, petrous-temporal bones, nasal cavities, and nasopharynx (Kapatkin et al., 1990).
  C. Radiographs may reveal a soft-tissue density within the nasopharynx and thickening of the bulla.
  D. Soft-tissue density with loss of normal turbinate structure may be seen with nasal polyps (Galloway et al., 1997).
III. Rhinoscopy
  A. Generally not required in the diagnosis of nasopharyngeal polyps
  B. Can be helpful in the diagnosis of nasal polyps

Differential Diagnosis

I. Nasal and/or nasopharyngeal mass or foreign body
II. Nasopharyngeal stenosis
III. Pharyngeal and laryngeal disorders

Treatment

I. In animals with radiographic evidence of middle ear thickening, a ventral bulla osteotomy is recommended (see Chapter 108).
II. Polyp removal is achieved by gentle traction placed at the base of its stalk.
III. Treatment of choice for nasal polyps is ventral or dorsal rhinotomy and curettage of the nasal cavity to remove all polypoid material.
  A. Postoperative antiinflammatory medications may be helpful (Galloway et al., 1997).
  B. The efficacy of surgery alone is approximately 85% (Mortellaro, 1989).

Monitoring of Animal

I. Complications associated with ventral bulla osteotomy include facial nerve paresis, Horner's syndrome, and vestibular abnormalities, all of which usually resolve over 3 to 6 weeks (see Chapter 108).
II. Recurrence of polyps is common when bulla osteotomy is not performed (Kapatkin et al., 1990).
III. Resolution of clinical signs after bulla osteotomy and polyp removal is >90% (Kapatkin et al., 1990).

Malignant Tumors

Definition

I. Nasal tumors account for 1% to 2% of all neoplasms in the dog and 1% to 5% of all neoplasms in the cat (Madewell et al., 1976).
II. Nasal tumors are more common in middle-aged and older dogs (8 to 10 years) of the dolichocephalic and mesocephalic breeds (Theisen et al., 1996).

Causes

I. Eighty percent of canine tumors are malignant; 60% to 75% are of epithelial origin (Legendre, 1983).
  A. Most common tumors: adenocarcinoma, squamous cell carcinoma, and undifferentiated carcinoma
  B. Others: osteosarcoma, fibrosarcoma, chondrosarcoma, lymphosarcoma, melanoma, transmissible venereal tumor

II. The most common tumors in the cat are adenocarcinoma, undifferentiated carcinoma, and lymphoma (O'Brien et al., 1996).
III. Less common in the cat are fibrosarcomas, lymphohistiocytic sarcomas, chondrosarcomas, and chondromas (O'Brien et al., 1996).

Pathophysiology

I. Tumor mass within the nasal cavity can cause upper airway obstruction.
II. Invasion of adjacent structures leads to facial asymmetry and possible neurological abnormalities (Smith et al., 1989).
III. Nasal tumors are locally aggressive and destructive; metastasis occurs very late in the course of disease, if at all.

Clinical Signs

I. Intranasal tumors in dogs and cats tend to follow a slow and insidious clinical course, with signs being present for months.
II. The most common signs in dogs include nasal discharge, sneezing, and epistaxis.
    A. The discharge may initially be unilateral and later become bilateral when the tumor erodes through the nasal septum.
    B. The discharge often starts as serous and later becomes serosanguineous.
    C. Epistaxis is rarely seen early in the course of the disease.
III. Other signs in dogs include epiphora, facial asymmetry, and neurological abnormalities from extension of the tumor through the cribriform plate.
IV. Clinical signs in cats include nasal discharge, sneezing, facial and/or nasal masses, epiphora, epistaxis, stertor, and CNS signs (Theon et al., 1994).

Diagnosis

I. Suspicious history and physical findings
    A. Most animals present with a chronic history of nasal discharge and sneezing.
    B. Cats may exhibit loss of teeth associated with bone erosion (O'Brien et al., 1996).
II. Plain radiography
    A. The most useful views are the dorsoventral intraoral view of the nasal cavity and the rostrocaudal view of the frontal sinuses.
    B. Other useful projections are the lateral and the ventral 20-degree rostral-dorsocaudal oblique (Russo et al., 2000).
    C. Abnormal findings with high predictive values for the diagnosis of neoplasia include the following in the dog (Russo et al., 2000).
        1. Lytic bone lesions compatible with bony invasion
        2. Lesions affecting the entire nasal cavity
        3. Soft-tissue or fluid opacity in the ipsilateral frontal sinus
        4. Loss of turbinate detail
        5. Generalized increased opacity
    D. Certain features assist in the diagnosis of intranasal neoplasia in cats.
        1. Unilateral aggressive lesions may be seen, including lysis of the lateral bones, nasal turbinate destruction, and loss of teeth.
        2. Severity of radiographic findings is not always a good indicator of neoplasia, as similar radiographic signs can be seen with chronic rhinitis.
III. CT and MRI
    A. CT and MRI are more sensitive for detecting bone destruction and extension into adjacent soft-tissue structures (Park et al., 1992).
    B. Both techniques provide higher contrast resolution, which increases visualization of soft-tissue structures.
    C. When compared with plain radiography, CT was less sensitive at detecting the presence of nasal cavity neoplasia in cats, but more sensitive at localizing changes and determining the extent of disease (Schoenborn et al., 2003).
IV. Nasal cytology
    A. Nasal flushing for cytological samples provides a diagnosis in only 50% of animals with neoplasia (MacEwan et al., 1977).
    B. Aspiration biopsies, using a large-bore tube (7-mm diameter) improve the diagnostic success rate to 97% in dogs (Withrow et al., 1977).
V. Rhinoscopy and histopathology
    A. Rhinoscopy-assisted biopsy provides a diagnosis in approximately 83% of cases (Lent and Hawkins, 1992).
    B. Endoscopic evaluation of the choanae in dogs and cats is very helpful in the diagnosis of neoplasia (Willard and Radlinsky, 1999).
VI. Rhinotomy
    A. It is performed if less-invasive methods fail to provide a diagnosis.
    B. It provides reliable samples for cytological and histopathologic analysis.

Differential Diagnosis

I. Nasal aspergillosis
II. Coagulopathies
III. Chronic, severe bacterial rhinitis

Treatment

I. Radiation therapy
    A. When orthovoltage radiation therapy is preceded by surgical curettage, reported median survival times are 17.5 months (Adams et al., 1987) and 7.4 months (Northrup et al., 2001).
    B. Megavoltage radiation has superior penetrating ability relative to orthovoltage radiation.
        1. Average survival time is 10.1 months (Adams et al., 1987).
        2. Pretreatment cytoreductive surgery is not needed before therapy.
        3. Dogs undergoing surgical exenteration of the nasal cavity following radiation had 2-year survival rates of 69% versus 44% for those dogs undergoing only radiation (Adams et al., 2005).

4. Chronic complications of rhinitis, osteomyelitis and osteonecrosis were higher in dogs treated with surgery and radiation compared to radiation alone (Adams et al., 2005).

C. Brachytherapy using iridium-192 for intranasal neoplasms in dogs after cytoreductive surgery had a mean survival time of 7.1 months (Thompson et al., 1992).

D. Extensive disease does not preclude radiation therapy for nasal tumors.

E. Radiation therapy is also efficacious for the treatment of feline nasal tumors, with median survival times of 20.8 (Evans and Hendrick, 1989) and 13 months (Straw et al., 1986).

F. Variables associated with decreased survival in dogs undergoing radiation include an age of >10 years, regional lymph node metastasis, advanced tumor stage, and total dose >55 Gy delivered (LaDue et al., 1999).

II. Surgery

A. Rhinotomy for surgical debulking is only efficacious if followed by radiation therapy.

B. Surgery alone does not improve survival, although it may improve quality of life for a short time.

III. Chemotherapy

A. With the exception of lymphosarcoma, chemotherapy has demonstrated little efficacy in the treatment of nasal tumors.

B. The use of cisplatin in dogs with nasal adenocarcinoma did not improve survival when compared with surgery alone or no treatment.

1. A combination of radiation and a slow-release cisplatin chemotherapy in dogs resulted in mean and median survival times of 570 and 474 days, respectively (Lana et al., 2004).
2. Cisplatin may have a palliative effect in decreasing nasal discharge, sneezing, and epistaxis (Hahn et al., 1992).

C. A clinical response to therapy has been demonstrated in dogs with nasal tumors using alternating doses of doxorubicin and carboplatin, in conjunction with oral piroxicam (Langova et al., 2004).

Monitoring of Animal

I. Acute complications associated with radiation include rhinitis, oral mucositis, dermatitis, and keratoconjunctivitis (Ogilvie and LaRue, 1992).

II. Chronic complications of radiotherapy include retinal damage, cataracts, bone necrosis, skin ulceration, and brain damage.

III. Metastasis is rare with nasal neoplasia, but, as the efficacy of radiation treatment improves and survival times increase, metastatic disease may become an issue.

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CHAPTER 15

Diseases of the Larynx and Pharynx

J. David Fowler | Ronald M. Bright

DEVELOPMENTAL DISORDERS

Ronald M. Bright

Brachycephalic Syndrome

Definition

I. Multiple abnormalities of the upper airway (anatomical and acquired) result in partial to severe obstruction.
II. One or several of the following conditions contribute to this syndrome:
  A. Stenotic nares
  B. Elongated soft palate extending 2 to 4 mm caudal to the tip of the epiglottis
  C. Redundant pharyngeal mucosa
  D. Tracheal hypoplasia (primarily English bulldog)
  E. Everted laryngeal saccules
  F. Laryngeal collapse

Causes

I. The syndrome occurs primarily in brachycephalic breeds, such as the English bulldog, Boston terrier, pug, Pekingese, shih tzu, French bulldog, and boxer.
II. Sometimes, brachycephalic cats (Himalayan, Persian breeds) have similar problems.
III. The genetic influence related to this syndrome has not been well defined.
IV. Additional factors can contribute to the severity of signs.
  A. Excitement
  B. Strange environment
  C. Enclosed area (cage)
  D. Hyperthermia
  E. Obesity
  F. Anesthetic episode

Pathophysiology

I. The skull of the brachycephalic breeds is shortened rostrally from an inherited developmental defect in the bones of the skull.
  A. Compression of the nasal passages occurs, and cartilage plates of the external nares are shortened, thickened, and medially displaced.
  B. There is distortion of the pharyngeal tissues.
  C. There is an increased resistance to airflow.
  D. The work of breathing is increased.
  E. The degree of obstruction varies among animals but increases with age.
II. Greatly increased negative pressures are generated during inspiration through the obstructed nares, pharynx, or both.
  A. Inflammatory changes are often seen in the oropharynx.
  B. Secondary changes, such as everted laryngeal saccules, laryngeal edema, edematous soft palate, and redundant pharyngeal mucosa, develop in most dogs to some degree.
  C. Persistent negative pressures during inspiration can cause inflammation, stretching, and, finally, collapse of the laryngeal tissues.
  D. Some upper gastrointestinal (GI) problems may occur secondary to the airway problem(s) (Poncet et al., 2006).
III. Over time the obstructed airway can result in an increased inspiratory effort, excessive muscle activity, hyperthermia, dyspnea, cyanosis, and collapse.

Clinical Signs

I. Stertorous breathing
  A. Increased efforts are required to overcome the obstruction.
  B. The soft palate flutters and vibrates.
  C. Turbulence further traumatizes the soft palate.
  D. Inflammation, edema, and swelling develop.
II. Gagging, coughing up phlegm
III. Regurgitation and/or vomiting (occasionally)
IV. Severe snoring when animal is in a state of relaxation or sleep
V. Excessive panting
VI. Dyspnea, cyanosis
VII. Exercise intolerance, collapse

Diagnosis

I. Signalment: brachycephalic breed
II. History of inspiratory-related signs of distress, stertorous breathing
III. Physical examination findings
  A. Stenotic nares
  B. Difficult auscultation of lungs owing to referred sounds
  C. Exacerbation of signs with stress
  D. Obesity common
  E. Hyperthermia

IV. Oropharyngeal examination under light anesthesia
  A. Elongated soft palate
  B. Thickened and inflamed soft palate and laryngeal mucosa
  C. Everted, edematous lateral (laryngeal) saccules
  D. Laryngeal collapse that worsens on inspiration
V. Radiography of the thorax and cervical region
  A. Evaluate trachea for hypoplasia.
  B. Look for lower airway disease and cardiac changes.
  C. Assess concurrent upper airway problems.
  D. Look for evidence of concurrent megaesophagus or hiatal hernia (English bulldog, shar-pei).

Differential Diagnosis

I. Nasopharyngeal polyps (cats) or tumor involving oropharynx or larynx
II. Laryngeal paralysis, stenosis
III. Pharyngeal (salivary) mucocele
IV. Tracheal mass, foreign body, granuloma, stenosis

Treatment

I. Resolution of brachycephalic syndrome requires surgical corrective procedures.
II. Upper GI disorders are evaluated endoscopically to rule out inflammatory diseases that may require treatment before surgical correction of the brachycephalic syndrome (Poncet et al., 2006).
III. Anesthetic induction and recovery are critical in these animals.
  A. Give oxygen preoperatively via oxygen mask or cage.
  B. Tracheostomy is an optional procedure.
    1. It allows the administration of maintenance gas anesthesia after induction, thereby enhancing visualization of the pharynx and larynx.
    2. It helps ameliorate any problems related to postoperative dyspnea secondary to airway edema and inflammation.
  C. The animal is intubated rapidly after induction.
    1. Have a small-diameter endotracheal tube ready for dogs with possible tracheal hypoplasia.
    2. Leave the endotracheal tube in place as long as possible postoperatively.
    3. Remove the endotracheal tube gently with the cuff partially inflated.
IV. Take steps to avoid aspiration pneumonia or reflux esophagitis postoperatively.
  A. Preoperatively, fast the dog for a longer period (18 to 24 hours).
  B. Administer metoclopramide 0.2 to 0.4 mg/kg SC 30 minutes before anesthetic induction to decrease gastroesophageal reflux during surgery and the immediate postoperative period.
  C. Increase the pH of gastric contents to diminish injury to esophagus or respiratory tract if reflux occurs.
    1. Ranitidine 0.1 to 0.2 mg/kg IV
    2. Famotidine 0.5 mg/kg IV
    3. Pantoprazole 1.0 mg/kg IV (Bersenas et al., 2005)
    4. Given 30 minutes before induction of anesthesia
  D. Repeat metoclopramide and an injectable antacid TID for a total of 4 to 5 doses.
V. Use antiinflammatories preoperatively to decrease postoperative swelling.
  A. Dexamethasone 0.5 to 2.2 mg/kg IV, SC, IM
  B. Prednisolone 1.5 to 2.0 mg/kg SC, IM
  C. Repeated 4 to 6 hours after surgery
VI. Surgical options include the following:
  A. Stenotic nares surgery (rhinoplasty) is ideally performed early in life (4 to 6 months of age).
    1. Remove a vertically oriented wedge of tissue from the wing of the nostril to include the alar cartilage.
    2. The edges of the wound are sutured together with 4-0 or 5-0 synthetic multifilament suture.
    3. An alternative technique has recently been described (Ellison, 2004).
  B. Soft palate resection (staphylectomy) may be performed as follows:
    1. The soft palate is surgically incised at a point between the caudal edges and midpoint of the tonsillar crypts.
    2. A "cut-and-sew" technique is recommended (Bright and Wheaton, 1983).
    3. Laser surgery may also be performed (Clark and Sinabaldi, 1994).
  C. Everted saccules are amputated via a transoral approach.
  D. Laryngeal collapse is difficult to correct (see under Laryngeal Collapse).
    1. Laryngeal collapse is thought to be an end-stage airway obstruction secondary to the brachycephalic syndrome.
    2. Correcting the brachycephalic syndrome may be sufficient in some dogs with varying degrees of laryngeal collapse (Torrez and Hunt, 2006).
      a. Laryngeal collapse was present in 53% of the brachycephalic dogs.
      b. Correction of the brachycephalic-related problems improved 56.5% of the dogs; 10.9% did not improve.
      c. Laryngeal collapse can occur in puppies <6 months of age, so assess for brachycephalic syndrome when early signs are apparent.

Monitoring of Animal

I. Closely monitor for signs of aspiration pneumonia and reflux esophagitis postoperatively.
II. Place the animal in an oxygen-rich and humidified environment 6 to 8 hours postoperatively.
III. Prognosis is better when surgery is performed in a younger animal.
IV. Postoperative complications (primarily aspiration pneumonia) are greatest in the English bulldog (Lorinson et al., 1997).
  A. Concurrent esophageal motility problems may be present.
  B. Hiatal hernia is often a complicating factor, possibly from abnormalities of the thoracic bellows that result

from severe respiratory effort over time (Hardie et al., 1998).

DEGENERATIVE DISORDERS

J. David Fowler

Laryngeal Paralysis

Definition and Causes

I. Laryngeal paralysis is a dynamic inspiratory airway obstruction caused by paralysis of the cricoarytenoideus dorsalis (CAD) muscle.
II. Laryngeal paralysis may occur as a congenital defect in the Siberian husky, the Bouvier des Flandres, and bull terrier.
III. Laryngeal paralysis develops as part of a polyneuropathy complex in young Dalmatians and rottweilers (Braund et al., 1994: Mahony et al., 1998).
IV. Laryngeal paralysis occurs spontaneously in white-coated German shepherd dogs (Ridyard et al., 2000).
V. Juvenile laryngeal paralysis has been reported in Siberian husky and Alaskan malamute puppies (Polizopoulou et al., 2003).
VI. Acquired laryngeal paralysis occurs more frequently than congenital laryngeal paralysis.
    A. Idiopathic laryngeal paralysis
        1. Most common form of laryngeal paralysis
        2. Occurs in older large-breed dogs, especially Labrador retrievers
    B. Iatrogenic laryngeal paralysis
        1. Direct injury to the recurrent laryngeal nerve
        2. Surgery of the neck, especially following tracheal manipulation
        3. Surgical dissection of the cranial mediastinum
    C. Traumatic laryngeal paralysis following cervical trauma
        1. Bite wounds
        2. Strangulation
    D. As a component of any polyneuropathy syndrome (e.g., myasthenia gravis, hypothyroidism) (Braund et al., 1989)

Pathophysiology

I. Arytenoid cartilages
    A. Paired cartilages forming the rima glottis
    B. Lie within the thyroid cartilage and cranial to the cricoid cartilage
    C. Articulate with the cricoid cartilage
    D. Muscle process where CAD attaches
II. CAD muscle
    A. It originates on the dorsolateral margin of the cricoid cartilage, and inserts on the muscular process of the arytenoid cartilage.
    B. Contraction pulls the arytenoid cartilage into an abducted position.
    C. It is innervated by the recurrent laryngeal nerve.
III. Pathogenesis of laryngeal paralysis
    A. Traumatic disruption of recurrent laryngeal nerves
    B. Idiopathic demyelination of recurrent laryngeal nerves
    C. As a component of systemic neuromuscular disease (myasthenia gravis)
    D. As a component of a polyneuropathy

Clinical Signs

I. The hallmark of dynamic laryngeal obstruction is inspiratory stridor.
    A. High-pitched or raspy inspiratory noise
    B. Exacerbated during times of increased inspiratory effort (exercise or heat stress)
II. Voice change is often reported.
III. Gagging, coughing, and nasal discharge may also be seen.
IV. Cyanosis, hyperthermia, and collapse are often consequences of severe laryngeal obstruction.

Diagnosis

I. Diagnosis is based on direct visualization of laryngeal motion.
    A. Opioid sedation is sometimes adequate to allow laryngeal examination.
    B. Light general anesthesia is required in most cases.
        1. Minimal dose of thiobarbiturate IV is preferred (Jackson et al., 2004).
        2. Acepromazine with isoflurane mask induction is also effective (Jackson et al., 2004).
        3. Minimal dose of propofol IV can be used.
        4. Doxapram IV is helpful to stimulate respiration and aid in diagnosis (Tobias et al., 2004).
    C. A deeper plane of anesthesia obliterates normal laryngeal reflexes, resulting in a possible false-positive diagnosis of laryngeal paralysis.
    D. The hallmark feature of laryngeal paralysis is failure of the laryngeal walls to abduct during the inspiratory phase.
        1. Paralysis can be unilateral or bilateral.
        2. A paradoxical motion of laryngeal adduction during inspiration may be noted and is caused by negative airway pressure.
    E. Secondary hyperemia and edema of laryngeal mucosa are common.
II. Ultrasound assessment of laryngeal motion correlates closely with direct laryngoscopy and may provide a noninvasive means of diagnosis (Rudorf et al., 2001).
III. Cervical and thoracic radiographs are required for a complete assessment.
    A. To rule out cervical and cranial mediastinal neoplasia or masses
    B. To assess for megaesophagus, which is common with myasthenia gravis
IV. Complete blood count and biochemistry tests are recommended to rule out systemic diseases in older animals.

Differential Diagnosis

I. Laryngeal collapse
    A. Collapse may be secondary to brachycephalic airway syndrome.
    B. Signalment is helpful to differentiate collapse from paralysis.
    C. Rarely, they can occur concomitantly.

II. Fixed laryngeal obstruction
  A. Laryngeal neoplasia
  B. Laryngeal granuloma
III. Cervical tracheal collapse presenting with dynamic inspiratory dyspnea
  A. Tracheal collapse is most often seen in small-breed dogs.
  B. Tracheal collapse is usually associated with chronic cough.
IV. Tracheal or laryngeal foreign body

Treatment

I. Initial treatment is aimed at stabilization of the animal.
II. Reduce body temperature if hyperthermic (see Chapter 135).
III. Sedation is indicated to help relieve anxiety.
  A. Increased respiratory effort increases negative airway pressure and worsens dynamic adduction of arytenoid cartilages.
  B. Narcotic sedation is recommended for most dogs.
    1. Butorphanol 0.1 to 0.2 mg/kg IV
    2. Oxymorphone 0.05 to 0.1 mg/kg IV
    3. Hydromorphone 0.05 mg/kg IV
  C. Acepromazine 0.02 to 0.05 mg/kg IV can be used if the animal is normotensive.
IV. Administer oxygen if the animal is in respiratory distress (see Chapter 3).
V. Intravenous fluid therapy is usually indicated and allows rapid IV drug administration.
VI. Administration of rapid IV anesthetics allows intubation if the animal is not responsive to the previous measures.
VII. Insertion of a tracheostomy tube is indicated for temporary management of continued dynamic obstruction (see Chapter 3).
VIII. Surgery is required for definitive correction of the problem.
  A. Cricoarytenoid lateralization
    1. Using a lateral approach to the larynx, the cricothyroid and cricoarytenoid articulations are dissected.
    2. The CAD is transected and elevated from the cricoid cartilage, and two monofilament nonabsorbable sutures are placed from the dorsolateral cricoid cartilage to the muscular process of the arytenoid cartilage (LaHue, 1989).
    3. The suture is tied under moderate tension to abduct the arytenoid cartilage but not overly deform the rima glottides (Bureau and Monnet, 2002).
    4. The procedure is performed unilaterally.
      a. Left approach is best for the right-handed surgeon and vice versa.
      b. Avoid bilateral procedures because of risk of aspiration pneumonia.
  B. Thyroarytenoid lateralization
    1. Perform a lateral approach to the larynx, as described previously.
    2. Monofilament nonabsorbable suture is placed from the muscular process of the arytenoid cartilage through the opposing surface of the thyroid cartilage (White, 1989).
    3. It does not actively abduct the arytenoid cartilage, but prevents dynamic adduction of the arytenoid during inspiration (Griffiths et al., 2001).
    4. It is sometimes combined with a single cricoarytenoid lateralization suture, with results similar to cricoarytenoid lateralization (Demetriou and Kirby, 2003).
  C. Contraindications to lateralization procedures (MacPhail and Monnet, 2001)
    1. Dysphagia
    2. Esophageal dysfunction
    3. Increased risk of aspiration pneumonia
  D. Partial arytenoidectomy or ventriculocordectomy
    1. Combinations of unilateral or bilateral partial resection of the arytenoid cartilage, aryepiglottic fold, and vocal folds may be considered (Holt, 1994; Trout et al., 1994).
    2. Techniques increase the glottic opening but do not preclude dynamic adduction of the arytenoid cartilage.
    3. There is an increased risk of postoperative aspiration pneumonia compared with lateralization procedures (Ross et al., 1991).
IX. Check for adequate arytenoid abduction immediately after surgery by temporarily extubating while the animal is still under general anesthesia.
X. Consider administering an antiinflammatory dose of corticosteroids if laryngeal mucosal edema is extensive.
  A. Dexamethasone 0.5 to 1.0 mg/kg IV, SC
  B. Prednisolone 0.5 to 2 mg/kg IM, PO

Monitoring of Animal

I. Allow access to water PO after full recovery from anesthesia, and observe for evidence of aspiration.
  A. A soft cough is common after drinking and may occur for days to weeks after surgery.
  B. Excessive or persistent coughing suggests excessive aspiration.
    1. Reevaluate the degree of arytenoid abduction and glottic deformation.
    2. Consider a second surgery to correct an enlarged or deformed glottic opening.
    3. Reassess for worsening of myasthenia gravis or megaesophagus following anesthesia and surgery.
II. Allow access to food 12 to 24 hours after surgery.
  A. Do not offer food if there is evidence of aspiration after drinking water.
  B. Observe dog while eating and withdraw food if aspiration occurs.
  C. Hand-feeding small balls of canned dog food for 1 to 2 weeks after surgery controls the rate of ingestion and may decrease the risk of aspiration.
III. Warn the owners of a voice change because fixed unilateral abduction of the arytenoid cartilage and vocal fold results in a soft, hoarse bark.
IV. Prognosis varies depending on the cause of the paralysis.

A. Good to excellent with unilateral arytenoid lateralization techniques in dogs with idiopathic or congenital forms of laryngeal paralysis
   1. Approximately 85% of owners report improved quality of life following surgical correction (Snelling and Edwards, 2003).
   2. Results are poorer in dogs weighing <10 kg, with 55% of owners reporting improved quality of life (Snelling and Edwards, 2003).
B. Variable to poor with other acquired forms

Laryngeal Collapse

Definition

I. Laryngeal collapse arises secondary to loss of structural integrity of the laryngeal cartilages.
II. The severity of collapse is classified into three types.
   A. Stage 1 laryngeal collapse occurs with eversion of the laryngeal saccules.
   B. Stage 2 laryngeal collapse occurs with medial deviation of the cuneiform process of the arytenoid cartilage and aryepiglottic fold.
   C. Stage 3 laryngeal collapse denotes medial deviation or collapse of the corniculate process of the arytenoid cartilage.

Causes

I. May arise subsequent to direct laryngeal trauma and disruption of laryngeal cartilages
II. Most commonly occurs secondary to chronic upper airway obstruction, particularly as a consequence of brachycephalic airway syndrome

Pathophysiology

I. Upper airway obstruction causes increased airway resistance, increased negative intraluminal pressure, and increased flow velocity.
II. Changes in airflow dynamics cause edema of laryngeal mucosa, with eventual eversion of laryngeal saccules into the laryngeal lumen.
III. Laryngeal saccule eversion worsens airway obstruction and exacerbates abnormal airflow.
IV. Negative intraluminal pressure eventually fatigues laryngeal cartilage and causes medial deviation and eventual collapse of the arytenoid cartilages.

Clinical Signs

I. Typically presents as a worsening of chronic clinical signs associated with upper airway obstruction.
II. Often associated with stridor, but can be masked by stertor from an overlong soft palate
III. Most cases seen in brachycephalic animals >2 years of age
   A. Younger age does not preclude a diagnosis of laryngeal collapse.
   B. All animals presenting with clinical signs of brachycephalic airway syndrome or other forms of upper airway obstruction must be evaluated for laryngeal collapse.

Diagnosis

I. Definitive diagnosis is made on laryngoscopic examination under general anesthesia.
II. Everted laryngeal saccules appear as bilaterally symmetrical mucosal masses located immediately cranial to, and obliterating visualization of, the vocal cords.
III. Aryepiglottic collapse appears as medial deviation of the aryepiglottic folds and the cuneiform processes of the arytenoid cartilages.
IV. Corniculate collapse appears as medial deviation and deformation of the corniculate processes of the arytenoid cartilages.

Differential Diagnosis

I. Laryngeal collapse must be differentiated from laryngeal paralysis, and the two may occur concomitantly.
   A. Younger brachycephalic breeds are predisposed to laryngeal collapse.
   B. Older large breeds are predisposed to idiopathic laryngeal paralysis.
II. Other causes of laryngeal or pharyngeal obstruction can mimic laryngeal collapse.
   A. Laryngeal or pharyngeal neoplasia
   B. Granulomatous laryngitis
   C. Pharyngeal or laryngeal foreign body
   D. Pharyngeal mucocele or abscess

Treatment

I. Concurrent causes of upper airway obstruction must be alleviated (see Brachycephalic Syndrome).
   A. Correct congenital stenotic nares.
   B. Resect overlong soft palate.
   C. Everted laryngeal saccules are amputated using a transoral approach.
   D. Correction of stenotic nares and elongated soft palate can improve clinical function in many dogs with laryngeal collapse (Torrez and Hunt, 2006).
II. Mild to moderate stage 2 laryngeal collapse can be managed by unilateral aryepiglottic fold resection.
   A. Grasp the aryepiglottic fold and cuneiform process using an Allis tissue forceps.
   B. Resect the fold and cuneiform process using Mayo scissors.
   C. Allow healing by second intention.
   D. Avoid bilateral aryepiglottic fold resection because of risk of aspiration pneumonia.
III. Severe stage 2 or stage 3 laryngeal collapse requires permanent tracheostomy.
IV. Lateralization procedures, as described for laryngeal paralysis, are not effective for laryngeal collapse owing to the loss of structural integrity of the laryngeal cartilages.

Monitoring of Animal

I. Endotracheal tubes are maintained as long as possible during anesthetic recovery.
II. Observe carefully for respiratory obstruction following removal of the endotracheal tube.

A. If severe respiratory embarrassment occurs, the animal must be reevaluated for severity of collapse or the presence of laryngeal mucosal edema.
B. Administer an antiinflammatory dose of corticosteroids if mucosal edema is present.
C. Temporary tracheostomy is performed if needed and the tracheostomy tube maintained until edema is resolved, usually in 24 to 72 hours.
D. Permanent tracheostomy is performed if severe laryngeal collapse is noted on reevaluation.

III. The prognosis associated with laryngeal collapse varies with the stage of disease.
A. Stage 1 collapse has a favorable prognosis with correction of predisposing causes of upper airway obstruction.
B. Stage 2 collapse has a guarded prognosis because it often progresses to stage 3 collapse.
C. Stage 3 collapse has a poor prognosis for preservation of laryngeal function and requires a permanent tracheostomy.

INFLAMMATORY DISORDERS

Laryngitis

J. David Fowler

Definition and Causes

I. Laryngitis denotes inflammation of the larynx.
II. Laryngitis may be either primary or secondary.
A. Primary causes
1. Canine distemper virus infection
2. Infectious canine tracheobronchitis (kennel cough)
a. Adenovirus type 2
b. *Bordetella bronchiseptica*
c. Parainfluenza virus
3. Feline rhinotracheitis and calicivirus infections
B. Secondary causes
1. Upper respiratory irritation: smoke inhalation, regurgitation and aspiration
2. Granulomatous inflammation: etiology poorly understood
3. Iatrogenic injury during intubation and anesthesia
4. Trauma

Clinical Signs

I. Primary causes of laryngitis also result in inflammation of other upper respiratory organs (e.g., nasal cavity, trachea, bronchi).
II. Clinical signs are usually referable to organs other than the larynx (e.g., nasal discharge, cough).
III. Smoke inhalation and regurgitation and aspiration are usually associated with inflammation beyond the larynx (see Chapter 18).
IV. Inflammation restricted to the larynx is seen following laryngeal trauma or with granulomatous laryngitis.
V. Clinical signs of laryngitis include the following:
A. Cough
B. Dysphagia
C. Laryngeal obstruction: inspiratory stridor, exercise intolerance
D. Voice change

Diagnosis

I. Signalment, history, and clinical signs referable to organs other than the larynx are seen with kennel cough, feline upper respiratory viral infections, and aspiration.
II. Direct laryngeal trauma may cause fractures of laryngeal cartilages and disruption of the airway.
A. Unstable laryngeal cartilage on palpation
B. Crepitus, if subcutaneous emphysema present
C. Cartilage fractures or subcutaneous emphysema on cervical radiographs
III. Laryngoscopy under general anesthesia is required for definitive diagnosis of granulomatous laryngitis and to differentiate granulomas from other mass lesions of the larynx.
A. Partial resection and histopathologic examination are performed if lesions are extensive.
B. Total excisional biopsy may be done if lesions are focal.

Differential Diagnosis

I. Tracheitis or tracheobronchitis
II. Other causes of coughing
III. Other causes of dysphagia
IV. Neoplasia, especially for granulomatous laryngitis

Treatment

I. Acute laryngitis is usually self-limiting and may be treated symptomatically if coughing is a persistent problem.
A. Butorphanol 0.05 to 0.1 mg/kg PO BID to TID (dogs)
B. Hydrocodone bitartrate 0.22 mg/kg PO SID to TID (dogs)
II. Granulomatous laryngitis is treated by excision of granulomatous masses and use of antiinflammatory doses of prednisone at 1 to 2 mg/kg PO SID.
III. Most cases of laryngeal trauma respond to conservative management.
A. A temporary tracheostomy is required if laryngeal inflammation and edema cause obstruction.
B. Systemic antibiotics are indicated with extensive local edema or subcutaneous emphysema.
C. Antiinflammatory medications, such as corticosteroids or nonsteroidal antiinflammatory drugs, may help reduce inflammation and speed resolution of edema.
D. Surgical reconstruction of the larynx is required if trauma causes loss of the structural integrity of the airway.
E. Occasionally a permanent tracheostomy is needed following severe laryngeal trauma.
IV. Animals with laryngeal edema, loss of structural integrity, or granulomatous masses are subject to airway obstruction, and their condition may become critical.
A. Supplemental oxygen delivered via a nasopharyngeal tube or oxygen cage is beneficial if airway obstruction is suspected.
B. Consider sedation if increased respiratory effort and signs of obstruction worsen.

Monitoring of Animal

I. Keep animals with laryngitis cool and in a calm and quiet environment.
II. Avoid excitement during handling.
III. Monitor body temperature, because obstruction to airflow limits the ability to cool through panting.
IV. Combat any hyperthermia because it causes increased respiratory effort with a relative worsening of airway obstruction (see Chapter 135).

Acquired Laryngeal Stenosis

J. David Fowler

Definition

Acquired laryngeal stenosis occurs secondary to restrictive laryngeal intraluminal scar formation.

Causes and Pathophysiology

I. Bilateral ventriculocordectomy (debarking)
  A. Excessive removal of vocal folds ventrally disrupts laryngeal mucosa across the midline.
  B. Denuded areas of mucosa heal by formation of granulation tissue and wound contraction.
  C. The glottic area is reduced in size as scar tissue forms and as arytenoid cartilages are pulled into the adducted position.
II. Laryngeal trauma with loss of structural integrity
III. Extensive inflammatory disease such as granulomatous laryngitis

Clinical Signs

I. Laryngeal stenosis causes a fixed laryngeal obstruction.
  A. Both inspiratory and expiratory dyspnea are present.
  B. Inspiratory effort is usually more severe.
  C. Inspiratory stridor is usually present.
  D. Expiratory noises are sometimes present.
II. Severity of dyspnea worsens as respiratory effort increases during exercise or heat stress.

Diagnosis

I. Laryngoscopy under general anesthesia is required for definitive diagnosis.
  A. Various sizes of endotracheal tubes should be available because intubation is often difficult and requires a relatively small-diameter tube.
  B. Be prepared for insertion of a temporary tracheostomy if intubation is unsuccessful (see Chapter 3).
  C. Preoxygenation via mask delivery of 100% oxygen for 5 minutes before anesthesia reduces the risk of hypoxia during induction.
II. Laryngoscopy reveals narrowing of the airway in the presence of fibrotic scar tissue.

Differential Diagnosis

I. Laryngeal paralysis
II. Laryngeal collapse
III. Laryngeal neoplasia
IV. Laryngeal foreign body

Treatment

I. Goals of treatment
  A. Resect proliferative granulation or fibrous tissue within the lumen of larynx.
  B. Establish an intact mucosal surface, especially across the midline.
    1. Elevate mucosal advancement flaps.
    2. Reappose mucosa using 4-0 or 5-0 synthetic absorbable suture material.
  C. Reconstruct or stabilize laryngeal cartilage if necessary.
II. Ventral laryngotomy: preferred approach for most cases
III. Transoral approach appropriate in some cases
  A. Recurrence rate is higher.
  B. Unsuccessful mucosal reconstruction is the reason for recurrence.

Monitoring of Animal

I. Systemic antibiotics are administered for 5 to 10 days after surgery, because the surgical field is contaminated.
II. Acute postoperative respiratory distress may occur with severe laryngeal mucosal edema.
  A. Administer prednisone 1 to 2 mg/kg PO SID to BID or dexamethasone 0.2 to 1.0 mg/kg SC BID to TID to reduce postoperative inflammation.
  B. Delicate tissue handling and hemostasis also help to reduce the risk of significant postoperative edema.
III. Recurrence of stenosis may arise from postoperative scar formation 6 to 12 weeks after surgery.
IV. Prognosis is good with precise reconstruction.

Nasopharyngeal Polyps

Ronald M. Bright

Definition

I. Inflammatory soft-tissue growth originating in the auditory tube or middle ear
II. May cause obstruction of nasopharynx and contribute to chronic otitis externa and media

Causes

I. Chronic inflammation of nasopharynx
II. Ascending infection of nasopharynx
III. Feline calicivirus
IV. Chronic otitis media or externa
V. Branchial arch remnant

Pathophysiology

I. Polyps may be single or multiple.
II. They can involve one or both auditory tubes.
III. They may grow to be 1 to 2 cm in diameter and develop on a stalk.
IV. They sometimes involve the nasopharynx and lie under the edge of the soft palate.

V. The opening of the larynx may become partially obstructed.
VI. The ear canal, middle ear (bulla), and nasopharynx can be involved singly or in combination (see Chapter 108).

Clinical Signs

I. Sneezing, inspiratory stridor
II. Serous or purulent nasal discharge: unilateral or bilateral
III. Otic discharge: usually unilateral
IV. Occasionally, dysphagia with large nasopharyngeal masses
V. Rarely, vestibular signs: head tilt, nystagmus

Diagnosis

I. History and clinical signs are often suspicious.
II. Physical examination findings include the following:
  A. Otic examination
    1. Otic discharge, ulceration
    2. Pedunculated smooth or nodular pink masses
    3. Possibly ruptured tympanic membrane
  B. Oral examination
    1. Distorted soft palate from presence of a mass
    2. Often requires retraction of soft palate to demonstrate mass(es)
  C. Radiography
    1. Increase in radiodensity of the bulla(e)
    2. Possible soft-tissue mass in pharyngeal region
    3. Possibly soft-tissue density within the horizontal ear canal

Differential Diagnosis

I. Laryngeal neoplasia
II. Foreign body
III. Tumor involving tissue of oro- or nasopharynx
IV. Chronic rhinitis or sinusitis
V. Otitis externa (see Chapter 107)

Treatment and Monitoring

I. Gentle traction is applied to the polyp until it is pulled free.
II. Incise soft palate to help access the polyp.
III. Regardless of whether there is radiographic evidence of a polyp in the bulla, a ventral bulla osteotomy is recommended on the side(s) involved.
  A. The surgery allows easier access to a mass located in the horizontal ear canal that has grown through the tympanic membrane.
  B. The mass can be pulled from the ear canal more easily after the surgeon releases it from its attachment in the bulla.
IV. Topical otic antibiotics are given for 5 to 7 days after a single dose of preoperative antibiotics.
V. Recurrence is less common if a ventral bulla osteotomy is done (Kapatkin et al., 1990).
VI. An antiinflammatory dose of dexamethasone 0.5 to 2.0 mg/kg IV, SC, or IM or prednisolone 1.5 to 2.0 mg/kg SC, IM is given postoperatively to decrease inflammation and edema secondary to surgery.

LARYNGEAL NEOPLASIA

J. David Fowler

Definition and Causes

I. All forms of laryngeal neoplasia are relatively uncommon in the dog and cat.
II. Canine tumors include the following (Carlisle et al., 1991):
  A. Laryngeal rhabdomyoma (oncocytoma)
    1. Benign tumor arising from striated muscle
    2. Most common in younger dogs; no apparent sex predilection
  B. Locally invasive malignant tumors with significant metastatic potential
    1. Squamous cell carcinoma
    2. Adenocarcinoma
    3. Fibrosarcoma
    4. Mast cell tumor
    5. Osteosarcoma and chondrosarcoma
III. Lymphoma is the most commonly reported feline laryngeal tumor, followed by squamous cell carcinoma.

Clinical Signs

I. Voice change, stridor
II. Dysphagia
III. Coughing
IV. Dyspnea

Diagnosis

I. Most laryngeal tumors are not palpable.
II. Radiography often reveals a mass lesion encroaching on the laryngeal lumen.
III. Definitive diagnosis requires laryngoscopy and histopathologic and/or cytological examination of biopsy specimens.
IV. Staging includes assessment of regional lymph nodes and lungs for possible metastasis and is indicated for suspected malignant disease.

Differential Diagnosis

I. Laryngeal paralysis
II. Laryngeal collapse
III. Granulomatous laryngitis
IV. Pharyngeal mucocele

Treatment

I. Local resection with preservation of laryngeal function is indicated for the treatment of rhabdomyoma.
II. Treatment of malignant laryngeal neoplasia varies with the tumor type.
  A. Radiation therapy is effective for local tumor control, particularly with lymphoma, squamous cell carcinoma, and mast cell tumor.
  B. Chemotherapy is indicated for the management of lymphoma, but its use and results for other tumor types are not well documented.
  C. Total laryngectomy with permanent tracheostomy can be considered, but is rarely performed in animals.

Monitoring of Animal

I. Respiratory function must be monitored closely after biopsy or surgical removal or during the course of chemotherapy or radiation therapy.
   A. Antiinflammatory doses of corticosteroids may help alleviate mucosal edema.
   B. Temporary or permanent tracheostomy is considered if respiratory embarrassment is severe.
II. Animals are monitored for local recurrence and metastatic disease every 2 to 3 months.
III. The prognosis associated with rhabdomyoma is favorable.
IV. Prognosis associated with malignant neoplasms is often guarded to poor, although outcome is poorly documented.

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CHAPTER 16

Diseases of the Trachea

Lynelle R. Johnson

CONGENITAL DISORDERS

Hypoplastic Trachea

Definition

I. Tracheal hypoplasia is a congenital malformation that results in fixed narrowing of the tracheal lumen.
II. It can be segmental or may involve the entire tracheal length.
III. The ends of the tracheal rings meet or overlap rather than being C-shaped, and the dorsal tracheal membrane is typically short or absent.
IV. In some cases, the tracheal cartilages are V-shaped or triangulated.

Causes

I. A congenital or inherited lesion is proposed.
II. An increased incidence has been reported in the bulldog, Boston terrier, and boxer (Coyne and Fingland, 1992).
III. The disorder has also been reported in the Labrador retriever, German shepherd dog, Weimaraner, basset hound, and a litter of husky-mix dogs (Van Pelt, 1988).
IV. Males (2:1) are affected more often than females (Coyne and Fingland, 1992).

Pathophysiology

I. Narrowing of the tracheal lumen results in primarily inspiratory respiratory difficulty and a failure to clear respiratory secretions.
II. Although retained secretions can potentially predispose to recurrent respiratory infections, this has not been documented in retrospective studies.
III. Hypoplastic trachea is associated with an increased incidence of other congenital anomalies, including elongated soft palate, stenotic nares, cardiac defects (pulmonic or aortic stenosis), and megaesophagus.

Clinical Signs

I. Inspiratory difficulty
II. Stridorous sounds on inspiration
III. Coughing or gagging frequently noted
IV. Exercise intolerance from hypoventilation
V. Syncope related to hypoxia or cardiac defects
VI. Regurgitation, if megaesophagus also present
VII. Worsening of signs with excitement.

Diagnosis

I. History, signalment, and the presence of typical, clinical signs in a breed commonly affected by tracheal hypoplasia are suggestive of the diagnosis.
II. Physical examination can reveal some or all of the following findings.
  A. The trachea can feel narrow on palpation.
  B. High-pitched inspiratory sounds may be ausculted over the trachea related to turbulent airflow through the narrowed lumen.
  C. The opening of the nares must be compared to breed standards to detect stenosis.
  D. Thorough cardiac auscultation is necessary to detect concurrent congenital anomalies.
III. Radiographs of the chest establish the diagnosis.
  A. The cardinal finding is decreased tracheal diameter.
  B. Two methods may be used to evaluate tracheal diameter.
    1. The ratio of the tracheal lumen diameter (TD) at the thoracic inlet to the diameter of the thoracic inlet (TI) is calculated (Harvey and Fink, 1982).
      a. Tracheal hypoplasia is present if TD:TI is less than the normal value.
      b. The normal value for the bulldog is 0.127, for non-bulldog brachycephalic breeds is 0.160, and for nonbrachycephalic dogs is 0.204.
    2. The ratio of the TD halfway between the thoracic inlet and the carina to the width of the third rib (3R) is calculated (Suter, 1984).
      a. Normal is >3.0.
      b. Tracheal hypoplasia is present if TT:3R is <3.0.
  C. Radiographs are closely evaluated for evidence of pulmonic or aortic stenosis (see Chapter 8) and for megaesophagus (see Chapter 30), although echocardiography is needed to rule out the former conditions in a dog with a heart murmur.

Differential Diagnosis

I. Brachycephalic upper airway syndrome
II. Tracheal obstruction or neoplasia
III. Tracheal collapse
IV. Primary ciliary dyskinesia

Treatment

I. The severity of clinical signs is related to the presence of other disorders rather than the degree of reduction in tracheal diameter.
II. Concurrent respiratory or cardiac abnormalities associated with tracheal hypoplasia must be identified and managed.
   A. Upper airway abnormalities that can be surgically corrected (e.g., elongated soft palate, everted laryngeal saccules, stenotic nares) are managed early in life to reduce clinical signs.
   B. Respiratory infections must be controlled early in the course of disease.
   C. Management of obesity is strongly recommended.
   D. Judicious use of diuretics and vasodilators is indicated for treatment of congestive heart failure (see Chapter 9).

Monitoring of Animal

I. Many dogs with tracheal hypoplasia enjoy a good quality of life and can be maintained relatively free of clinical signs or respiratory distress; however, other animals are severely debilitated by disease.
II. No specific therapy is available to widen the tracheal lumen.
III. Hot and humid conditions adversely affect dogs with tracheal hypoplasia and should be avoided.
IV. Recheck examinations are advised at least yearly for early detection of complicating diseases.

DEGENERATIVE DISORDERS

Tracheal Collapse

Definition

I. Tracheal collapse is characterized by reduction in the luminal diameter of the cervical and/or intrathoracic trachea.
II. Flattening of the tracheal rings typically occurs dorsoventrally and leads to lengthening of the dorsal tracheal membrane.
III. Prolapse of the dorsal membrane into the tracheal lumen results in dynamic collapse.

Cause

I. The etiology is unknown; however, hypocellular cartilage has been detected histologically in some affected dogs.
II. Abnormal chondrocyte function with deficient production of the matrix components may result in altered integrity of the cartilage ring structure and a predisposition to collapse.
III. An increased incidence of disease is seen in small-breed dogs, such as the poodle, Yorkshire terrier, Pomeranian, and Chihuahua.
   A. Clinical signs are often seen at an early age, and it is possible that this disorder is congenital.
   B. Poor nutrition or metabolic influences may contribute to a failure of chondrogenesis and the development of abnormal cartilage metabolism in these breeds.

Pathophysiology

I. In normal animals, the trachea is a rigid but flexible structure and exhibits only minor changes in intraluminal diameter in response to pressure changes that occur during respiration.
   A. As the chest wall expands during inspiration, intrapleural pressure becomes increasingly negative.
   B. This pressure is translated across the airways and results in airflow from the glottis toward the alveolar region.
   C. On passive expiration, intrapleural pressure becomes less negative and air flows down the pressure gradient toward an equal pressure point near the thoracic inlet, where the transmural pressure difference is zero.
   D. In the normal dog, rigid cartilage within the airway walls prevents airway collapse within the thorax on expiration.
II. In some dogs with tracheal collapse, there is a deficiency in chondroitin sulfate and glycosaminoglycan in the cartilage ring structure of the trachea, which results in decreased water binding within the cartilage matrix and weakening of the tracheal cartilage (Dallman et al., 1988).
   A. Decreased rigidity in the cartilage matrix allows the cervical tracheal rings to flatten when negative pressure develops in the airway during inspiration.
   B. During forced expiration or coughing, intrathoracic pressures rise and exert positive pressure on airway walls, with collapse of the intrathoracic trachea on expiration.
III. Chronic intermittent airway obstruction results in respiratory distress and coughing, which perpetuate laryngeal, tracheal, and bronchial irritation (Done et al., 1976).
   A. Affected animals may suffer frequent, repeated episodes of respiratory distress or coughing before veterinary attention is sought.
   B. The presence of concurrent disorders, such as upper airway obstruction, chronic bronchitis, or cardiac failure, may produce serious clinical signs in a previously asymptomatic dog.
   C. Other trigger events include endotracheal intubation and respiratory infections.
   D. Obesity results in poor thoracic compliance and decreased diaphragmatic excursion, and the ability of the lung to expand on inspiration is diminished, which result in relative pulmonary atelectasis, abnormal pressure gradients along the airways, and an increased tendency toward airway collapse.
IV. Two sites of tracheal collapse have been described.
   A. Cervical (extrathoracic) tracheal collapse is characterized by signs of coughing or distress on inspiration, and upper airway obstruction from laryngeal paralysis, everted laryngeal saccules, or an elongated soft palate as the pressure drops across the upper airway.
   B. Intrathoracic tracheal collapse causes clinical signs on expiration when intrapleural pressure exceeds intraluminal airway pressure and results in airway collapse.
      1. Signs are generally more severe during forced expiration or coughing, and are enhanced by bronchitis or infection.

2. Collapse of the mainstem bronchi can occur with or without tracheal collapse.

C. Cervical and intrathoracic tracheal collapse can occur alone but are found concurrently in many dogs.

Clinical Signs

I. Long history of respiratory abnormalities
   A. Inspiratory difficulty with cervical collapse
   B. Worsened clinical signs on expiration with intrathoracic tracheal collapse or collapse of the mainstem bronchi
II. Paroxysms of coughing, classically described as a "goose honk" cough
III. Signs elicited by excitement, pressure exerted on the trachea, high heat or humidity, and eating or drinking
IV. Coughing followed by retching
V. Respiratory distress, exercise intolerance, cyanosis, and syncope in severe cases

Diagnosis

I. Signalment and clinical signs are often very suggestive of the diagnosis.
II. The following may be noted on physical examination:
   A. Affected dogs are often obese, and hepatomegaly of undetermined etiology may be present.
   B. The animal may appear normal at rest; however, excitement often induces a honking cough, airway obstruction, or respiratory distress.
   C. Marked tracheal sensitivity is typical, and even gentle palpation can precipitate a medical crisis.
   D. When the cervical trachea is severely flattened, the free edges of the cartilage rings can be palpated along their lateral aspect.
   E. Tracheal auscultation reveals musical inspiratory noises with cervical collapse.
      1. Specific attention must be paid to laryngeal auscultation.
      2. Stridor on inspiration is suggestive of concurrent laryngeal paralysis, which has been reported in 14% to 30% of dogs with tracheal collapse (Buback et al., 1996; Tangner and Hobson, 1982).
   F. Intrathoracic tracheal collapse is characterized by respiratory difficulties on expiration, with an end-expiratory snap sometimes heard over the thoracic cage.
   G. Wheezes or harsh crackles suggest the presence of concurrent bronchitis.
   H. Cardiac auscultation often reveals the presence of coexisting mitral valve insufficiency.
      1. Congestive heart failure may or may not be present.
      2. The presence of a right-sided heart murmur, gallop rhythm, or a split-second heart sound indicates that pulmonary hypertension may have developed as a complicating factor.
III. Lateral thoracic radiographs are taken on full inspiration and on expiration to detect the dynamic nature of cervical and intrathoracic tracheal collapse.
   A. The cervical trachea may be collapsed on inspiration or "balloon" open on expiration.
   B. The intrathoracic trachea collapses on expiration and may "balloon" open at the carina on inspiration.
   C. Normal static films do *not* rule out the diagnosis of tracheal collapse.
   D. Fluoroscopy is useful in suspected cases of tracheal collapse that have normal chest radiographs.
   E. When fluoroscopy is unavailable, obtaining radiographs during a cough can aid in the detection of collapsing airways.
   F. Cervical tracheal collapse also can be detected with ultrasonography; however, a high level of expertise is required because of the difficulty in delineating structures at the air-tissue interface (Rudorf et al., 1997).
IV. Both lateral and ventrodorsal thoracic radiographs are closely evaluated to identify concurrent pulmonary disease or cardiac failure.
   A. Obesity confuses interpretation of pulmonary infiltrates and can lead to artifactual enlargement of the cardiac silhouette.
   B. The degree of obesity can be demonstrated by measuring the thickness of the fat pad between the ribs and the skin on the ventrodorsal radiograph.
V. Confirmation of tracheal collapse and identification of underlying infectious or inflammatory airway disease are best achieved through bronchoscopy.
   A. Bronchoscopy can be used to obtain respiratory samples and to visualize dynamic airway changes.
   B. The grade, extent, and severity of tracheobronchial collapse can be definitively documented.
   C. Airway sampling is recommended to identify underlying pulmonary infection or inflammation.
   D. If a tracheal wash is performed, a transoral approach using a small-diameter endotracheal tube is recommended rather than a transtracheal technique in order to diminish tracheal trauma.
VI. Perform cytologic analysis and cultures for bacteria and *Mycoplasma* spp.
   A. Oropharyngeal contamination is indicated by the presence of squamous cells or *Simonsiella* spp. bacteria.
   B. The trachea is not a sterile environment (McKiernan and Smith, 1982).
   C. Positive qualitative cultures may be found in most dogs with tracheal collapse and must be interpreted in light of clinical and cytologic findings.
   D. True bacterial infection is supported by septic, suppurative inflammation on cytology and positive bacterial cultures.
   E. Quantitative bacterial cultures may be required for definitive diagnosis of lower respiratory tract infection.
VII. When either a tracheal wash or bronchoscopy is performed, upper airway structure and function should be evaluated at the beginning of the procedure to rule out laryngeal paresis or paralysis.

Differential Diagnosis

I. Infectious tracheobronchitis
II. Tracheal obstruction

III. Chronic bronchitis
IV. Congestive heart failure

Treatment

I. Treatment of coexisting medical and respiratory problems is essential.
II. Dogs that have upper airway abnormalities, such as laryngeal paralysis or everted laryngeal saccules, may become less symptomatic for tracheal collapse when these obstructive disorders are corrected surgically.
III. Dogs with bronchitis require treatment of their primary airway disease, generally with corticosteroids (see Chapter 17).
IV. Dogs with marked epithelial injury from tracheal irritation may require a short course of corticosteroids (5 to 7 days of a tapering dose) to reduce inflammation.
V. Inhaled steroids can be used to reduce tracheal or bronchial inflammation and are associated with fewer side effects.
   A. Administer fluticasone propionate (110 μg/puff) at a dose of 1 puff BID to QID, ensuring that the dog takes 8 to 10 breaths and does not pant.
   B. Administer via a spacing chamber and face mask.
VI. Bronchodilators can result in some reduction in clinical signs in dogs with intrathoracic airway collapse by dilating small airways and reducing the pressure gradient within intrathoracic airways.
   A. Extended-release theophylline 10 mg/kg PO BID
   B. Terbutaline 1.25 to 2.5 mg PO BID to TID
   C. Albuterol 50 μg/kg PO BID to TID
VII. Antibiotics are warranted when infection is documented by cytology and culture results.
VIII. Cough suppressants are used to reduce mechanical irritation of the tracheal epithelium when infectious or inflammatory processes have been adequately treated.
   A. The severity of cough in dogs with tracheal collapse may require the use of narcotic agents.
   B. Give butorphanol 0.5 to 1.0 mg/kg PO BID to QID or hydrocodone 0.22 mg/kg PO every 4 to 8 hours, as needed.
IX. Obese animals are started on a gradual weight loss program of regular exercise combined with a low-fat diet.
X. During leash walking, the use of a harness is encouraged to avoid mechanical irritation to the trachea.
XI. Dogs with tracheal collapse are susceptible to worsening of clinical signs when exposed to heat and humidity, so avoid these elements.
XII. Excessive excitement and stress must also be avoided; judicious use of tranquilizers may be considered.
XIII. Use of intratracheal stents has shown promise in the short-term management of dogs with life-threatening tracheal collapse (Moritz et al., 2004).
   A. Migration of the stent may worsen coughing, and the development of granulomatous lesions can limit their use.
   B. Dorsoventral collapse of stents has also been reported (Radlinsky et al., 1997).
XIV. Surgical placement of external ring prostheses can be used in animals with cervical tracheal collapse that fail to respond to medical management, although controversy exists on the role of surgery in the management of tracheal collapse (White and Williams, 1994).
   A. Placement of tracheal ring prostheses is technically demanding.
   B. In one study, laryngeal paralysis occurred postoperatively in 19% and necessitated a permanent tracheostomy or arytenoid lateralization (Buback et al., 1996; White 1995).
   C. Although a relatively high rate of both immediate and long-term complications such as continued coughing and respiratory distress occur after surgery, these conditions are usually manageable and acceptable to owners.
   D. Most animals that have undergone surgical intervention have an improved quality of life and reduction in clinical signs.
   E. Young dogs that undergo surgery may have a better prognosis than older dogs.

Monitoring of Animal

I. Dogs with tracheal collapse have variable clinical signs throughout their entire life, and some coughing will always be present.
II. It is likely that collapse of the lower airways can progress in severity.
III. For dogs that are managed surgically, inform owners that the duration of benefit from surgery varies.
IV. Counsel owners regarding risk factors that exacerbate disease and the need for follow-up examinations.
V. Concurrent diseases and/or obesity require rigorous monitoring.

INFLAMMATORY DISORDERS

Infectious Tracheobronchitis

Definition and Causes

I. Tracheitis is characterized by inflammation of the epithelial lining of the trachea and is typically associated with erosion of the mucosal surface, goblet cell hyperplasia, mucus accumulation, and disruption of the mucociliary clearance apparatus.
II. Viral agents (e.g., parainfluenza virus, canine adenovirus, canine distemper virus) infect respiratory epithelial cells.
III. Viral damage to the epithelium predisposes the animal to secondary infection with bacteria, primarily *Bordetella* spp. or *Mycoplasma* spp. (see also Chapter 114).
IV. The highly contagious nature of the disease leads to rapid spread among susceptible animals, with clinical signs seen 2 to 10 days postexposure.
V. Neonates and immune-compromised animals are susceptible to *Bordetella* spp. or *Mycoplasma pneumoniae.*

Clinical Signs

I. Sudden development of a dry, paroxysmal, "seal bark" cough
II. Absence of systemic signs of illness
III. Coughing easily elicited by tracheal manipulation

Diagnosis

I. Diagnosis is often based on the history of exposure to a potential carrier and on detection of the typical clinical signs in an otherwise healthy animal.
II. The primary physical examination finding is marked tracheal sensitivity.
  A. Lung sounds are normal in uncomplicated cases.
  B. Fever, anorexia, lethargy, or nasoocular discharge are indicators of systemic disease.
III. A complete diagnostic work-up is reserved for animals with systemic illness.
IV. A complete blood count may reveal the following:
  A. Lymphopenia suggests a viral etiology but is only present early in the course of disease.
  B. Neutrophilia can indicate the presence of concurrent bacterial infection, especially bronchopneumonia.
V. Thoracic radiographs are often normal.
  A. A generalized interstitial pattern is compatible with viral pneumonia.
  B. The presence of an alveolar infiltrate is suggestive of secondary bacterial pneumonia.
VI. In complicated cases, a transoral tracheal wash is performed for cytological analysis, bacterial and *Mycoplasma* spp. cultures, and antibiotic sensitivity testing.

Differential Diagnosis

I. Tracheal collapse
II. Tracheal obstruction
III. Pneumonia
IV. Acute bronchitis
V. Parasitic bronchitis or pneumonia
VI. Tracheal irritation

Treatment

I. Supportive care measures such as maintaining a warm, draft-free environment, ensuring adequate systemic hydration, and providing good nutritional support are implemented.
II. Antibiotics are indicated for treatment of secondary infection.
  A. Local antimicrobial therapy with an aminoglycosides is most likely to reduce bacterial numbers.
  B. Nebulization or intratracheal injection of gentamicin (3 to 5 mg/kg SID for 5 days) can reduce the number of bacteria present in the trachea and enhance clearance of the organism from the airway surface (Bemis and Appel, 1977).
  C. Systemic antibiotics may have limited efficacy against *Bordetella* spp. infection because this organism resides on the surface of airway epithelial cells and does not penetrate cells.
  D. Antibiotics with in vitro efficacy against *Bordetella* spp. and *Mycoplasma* spp. are possibly indicated for 7 to 10 days to reduce the spread of bacteria.
    1. Doxycycline 3 to 5 mg/kg PO BID; may stain teeth of young animals
    2. Amoxicillin-clavulanic acid 10 to 15 mg/kg PO BID; no efficacy against *Mycoplasma* spp.
    3. Enrofloxacin 2.5 to 5.0 mg/kg PO SID; possible cartilage deformation in young animals (Speakman et al., 2000)
III. Judicious use of antitussives is indicated after infection is cleared.
  A. Narcotic antitussives are often required.
  B. If antitussives are used too early, they can encourage development of pneumonia from trapping of bacteria in the lower airways.
IV. Owners are instructed to avoid use of a collar to reduce direct tracheal irritation.
V. Isolation of infected animals is recommended, humidity in the environment is reduced, and adequate ventilation is ensured.

Monitoring of Animal

I. Infectious tracheobronchitis is generally a self-limiting disease, with signs resolving within 7 to 10 days.
II. Contact with other dogs must be discouraged given the highly infectious nature of the disease.
III. Bleach can be used to disinfect the area contaminated by an infected dog (see Chapter 114).
IV. Use of a parenteral or intranasal vaccine against *Bordetella bronchiseptica* reduces the severity of infection in susceptible animals, and sequential administration of both types of vaccines may provide the highest level of protection (Ellis et al., 2001).

Parasitic Tracheitis

Definition and Causes

I. *Oslerus osleri* is a nematode parasite that resides beneath the epithelium of the carina and major bronchi in dogs.
II. The parasite has a worldwide distribution, is responsible for disease in both wild and domestic canids, and more commonly infects younger animals.

Pathophysiology

I. Transmission from bitch to offspring is believed to occur primarily through grooming activity or possibly regurgitant feeding.
II. Direct, horizontal transmission has been demonstrated experimentally (Lappin and Prestwood, 1988) but is unlikely to occur in the natural setting.
III. Infection occurs through ingestion of first-stage (L1) larvae that migrate from the intestine to the right heart and then to the tracheal wall during a 10- to 21-week prepatent period.
IV. Adult parasites live in nodules within the larger airways, often at the carina, which irritates the trachea and causes coughing.
V. Eggs and infective L1 larval stages are coughed up, swallowed, and shed intermittently in the feces.

Clinical Signs

I. Chronic, dry cough unresponsive to antibiotic therapy
II. Inspiratory respiratory distress, anorexia, and exercise intolerance

Diagnosis

I. Physical examination findings are often nonspecific, and increased tracheal sensitivity is usually present.
II. Fecal examination using the Baermann technique or zinc sulfate flotation is performed to detect first stage larvae; however, samples are often falsely negative owing to intermittent shedding.
III. Tracheal nodules associated with *O. osleri* are occasionally visible on radiographs.
IV. Bronchoscopy allows visualization of nodules at the carina, and biopsy can be performed for definitive diagnosis.
V. Transtracheal wash or bronchoalveolar lavage cytology or tracheal swabs may reveal larvae or eggs.
VI. Eosinophilia is variably present on a complete blood count or on cytology of airway washes.

Differential Diagnosis

I. Chronic bronchitis
II. Parasitic pneumonia or lungworm infection
III. Infectious or irritant tracheobronchitis
IV. Tracheal collapse

Treatment

I. No single therapy has proven efficacious for eradication of *O. osleri*, and combinations of drugs may be required for resolution of disease.
   A. Ivermectin 200 to 400 µg/kg PO or SC once weekly in breeds not susceptible to ivermectin toxicity (Outerbridge and Taylor, 1998)
   B. Fenbendazole 50 mg/kg/day PO for 10 to 30 days
   C. Thiabendazole 32 to 140 mg/kg/day PO for 10 to 23 days
II. Horizontal transmission in a kennel situation is unlikely; however, routine cleaning and hygienic maintenance are recommended.
III. Removal of infected bitches from a breeding colony reduces the incidence of disease in the offspring.

Monitoring of Animal

I. Resolution of clinical signs is the easiest method for following response to therapy, although it does not confirm the efficacy of treatment.
II. Fecal examinations are unreliable given the intermittent shedding of larvae.
III. Use radiographs to follow resolution of tracheal nodules if they were visualized on initial films.
IV. Use bronchoscopy to follow regression of intraluminal nodules with therapy.

Irritant Tracheitis

Definition and Causes

I. Tracheal irritation results from direct trauma to the cervical region, inhalation of noxious fumes, use of an overly large endotracheal tube, overdistension of an endotracheal tube cuff, or as a chronic sequela to bronchial or pulmonary disease.
II. Direct epithelial injury increases mucus production and stimulates a cough.
III. Chronic cough then results in a cycle of epithelial erosion and desquamation, increased mucus production, and trapping of secretions that perpetuate tracheal inflammation.

Clinical Signs

I. Chronic, nonproductive cough and increased tracheal sensitivity
II. Facial burns associated with smoke inhalation or cervical swelling related to choke chain trauma (see Chapter 133)

Diagnosis

I. History of smoke inhalation, recent endotracheal intubation, or recent pulmonary disease increases the suspicion of this disorder.
II. Other causes of cough must be dismissed.
III. Bronchoscopic evaluation of the airway shows irritations, hypervascularity of mucosa, increased mucus, and hemorrhage in the trachea.

Differential Diagnosis

I. Infectious tracheobronchitis
II. Tracheal collapse
III. Parasitic tracheobronchitis

Treatment

I. Eliminate environmental features, such as excessive smoke or noxious fumes.
II. Antitussives are used to decrease chronic irritation associated with coughing, but infectious diseases must be ruled out first.
III. Prednisone 0.5 mg/kg/day PO for 2 to 5 days can help alleviate tracheitis.
IV. Alternately, inhaled steroids can be used (see Tracheal Collapse).

Monitoring of Animal

I. Use of a harness may facilitate resolution of clinical signs by decreasing pressure on the trachea.
II. Cases with severe inflammation may be monitored with repeated bronchoscopy.
III. Severely affected cases are at risk for developing tracheal stenosis.
IV. Tracheal necrosis can also occur resulting in air leakage into the subcutaneous space.

TRACHEAL OBSTRUCTION

Definition and Causes

I. Tracheal obstruction results from narrowing of the tracheal lumen by internal obstruction, stenosis, or by external compression.
II. Foreign bodies that may cause airway obstruction include grass awns, tree needles, teeth, or dental tartar.
III. Intratracheal mass lesions can be caused by neoplasia, abscess formation, and parasitic or fungal granulomas.

IV. Tracheal stenosis can result from a congenital deformation, but more commonly occurs secondary to trauma (e.g., endotracheal intubation, automobile crash, tracheostomy, penetrating injury).
V. Extraluminal obstruction of the trachea can result from an esophageal mass or diverticulum, megaesophagus, thyroid cyst, lymphadenopathy, or from a mediastinal mass, abscess, or hemorrhage.
VI. Tracheal narrowing results in increased resistance to airflow, mechanical irritation of the trachea, stimulation of cough receptors, and increased susceptibility to airway infection.

Clinical Signs

I. Acute or chronic cough, with or without hemoptysis
II. Acute or progressive respiratory distress, panting
III. Anxiety, pawing at the face
IV. Dysphagia, halitosis
V. Exercise intolerance

Diagnosis

I. History of vomiting, intubation, or trauma raises the suspicion of a tracheal foreign body or obstruction.
II. Physical examination often reveals increased tracheal sensitivity.
   A. High-pitched, musical sounds can be heard over the trachea when the lumen is narrowed by an obstruction or increased secretions.
   B. Stridor may be detected in animals with high cervical tracheal obstruction.
   C. A cervical mass or esophageal enlargement may result in palpable thickening of the neck region.
III. Radiographs may reveal a radiodense foreign body or soft-tissue mass within the tracheal lumen, a focal narrowing of the tracheal air column (stenotic lesion), or an external mass impinging on the tracheal lumen.
IV. Use bronchoscopy to confirm the diagnosis of an intraluminal mass or foreign body, stenotic lesion, or extraluminal obstruction.

Differential Diagnosis

I. Tracheal collapse
II. Infectious tracheobronchitis
III. Tracheal hypoplasia
IV. Parasitic tracheitis
V. Feline bronchial disease

Treatment

I. Tracheal foreign bodies are best removed via bronchoscopy when possible.
   A. Infection with *Nocardia* spp. may be associated with foreign bodies (Lotti and Niebauer, 1992).
   B. Both aerobic and anaerobic bacterial cultures are performed, as *Actinomyces* spp. or anaerobes can be found.
II. Bougienage, balloon dilatation, or laser resection can be attempted for tracheal stenosis.
   A. The inflammatory response generated by the procedure can lead to rapid reformation of the stricture.
   B. The risk of tracheal laceration leading to pneumomediastinum or subcutaneous emphysema must be considered.
III. Tracheal stenosis usually requires surgical resection and anastomosis, with lesions involving <8 to 10 tracheal rings being resected without excessive stress on the incision site.
IV. Extraluminal compressive lesions are best evaluated by computed tomography, followed by surgical exploration of the region.

Monitoring of Animal

I. Recurrent hemoptysis, pneumonia, and chronic coughing are indications that either a foreign body or infection persists.
II. After tracheal resection and anastomosis, cough suppressants are used to reduce irritation of the tracheal mucosa.
III. Harness-style restraints can also be used to restrict excessive neck motion and reduce tension at the anastomotic site.

NEOPLASIA

Definition and Causes

I. Neoplasia results from uncontrolled overgrowth of abnormal epithelial or mesenchymal cells within the airways.
II. Adenocarcinoma, lymphosarcoma, squamous cell carcinoma, melanoma, plasmacytoma, and chondrosarcoma occur in the dog and cat (Carlisle et al., 1991).
III. Osteochondroma is the most common tracheal tumor and is usually found in young dogs (Carlisle et al., 1991).
IV. Mass lesions within the trachea cause upper airway obstruction or respiratory distress from narrowing of the tracheal lumen and increased resistance to air flow.

Clinical Signs

I. Inspiratory difficulty or respiratory distress, panting, or abnormal respiratory movements
II. Exercise intolerance
III. Coughing
IV. Increased inspiratory noises
V. Cyanosis, syncope
VI. Systemic signs often absent

Diagnosis

I. Physical examination often reveals abnormal respiratory sounds.
   A. Musical or wheezing noises can be heard over the trachea.
   B. Increased tracheal sensitivity may also be present.
II. Radiographs may show an intraluminal mass lesion.
III. Bronchoscopy often allows visualization and biopsy of the mass; occasionally, resection or debulking can be performed.

Differential Diagnosis

I. Tracheal collapse
II. Tracheal obstruction: foreign body, granuloma, *O. osleri*
III. Laryngeal paralysis

IV. Congestive heart failure
V. Chronic bronchitis
VI. Pulmonary hypertension

Treatment

I. Prepare for an emergency tracheotomy in any case in which neoplasia of the cervical trachea is suspected.
II. Mass removal via bronchoscopy may be possible when the mass is attached to the mucosa by a pedunculated stalk.
III. Tracheal resection and anastomosis can be curative in some cases with only local disease.
IV. Involvement of >8 to 10 tracheal rings may prohibit surgical treatment because of the risk of excessive tension on the suture line after anastomosis.
V. Aggressive neoplasms often require subsequent chemotherapy or radiation therapy.
   A. Lymphoma involving the trachea often responds to standard chemotherapy regimens.
   B. Palliation of clinical signs may be achieved through a permanent tracheostomy distal to the tumor, with radiation therapy and/or chemotherapy.

Monitoring of Animal

I. Closely monitor the animal for signs of metastasis and local recurrence through bimonthly radiographs.
II. Osteochondromas are associated with an excellent prognosis when the tumor can be fully resected.
III. Response to therapy is variable for malignant neoplasms affecting the trachea.

TRAUMA

Definition and Causes

I. Tracheal trauma usually results from penetrating neck injuries, bite wounds, gun shot wounds, or from an automobile accident.
II. Iatrogenic trauma most commonly occurs with overinflation of an endotracheal tube cuff.
III. In cats, 1.6 ± 0.7 mL of air sufficiently inflates the cuff of most endotracheal tubes (Hardy et al., 1999).
IV. Use of excessive force during endotracheal intubation or application of high intrapulmonary pressures during anesthesia or ventilator therapy can lead to tracheal injury or rupture.
V. Breakdown of a tracheotomy or tracheostomy site results in clinical signs similar to those found with penetrating injuries to the trachea.

Pathophysiology

I. Damage to the tracheal cartilage or annular ligament allows leakage of air into the fascial planes of the cervical region with each inspiration.
II. In cats the most common lesion is a linear tear in the dorsal trachealis muscle near the thoracic inlet or in the thoracic trachea (Hardy et al., 1999).
III. Excessive air accumulation within the neck region may compress the trachea.
IV. Decreased flow of oxygen into the lung results in alveolar hypoventilation and respiratory embarrassment.

Clinical Signs

I. May be delayed with tracheal necrosis
II. Subcutaneous emphysema
III. Inspiratory dyspnea, tachypnea, and occasionally cyanosis

Diagnosis

I. History of a predisposing event increases the probability of tracheal trauma, even if the onset of signs is delayed.
II. In cats, tracheal injury occurs most commonly after dental procedures (Hardy et al., 1999).
III. Physical examination may reveal the following:
   A. Subcutaneous emphysema usually originates in the neck region but may extend across the entire body.
   B. Bite wounds, lacerations, or other evidence of trauma may be found in the cervical region.
IV. Radiographs may show subcutaneous air accumulation in the cervical region, pneumomediastinum, or potentially, pneumothorax.
V. Tracheoscopy can locate tracheal lacerations in some cases.

Differential Diagnosis

I. Infection with gas producing bacteria
II. Other causes of tracheal stenosis and obstruction

Treatment

I. Conservative management is usually successful when signs are mild, such as in cases of blunt trauma without tracheal or airway penetration.
   A. Bandage the wound securely to prevent additional air leakage without restricting respiratory effort or venous return.
   B. Provide an oxygen-enriched environment to reduce respiratory distress and alleviate hypoxemia.
   C. Forced cage rest is important.
II. If significant respiratory distress develops because of severe subcutaneous emphysema, place 18- to 20-gauge needles under the skin to expel air from the subcutaneous space and relieve external compression of the airway.
III. Surgical treatment is required in severely affected cases to prevent further leakage of air into the subcutaneous space and to stabilize respiration.
   A. Surgical debridement and meticulous closure of tracheal rents are indicated in cases refractory to conservative therapy.
   B. Tracheal resection and anastomosis may be required in cases with substantial tracheal damage.

Monitoring of Animal

I. Subcutaneous air accumulation resolves within 7 to 10 days in uncomplicated cases, although it may persist for up to 6 weeks.
II. Closely monitor for complications related to laryngeal damage or paralysis, as well as esophageal injury.
III. Tracheal stenosis or stricture can occur weeks to months later.

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CHAPTER 17

Diseases of the Lower Airway

Astrid Nielssen | Susan M. Taylor

CONGENITAL DISORDERS

Primary Ciliary Dyskinesia

Definition

I. Primary ciliary dyskinesia is a heterogenous group of disorders causing congenital ciliary dysmotility or immotility associated with ultrastructural defect in ciliary axonemes.
II. The absence of normally functioning cilia can result in rhinitis, sinusitis, bronchitis, bronchiectasis, otitis media, hydrocephalus, dilatation of renal tubules, and infertility.
III. Kartagener's syndrome is a subsidiary disorder defined by the presence of partial or complete situs inversus, rhinosinusitis, and bronchiectasis.

Causes

I. Primary ciliary dyskinesia has an autosomal recessive inheritance pattern in dogs.
   A. It has been identified in the English springer spaniel, English pointer, Old English sheepdog, golden retriever, bichon frisé, border collie, bull mastiff, Chihuahua, chow chow, cocker spaniels, Dalmatians, Doberman pinscher, English setter, Irish wolfhound, miniature poodle, Newfoundland, rottweiler, Staffordshire terrier, and Chinese shar-pei.
   B. It is rarely reported in cats.
II. Acquired structural and functional disorders of cilia may also arise secondary to respiratory disorders, such as viral, bacterial, and mycoplasmal infections; inflammatory conditions; and exposure to inhaled toxins (e.g., smoke).
III. Acquired abnormalities are distinguished from primary inherited ciliary dyskinesia by ciliogenesis and the type of ultrastructural defects identified (Clercx et al., 2000).

Pathophysiology

I. Defects in the respiratory cilia of dogs with primary disease include dynein arm deficiency, abnormal microtubular patterns, absent radial spokes, and absence of central tubules.
   A. Defects with secondary disorders include peripheral microtubular abnormalities, partial dynein arm deficiency, and shortening of the dynein arms.
   B. With secondary disease, a much lower percentage of cells (<20%) are affected compared to primary dyskinesia.
II. Normal mucociliary transport in the airways requires coordinated beating of respiratory cilia and, without this normal defense mechanism, the upper and lower respiratory tracts become congested with mucus and are highly susceptible to infection.
III. Ciliary defects also result in signs of disease outside of the respiratory tract.
   A. In the auditory tube, impaired mucociliary clearance results in the accumulation of secretions and fluid within the middle ear, potentially resulting in a sterile, serous otitis media.
   B. Defective spermatozoal flagellum in the male and oviductal cilia in the female often causes impaired fertility.
   C. Hydrocephalus may arise from impaired cerebrospinal fluid circulation owing to dysfunctional ependymal cilia or early mycoplasmal infection (Daniel et al., 1995).
   D. Other abnormalities of uncertain origin also may be noted in dogs with primary disorders.
      1. Situs inversus (Edwards et al., 1992; Supp et al., 1997)
      2. Malformations of the axial skeleton, renal cortical fibrosis, cystic distal renal tubules, cleft palate, elongated soft palate, and corneal opacities
      3. Cardiac defects (Reichler et al., 2001)

Clinical Signs

I. Signs may develop any time from the neonatal period to the geriatric years, depending on the severity of the dyskinesia.
II. Initial signs include chronic mucoid or mucopurulent nasal discharge, sneezing, and coughing.
   A. The cough is typically productive and is easily elicited with tracheal palpation.
   B. Auscultation may reveal increased lung sounds over all lung fields.
   C. Respiratory distress (tachypnea, dyspnea, cyanosis) can occur in severely affected animals.

Diagnosis

I. A complete blood count often reveals a mature neutrophilia and lymphocytosis.
   A. Lymphocytosis is helpful in differentiating primary ciliary dyskinesia from canine distemper.
   B. Canine distemper typically causes lymphopenia.

II. Chronically ill animals may be hyperglobulinemic.
III. Arterial blood gas analysis may reveal hypoxemia and normo- or hypocapnia.
IV. Thoracic radiography may reveal bronchitis, bronchiectasis, consolidating pneumonia, and situs inversus.
V. Fluid from airway washes commonly grows one or more organisms, so aerobic, anaerobic, and mycoplasmal cultures are indicated.
VI. Nuclear scintigraphy reveals impaired nasal or tracheal mucociliary clearance (Edwards et al., 1992).
   A. Normal beagles have a tracheal clearance velocity of 8.83 + 3.3 mm/min (Whaley et al., 1987).
   B. With primary dyskinesia, tracheal clearance velocity is often 0 mm/min.
VII. Definitive diagnosis of primary ciliary dyskinesia requires electron microscopic analysis of nasal or other respiratory epithelium, or spermatozoa, to assess for the presence and extent of ciliary structural abnormalities (Edwards et al., 1992).
VIII. Functional ultrastructural analysis of ciliary beat frequency and synchrony are also helpful.
IX. Ciliogenesis identifies persistent primary defects and confirms the resolution of secondary defects.

Differential Diagnosis

I. Acquired respiratory tract diseases: bronchopneumonia, chronic bronchitis
II. Immunodeficiency syndromes: immunoglobulin A deficiency

Treatment

I. Treatment is directed at controlling infection through long-term, and sometimes lifelong, administration of broad-spectrum antibiotics (ideally chosen from culture of appropriate samples).
II. Improved clearance of respiratory secretions is promoted via airway humidification and chest coupage.
III. Cough suppressants are contraindicated.
IV. Do not breed close relatives of affected dogs in order to prevent genetic transmission of the disorder.

Monitoring of Animal

I. Evaluate response to therapy by periodically assessing clinical signs and thoracic radiography.
II. Mildly affected animals may do well with appropriate therapy.

DEGENERATIVE DISORDERS

Bronchiectasis

Definition

I. Irreversible dilatation of distal airways caused by chronic inflammation and damage to bronchial walls
II. Associated with pooling and poor clearance of airway secretions
III. Focal or diffuse disorder

Causes

I. Bronchiectasis arises secondary to a variety of congenital or acquired diseases.
II. Congenital conditions include primary ciliary dyskinesia or immotile cilia syndrome (most common) and bronchial dysgenesis (Edwards et al., 1992; Hoover et al., 1989; Killingsworth et al., 1987; LaRue et al., 1990).
III. Acquired conditions include chronic bronchitis and bronchopneumonia, obstructive airway disease, and neoplasia.

Pathophysiology

I. Primary airway disease results in the destruction of respiratory epithelium and cilia within the bronchioles.
II. Pooling of airway secretions and impaired mucociliary clearance predisposes to infection.
III. Inflammation leads to further bronchial wall destruction.
IV. Destruction of tissues supporting the airways allows for the distracting forces from the surrounding lung tissue to be unopposed, resulting in irreversible airway dilatation.

Clinical Signs

I. Dogs are more frequently affected than cats.
II. Older male cats may have a higher incidence of this disorder in comparison to the general feline population.
III. The American cocker spaniel, West Highland white terrier, miniature poodle, Siberian husky, English springer spaniel, and dogs >10 years of age have an increased risk for the disorder.
IV. Animals suffering from congenital disorders develop bronchiectasis at a young age.
V. Animals developing bronchiectasis secondary to chronic acquired airway disease are usually middle-aged or older.
VI. The most common clinical sign in dogs is a chronic productive cough, with or without increased respiratory effort.
VII. Hemoptysis may occur.
VIII. As many as 50% of affected cats may be asymptomatic, while others exhibit signs of lower respiratory tract disease (Norris and Samii, 2000).
IX. Auscultation reveals the presence of moist crackles and expiratory wheezes associated with increased effort.

Diagnosis

I. Symptoms and physical findings localize the disease to the lower respiratory tract.
II. The hemogram may be normal or may reveal a mature neutrophilia and monocytosis.
III. Hyperglobulinemia is common from chronic immune stimulation.
IV. Proteinuria may occur in association with reactive amyloidosis.
V. Thoracic radiography is considered an insensitive test, but classic findings may be present.
   A. Large bronchial lumen
   B. Visualization of large airway into the lung periphery
   C. Thickened bronchial walls
   D. Localized pulmonary consolidation, associated with an alveolar pattern

E. Possibly mixed bronchiolar, interstitial, and alveolar patterns

VI. Blood gas analysis reveals hypoxemia and an increased alveolar-arterial oxygen gradient.

VII. The most clinically useful tool for identifying bronchiectasis in affected dogs and cats is bronchoscopy.
   A. Bronchoscopy often reveals dilatation of small airways, increased airway secretions, and hyperemia of the respiratory mucosa.
   B. Bronchoalveolar wash samples often show suppurative inflammation.
   C. Aerobic and anaerobic cultures are indicated and frequently identify the presence of opportunistic infections.

VIII. Specialized tests may be needed to confirm the diagnosis of primary ciliary dyskinesia.

Differential Diagnosis

I. Chronic bronchitis without bronchiectasis
II. Bronchopneumonia without bronchiectasis
III. Emphysema
IV. Cystic or bullous lung disease

Treatment

I. Hospitalize and aggressively treat severely affected animals.
   A. Intravenous fluid therapy
   B. Parenteral broad-spectrum antibiotics
      1. Base antibiotic choice on results of culture and sensitivity testing.
      2. Long-term antibiotic therapy is indicated, even if culture results are negative, for at least 6 to 12 weeks, and permanently in some cases.
      3. If no culture and sensitivity results are available, use an antibiotic with good pulmonary tissue penetration, such as the following:
         a. Doxycycline 5 to 10 mg/kg PO SID
         b. Clindamycin 10 mg/kg PO BID
         c. Chloramphenicol 25 to 50 mg/kg PO TID (dogs)
   C. Bronchodilators
      1. Aminophylline 11 mg/kg IV, PO TID in dogs and 6.6 mg/kg PO BID in cats
      2. Theophylline
         a. Theo-Dur tablets: 20 mg/kg PO BID in dogs and 20 mg/kg PO SID in the evening in cats
         b. Slo-Bid Gyrocaps: 25 mg/kg PO BID in dogs and 25 mg/kg PO SID in the evening in cats

II. Nebulization and coupage therapy help with removal of the abnormal airway secretions buildup.

III. Lung lobectomy is indicated in dogs with very localized disease.

IV. Cough suppressants are contraindicated.

Monitoring of Animal

I. Affected animals are very prone to recurrent respiratory tract infections.

II. Assess therapy through historical clinical signs and regular rechecks, including follow-up thoracic radiography and airway washes if indicated.

III. Possible sequelae include amyloidosis, cor pulmonale, and sepsis.

IV. Bronchiectasis is not curable, requires lifelong therapy, and warrants a poor prognosis.

Emphysema

Definition and Causes

I. Emphysema occurs when there is overdistension of the alveolus with air secondary to destructive changes in the alveolar walls, and it is typically associated with decreased alveolar gas exchange.

II. In small animals, emphysema occurs infrequently, but may be a sequela to other respiratory tract disorders, such as chronic bronchitis or bronchiectasis.

III. Congenital lobar emphysema arises secondary to congential respiratory tract lesions, such as bronchial dysplasia.

Pathophysiology

I. Hyperinflation of the lung results in poor perfusion and partial ischemia, but does not (in the absence of other enzymatic damage) cause emphysema.

II. Inflammatory cell enzymes, such as collagenase and elastase, result in alveolar septal destruction.

III. Abnormal enzymatic control mechanisms (i.e., α_1-antitrypsin deficiency) may play a role in the development of emphysema.

IV. With destruction of alveolar septae, alveoli become confluent and form thin-walled cysts.

V. Bullae may develop when there is partial airway obstruction.

Clinical Signs

I. In acquired disease, signs are usually attributable to the primary condition.

II. In puppies with congenital lobar emphysema, the main signs are progressive dyspnea and cyanosis.
   A. Exercise-associated respiratory distress and tachypnea may be noted.
   B. Age of onset is dependent on the severity of the anatomical abnormalities present.
   C. Wheezes and crackles may be heard on auscultation.

Diagnosis

I. Thoracic radiography reveals pulmonary hyperlucencies or hyperinflation.
   A. A caudally flattened or displaced diaphragm
   B. Attenuation of the peripheral pulmonary vasculature
   C. Focal pulmonary hyperlucencies consistent with bullae

II. Ventilation-perfusion scans may identify abnormalities in ventilation and blood flow.

III. Sometimes bullae are not identified until thoracoscopic examination or thoracotomy.

IV. Definitive diagnosis requires histopathologic analysis of affected lung tissue.

Differential Diagnosis

I. For pulmonary hyperinflation
   A. Gas trapping secondary to obstructive lower airway disease

B. Compensatory hyperventilation from volume loss elsewhere in the lungs
C. Pulmonary hypoperfusion secondary to shock, pulmonary hypertension, or pulmonary artery thrombosis

II. For focal pulmonary hyperlucencies
A. Pulmonary cysts
B. Pulmonary abscesses
C. Cavitating neoplasms

Treatment

I. In acquired disorders, direct treatment toward managing the underlying disease.
II. In congential lobar emphysema, consider pulmonary lobectomy.

Monitoring of Animal

I. With acquired diseases, monitoring of the primary respiratory disease is imperative.
II. With congenital emphysema, assess respiratory function frequently, including monitoring of respiratory effort and rate, exercise tolerance, and blood gas analysis.
III. A decline in overall respiratory function necessitates prompt consideration of further medical and/or surgical therapies.

INFLAMMATORY/IMMUNOLOGICAL DISORDERS

Acute Bronchitis

Definition

I. Acute bronchitis is defined as a short-lived cough attributable to lower airway inflammation or irritation.
II. Acute bronchitis is not associated with irreversible airway damage.

Causes

I. Bacterial or viral infections: infectious tracheobronchitis, feline viral upper respiratory tract infection
II. *Mycoplasma* spp. infection
III. Parasites
IV. Inhaled foreign bodies
V. Airway irritation: smoke, dust
VI. Airway compression by a pulmonary neoplasm, enlarged hilar lymph nodes, or cardiomegaly
VII. Tracheal collapse
VIII. Allergic tracheobronchitis
IX. Tracheobronchitis secondary to material exuded into airways from lung disease

Pathophysiology

I. Reversible airway inflammation is induced by an infectious or irritant agent.
II. Stimulation of cough receptors occurs, with resultant coughing and increased production of mucus in the airway.

Clinical Signs

I. Acute bronchitis is associated with a productive or nonproductive cough of short (<2 months) duration.
A. Viral infection: typically dry cough
B. Bacterial infection: commonly productive cough
C. Tracheal collapse: nonproductive "goose-honking" cough

II. Systemic signs of illness (fever, malaise) may accompany tracheobronchitis if there is concurrent pulmonary inflammation.
III. Thoracic auscultation reveals increased bronchovesicular sounds, wheezes, and crackles.

Diagnosis

I. Suspected based on compatible clinical signs and physical examination
II. Identification of the underlying cause
A. Hemogram: often unremarkable, neutrophilic leukocytosis possible with bacterial disease
B. Thoracic radiography
1. Usually normal
2. Pulmonary parenchymal infiltrates with concurrent pneumonia
3. Possibly cardiomegaly, lymphadenopathy, or pulmonary masses
4. Inspiratory-expiratory views useful in diagnosing tracheal collapse
5. Fluoroscopy for dynamic assessment of tracheal collapse

C. Analysis of airway secretions
1. Secretions are collected by transtracheal aspiration, by endotracheal suction, or during bronchoscopy.
2. Increased eosinophils suggest allergic or parasitic disease.
3. Mild neutrophilic inflammation is common with tracheal collapse, cardiomegaly, solid lung masses, and inhaled irritants.
4. Neutrophilic inflammation with intracellular bacteria is typical of bacterial tracheobronchitis.
5. Culture is recommended to identify the organism(s) involved, especially for *Mycoplasma* spp.

D. Possible bronchoscopy findings
1. Foreign body within the airways
2. Parasitic tracheobronchitis: *Oslerus osleri*
3. Collapsing trachea
4. Tracheal or airway neoplasia

Differential Diagnosis

I. Cardiac enlargement, heart failure
II. Allergic bronchitis (see later discussion)
III. Parasitic tracheobronchitis, including heartworm disease
IV. Bronchopneumonia
V. Neoplasia
VI. Primary ciliary dyskinesia

Treatment

I. Some disorders resolve spontaneously once the inciting cause has been eliminated.

II. If an infectious cause of acute bronchitis is identified, it is treated with appropriate antibiotics based on culture and sensitivity testing.
III. If a tracheal foreign body is suspected, endoscopic retrieval is attempted.
  A. Retrieval under fluoroscopy has been reported in cats (Tivers and Moore, 2006).
  B. If unsuccessful, thoracotomy may be necessary.
IV. Eliminate inhaled irritants (e.g., passive smoke, dust, fumes).
V. Maintain airway hydration through nebulization to help mobilize secretions and soothe the inflamed tracheal mucosa.
VI. Cough suppressants may be indicated.
  A. They are not used if the cough is productive or if a transtracheal wash suggests infection.
  B. They help break the cycle of cough-induced inflammation that leads to further coughing.
  C. They are useful for severe paroxysmal cough.
  D. Several choices are available.
    1. Butorphanol 0.5 to 1 mg/kg PO BID to QID
    2. Hydrocodone 0.22 mg/kg PO BID to QID
    3. Codeine 1 to 2 mg/kg PO BID to TID
VII. Bronchodilators help to control signs in dogs with concurrent small airway obstruction and expiratory wheeze.
  A. Methylxanthines
    1. Theophylline
      a. Theo-Dur tablets: 20 mg/kg PO BID
      b. Slo-Bid Gyrocaps: 25 mg/kg PO BID
    2. Adverse effects: gastrointestinal upset, tachycardia, hyperactivity
    3. Caution warranted in dogs with heart disease
    4. Dose reductions necessary with drugs that inhibit metabolism, such as enrofloxacin
  B. β_2-Adrenergic agonists
    1. Terbutaline 1.25 to 5 mg PO TID (dogs)
    2. Albuterol 20 to 50 µg/kg PO BID to TID
    3. Adverse effects: hyperexcitability, tremors
    4. Use cautiously in dogs with heart disease
VIII. Short-term use of corticosteroids may be warranted to decrease airway inflammation in severe cases.
  A. It is important to wait to initiate treatment until all diagnostic tests are complete.
  B. Use these drugs for a 3-day course to resolve airway inflammation.
    1. Prednisone 0.25 to 0.5 mg/kg PO BID
    2. Dexamethasone 0.10 to 0.2 mg/kg IV, IM, SC, PO BID

Monitoring of Animal

I. Monitor animals carefully to ensure that the inciting cause and all clinical signs resolve.
II. Failure to eliminate the inciting cause can lead to chronic bronchitis.

Chronic Bronchitis

Definition

I. The presence of a chronic, unrelenting cough for >2 consecutive months
II. Associated with irreversible changes in the airways
III. Original inciting or underlying cause not identified

Causes

I. The underlying cause of the lower airway disease is usually no longer identifiable.
II. Chronic infections, allergies, or inhaled irritants are all possible causes.

Pathophysiology

I. Chronic mucosal inflammation and injury cause several changes.
  A. Hypertrophy and hyperplasia of goblet cells and mucous glands
  B. Hypertrophy of airway smooth muscle
  C. Fibrosis of the lamina propria
  D. Epithelial erosion with squamous metaplasia
  E. Excessive mucus accumulation in airways
    1. Contributes to small airway obstruction and collapse
    2. Possibly results in bronchiectasis
II. Chronic airway changes result in an increased risk for infection.

Clinical Signs

I. Signs are typically seen in middle-aged to geriatric small-breed dogs.
II. The presence of a persistent productive or nonproductive cough is the hallmark feature.
III. Systemic signs of illness are usually absent.
IV. Severely affected animals may have a history of exercise intolerance, intractable coughing fits, and respiratory distress.
V. Acute exacerbations of signs may arise in the presence of complicating infections, exposure to inhaled irritants, or excessive stress, and excitement.
VI. Auscultation reveals increased bronchovesicular sounds, wheezes, and crackles.
VII. Animals with pulmonary hypertension resulting from long-standing airway disease may have a loud or split second heart sound (see Chapter 18).

Diagnosis

I. The diagnosis of chronic bronchitis is one of exclusion and made only after an extensive evaluation of the respiratory system.
II. The hemogram is often unremarkable.
III. Thoracic radiography may be normal or reveal the following:
  A. Bronchial thickening with peribronchiolar cuffing
  B. Bronchiectasis, atelectasis, and pneumonia in severe cases
IV. Airway secretions are collected by transtracheal aspiration, endotracheal suction, or bronchoscopy.
  A. Allergic and parasitic diseases commonly produce eosinophilic inflammation.
  B. Tracheal collapse, cardiomegaly, solid lung masses, and inhaled irritants cause mild neutrophilic inflammation.

C. Bacterial infections cause neutrophilic inflammation with intracellular bacteria.
D. More than two intracellular bacteria per high power field on a Gram stain of bronchial lavage fluid is suggestive of significant lower tract infection (Peeters et al., 2000).
E. Culture and sensitivity of airway fluids is recommended, with special media used for culturing *Mycoplasma* spp.

V. Bronchoscopy can be useful to rule out the following:
A. Foreign bodies within the airways
B. Parasitic tracheobronchitis: *O. osleri*
C. Collapsing trachea
D. Tracheal or airway neoplasia

Differential Diagnosis

I. Cardiac enlargement, heart failure
II. Allergic bronchitis
III. Parasitic tracheobronchitis, including heartworm disease
IV. Bronchopneumonia
V. Neoplasia
VI. Primary ciliary dyskinesia

Treatment

I. Symptomatic treatment is indicated.
II. Avoidance of airway irritants and excitement is helpful.
III. Nebulization to humidify the airway helps to decrease the viscosity of airway secretions and soothes inflamed tracheal mucosa.
IV. Antibiotics are used to treat secondary infections.
A. Ideally based on culture and sensitivity testing
B. Empirical use of an antibiotic with good pulmonary tissue penetration (e.g., doxycycline, clindamycin, chloramphenicol)

V. Cough suppressants are not used if the cough is productive, or if the transtracheal wash suggests infection.
A. May be useful for paroxysmal cough in dogs
B. Butorphanol 0.5 to 1 mg/kg PO BID to TID
C. Hydrocodone 0.22 mg/kg PO BID to QID
D. Codeine 1 to 2 mg/kg PO BID to QID

VI. Bronchodilators are useful in dogs with small airway obstruction and expiratory wheeze.
A. Theo-Dur tablets: 20 mg/kg PO BID
B. Slo-Bid Gyrocaps: 25 mg/kg PO BID

VII. Short-term administration of corticosteroids may be warranted to decrease airway inflammation in severe cases.
A. Delay initiation of these drugs until all diagnostic testing is complete.
B. Options include prednisone 0.25 to 0.5 mg/kg PO BID and dexamethasone 0.10 to 0.2 mg/kg IV, IM, SC, PO BID.
C. Fluticasone propionate 110 µg BID may be delivered via aerosol in dogs <20 kg and 220 µg BID may be given to dogs >20 kg.

VIII. Weight control to eliminate obesity is also helpful.

Monitoring of Animal

I. Lifelong therapy is often required, because the disease is rarely cured.
II. The therapeutic goal is to control airway inflammation and prevent progression of disease.
III. Control of clinical signs is the best method to assess therapeutic efficacy.
IV. Inadequate control of clinical signs requires reassessment for new concurrent diseases (especially infections) and appropriate changes in therapy.
V. Reevaluate affected animals every 3 to 6 months, even if signs are stable.

Feline Allergic Bronchitis

Definition

I. It is a syndrome of reversible airway inflammation and narrowing that causes coughing, wheezing, and/or dyspnea.
II. Signs result from bronchial smooth muscle constriction (bronchoconstriction), bronchial wall edema, and excessive mucus secretion.
III. A classification scheme has been proposed (Moise and Dietze, 1989).
A. Bronchial asthma is reversible airway obstruction that results primarily from bronchoconstriction.
B. Acute bronchitis is reversible airway inflammation of short duration (<3 months).
C. Chronic bronchitis is irreversible airway damage resulting from chronic airway inflammation (>2 to 3 months).
D. Emphysema is overexpansion of alveolar airspaces caused by bronchiolar and alveolar wall destruction.

Causes

I. The acute (early) response in allergic feline bronchitis (asthma) represents a type I allergic reaction potentially triggered by inhaled allergens such as smoke, dust, and molds.
II. In most cases, the allergen is not identified.
III. Mycoplasma infection may trigger the bronchitis in some cats (Foster et al., 2004).
IV. Chronically, antigen-specific T lymphocytes in the airways secrete cytokines and leukotrienes.

Pathophysiology

I. The airways respond in a variety of ways to irritants or immunological stimuli.
A. The airway epithelium hypertrophies and undergoes metaplasia, resulting in airway narrowing.
B. Goblet cells and submucosal glands enlarge and increase production of mucus.
C. Bronchial smooth muscle constricts.
D. Cellular infiltration of the bronchial mucosa and submucosa results in airway edema.

II. Eosinophils play an important role in airway inflammation in some cats with asthma.
A. Eosinophils release chemical mediators.
B. These result in increased airway damage, fibrosis, and eosinophil chemotaxis.

Clinical Signs

I. Young and middle-aged cats are affected most often.
II. Presenting signs include cough, wheeze, and respiratory distress.
III. Systemic signs of illness (e.g., weight loss, anorexia, lethargy) rarely occur.
IV. Physical examination is often unremarkable between episodes of bronchoconstriction.
V. Physical examination during a symptomatic episode may reveal respiratory distress with increased expiratory effort, expiratory wheezes, and a barrel chest from prolonged air trapping.

Diagnosis

I. Clinical history and physical examination findings are used to make a tentative diagnosis.
II. Peripheral eosinophilia is an inconsistent finding on the hemogram.
III. Thoracic radiographic findings vary.
  A. Normal radiographs are common.
  B. Interstitial, bronchial, or alveolar patterns predominate.
  C. Atelectasis of the right middle lung lobe may occur as a result of bronchial obstruction.
  D. Lung parenchymal hyperlucency and expansion reflects air trapping, even in mildly symptomatic cats.
IV. Transtracheal wash or bronchoalveolar cytology typically reveals increased inflammatory cell and mucus content.
  A. The inflammatory cell content can be either neutrophilic or eosinophilic.
  B. Alveolar macrophages may be seen in some samples.
  C. The presence of oropharyngeal squamous cells and *Simonsiella* spp. indicates oropharyngeal contamination and the need to use caution in interpretation of the results.
V. Bronchoscopy reveals mild hyperemia and increased airway mucus secretions.
VI. Bacterial culture and antibiotic sensitivity testing of tracheal wash samples is recommended, because infection may contribute to airway inflammation and hypersensitivity.
  A. Gram staining of airway wash samples is a useful tool while culture results are pending.
  B. Remember that 77% of normal cats have positive culture results, and bacterial infection is rarely significant in affected cats (Dye et al., 1996).
  C. Bacteria isolated from normal cats include *Pasteurella, Pseudomonas, Staphylococcus, Streptococcus,* and *Micrococcus* spp., as well as *Eschericia coli* and *Bordetella bronchiseptica*.
  D. Growth of large numbers ($>10^3/\mu L$) of bacteria indicates infection requiring antibiotic treatment.
  E. Retrieval of *Mycoplasma* species from a cat with symptomatic bronchitis is considered significant and requires treatment.
    1. Use culture media specific for *Mycoplasma* spp.
    2. Avoid the use of wooden or cotton-tipped swabs for sample collection, as they may inhibit mycoplasmal growth.
VII. Heartworm testing is performed in endemic areas.
VIII. Fecal examinations are performed for airway and pulmonary parasites where prevalent.

Differential Diagnosis

I. Nonallergic airway inflammation or irritation
  A. Environmental irritants: smoke, dust
  B. Bacterial or mycoplasmal infections
  C. Lung parasitism (see Chapter 18)
  D. Neoplasia
  E. Bronchial foreign body
II. Pneumonia
III. Pharyngeal disease, obstruction (see Chapter 15)
IV. Pleural space disease

Treatment

I. Acute stabilization of the cat in respiratory distress
  A. Oxygen supplementation
  B. Rapid-acting corticosteroids
    1. Prednisolone sodium succinate 10 to 20 mg/kg IV
    2. Dexamethasone sodium phosphate 0.2 to 2.2 mg/kg IV, IM
  C. Bronchodilators
    1. Terbutaline 0.01 mg/kg IM, SC
    2. Aminophylline 5 mg/kg IV
    3. Albuterol 90 μg q 30 minutes for up to 4 hours, delivered with a metered dose inhaler, rebreathing spacer, and mask
II. Long-term management of cats with chronic disease
  A. Eliminate or reduce exposure to inhaled irritants and potential allergens.
    1. Replace clay litter with shredded newspaper; wood chips; or low-dust, clumping litter.
    2. Reduce passive smoke inhalation.
    3. Replace or clean dirty furnace air filters.
    4. Minimize exposure to aerosols, powders, perfumes, and fragrances.
  B. Corticosteroids are an important component of long-term management.
    1. It is preferable to administer steroids continuously rather than intermittently to control ongoing inflammation and prevent the development of chronic bronchitis.
    2. Fluticasone propionate is given at 110 to 220 μg BID via a metered dose inhaler (Kirschvink et al., 2005; Reinero et al., 2005; Schulman et al., 2004).
      a. Fluticasone propionote is preferred because of its potency, prolonged half-life, and minimal systemic absorption.
      b. For proper administration, shake the metered inhaler to open the valve, attach it to the spacer and mask, fit the mask to the cat, and watch for the animal to take 7 to 10 breaths after delivery of the drug.
      c. Correct placement of the mask minimizes the risk of conjunctivitis from the drug.
    3. Prednisone 0.5 to 1.0 mg/kg PO BID can also be used initially in cats with moderate to severe signs.
      a. Onset of effects of fluticasone is delayed, and some cats do not tolerate inhalant therapy.

b. After 7 to 10 days, decrease the dose if the cat is stable.
c. Eventually switch to alternate-day therapy.
d. Rapid dose tapering or drug withdrawal can result in worsening of symptoms.
e. Long-term therapy may be needed in refractory cases.

4. Treat cats that do not tolerate pilling or inhalant therapy with injectable methylprednisolone acetate at 10 to 20 mg IM every 2 to 8 weeks.
a. Possible increased risk for developing refractory disease
b. Increased risk of complications of chronic glucocorticoid administration, including urinary tract infection and diabetes mellitus
c. Anecdotal reports of injection-associated sarcomas with repeated administration
d. Not recommended for routine use

C. Bronchodilators help reduce signs of airway obstruction and bronchoconstriction.
1. Albuterol
a. Administered via metered dose inhaler at 90 µg per inhalation
b. Used as needed or up to QID
2. Terbutaline
a. Oral administration of 0.625 mg BID
b. Severe distress: 0.01 mg/kg IM, SC
c. Injectable terbutaline for at-home emergency use
3. Theophylline
a. Theo-Dur tablets: 25 mg/kg PO SID in the evening
b. Slo-Bid Gyrocaps: 25 mg/kg PO SID in the evening

D. Cyproheptadine may block allergen-induced bronchoconstriction and is given at 2 mg PO BID.

E. Cyclosporine is a possible adjunctive treatment for the small subpopulation of affected cats that are steroid resistant or require extremely large dosages of steroids.
1. Dose is 10 mg/kg PO BID.
2. Cyclosporine blood levels are checked weekly until trough blood levels of 500 to 1000 ng/mL are achieved.
3. Cats are relatively resistant to the side effects reported in other species.

F. The use of antileukotriene agents has not been justified because the role of leukotrienes in feline allergic bronchitis has been questioned.

Monitoring of Animal

I. The prognosis for control of clinical sings is good in most cats.
II. Ongoing therapy is usually required, and relapses are possible.
III. Lack of resolution of clinical signs with appropriate medical management warrants reassessment to ensure an appropriate diagnosis was made and complicating factors are not present.
IV. Inadequate control of airway inflammation may result in progression to chronic irreversible airway disease.
V. Exhaled breath condensate and barometric whole body plethysmography techniques for evaluating markers of airway inflammation and airflow restriction may provide more objective means of evaluating the response to treatment in the future.

Canine Allergic Bronchitis

Definition

I. Canine allergic bronchitis is an inflammatory condition of the airways that occurs in response to an inhaled allergen or a hematogenously carried antigen.
II. Unlike feline allergic bronchitis, acute bronchospasm is not a common component of the disease.

Causes

I. A variety of antigens may elicit a hypersensitivity reaction within the airways.
A. Dusts and molds
B. Cigarette smoke
C. Aerosol sprays
II. Parasitic infections *(Dirofilaria immitis)* and fungal infections, in particular *Aspergillus* spp., can cause a hypersensitivity response in the airways and result in allergic bronchitis.

Pathophysiology

I. Humoral and cell-mediated immune responses occur and involve the production of both immunoglobulins E and G.
II. Mediators such as histamine, serotonin, kinins, and eosinophil chemotactic factor are released, causing several reactions.
A. Airway inflammation and edema
B. Bronchoconstriction
C. Increased mucus production
III. Long-standing airway inflammation associated with the hypersensitivity reaction may cause permanent airway changes and result in chronic bronchitis.

Clinical Signs

I. Typically young to middle-aged dogs
II. Cough a consistent feature
A. The cough is usually unproductive.
B. Coughing is exacerbated by exercise, cold air, and chest or tracheal compression.
III. Respiratory distress associated with wheezing and increased expiratory effort (rare)

Diagnosis

I. A cough is easily elicited on tracheal palpation.
II. Occasionally, increased expiratory effort is noted.
III. Thoracic radiography may reveal bronchial wall thickening and peribronchial cuffing, or is occasionally normal.
IV. Airway washes typically reveal marked eosinophilia.
V. Heartworm testing and fecal examinations are performed to rule out parasitic disease in all dogs with an eosinophilic tracheal wash.
VI. Bronchoscopy may be considered, especially to evaluate for *O. osleri* infection.

Differential Diagnosis

I. Acute tracheitis or bronchitis syndromes
II. Chronic bronchitis
III. Bronchopneumonia
IV. Pulmonary edema
V. Pulmonary neoplasia

Treatment

I. If an infectious cause of the hypersensitivity reaction can be identified, treat it appropriately.
II. Institute environmental changes when inhalant allergens are identified.
III. Immunosuppressive doses of corticosteroids are recommended.
   A. Prednisone 1 to 2 mg/kg PO BID is initiated.
   B. Administer this dose for 14 days, then taper to the lowest effective dose.
IV. Bronchodilators are administered for signs of bronchoconstriction (e.g., increased expiratory effort, wheezing).
V. Inhalant medications (fluticasone propionate, albuterol) may also be considered.
VI. Humidification of airways decreases inflammation and improves mucociliary clearance.

Monitoring of Animal

I. Closely monitor, through repeated examinations, clinical response to treatment.
II. Resolution of airway inflammation and prevention of progression to chronic bronchitis is the goal.
III. Acute relapses require immediate reevaluation and adjustment of medications.

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CHAPTER 18

Pulmonary Parenchymal Diseases

O. Lynne Nelson

PULMONARY EDEMA

Definition

I. Pulmonary edema is fluid accumulation in the interstitium of the lung.
II. Cardiogenic pulmonary edema occurs when left-sided congestive heart failure (CHF) and increased pulmonary venous hydrostatic pressure are responsible for the edema.
III. Noncardiogenic edema is edema from any other cause.

Causes

I. The causes are typically divided into three or four major mechanisms.
   A. Decreased plasma oncotic pressure
   B. Increased vascular hydrostatic pressure
   C. Increased vascular permeability
   D. Miscellaneous
II. Causes are listed in Box 18-1.

Pathophysiology

I. Fluid translocates into the interstitial space from one of the major mechanisms above.
II. The lymphatic drainage systems cannot match the rate of fluid influx.
III. The interstitial space is eventually overwhelmed, and fluid accumulates in the alveoli.
IV. Gas exchange is impaired when airways become flooded.
V. Atelectasis, decreased lung compliance, and airway compression all increase pulmonary vascular resistance.
VI. Hypoxemia results from ventilation-perfusion mismatch.
VII. Hypoxemia contributes to increased pulmonary vascular resistance from hypoxemia-mediated pulmonary arterial vasoconstriction.

Clinical Signs

I. Most animals present with tachypnea, cough, or respiratory distress (severe hypoxia).
II. Symptoms are directly related to the cause and severity of the edema.
III. The respiratory character is usually that of increased effort (both inspiration and expiration).
IV. Severe edema may cause coughing with expectoration of blood-tinged fluid.
V. Auscultation may reveal several abnormalities.
   A. Crackles may be absent in early or mild edema, but subtle crackles at the end-inspiration to early expiration phase are common.
   B. Crackles may be heard on both inspiration and expiration in advanced pulmonary edema.
   C. Lung sounds may seem exceptionally quiet with very severe edema.
   D. Abnormal cardiac auscultation (murmurs, transient sounds, arrhythmias) indicates the presence of heart disease.
      1. Identification of a heart murmur does not always indicate the presence of cardiogenic edema.
      2. Some animals with CHF lack abnormal heart sounds (cardiomyopathies).

Diagnosis

I. Thoracic radiography, combined with historical and physical findings, is often diagnostic (Box 18-2).
II. Cardiogenic edema is characterized by "fluffy" interstitial opacities that rapidly progress to an alveolar pattern.
   A. In the dog, the opacities are most often located in the hilar lung regions.
   B. In the cat, the opacities are patchy and may be diffuse or focal.
   C. Pulmonary venous enlargement suggests pulmonary venous and left atrial hypertension consistent with CHF.
   D. Enlargement of the cardiac silhouette (particularly left sided) is commonly present.
III. Edema caused by increased vascular permeability is typically most severe in the caudodorsal lung lobes.
   A. Vascular permeability edema is caused by numerous disorders (see Box 18-1).
   B. History and laboratory parameters are helpful in identifying underlying causes (e.g., electrocution, smoke inhalation, pancreatitis).
   C. In many cases (e.g., sepsis, uremia), the edema is mild and not a part of the primary clinical complaint.
   D. Acute respiratory distress syndrome (ARDS) is a unique syndrome of increased pulmonary vascular permeability secondary to critical illness states (see under Idiopathic Disorders).
IV. Pulmonary edema from decreased plasma oncotic pressure usually has a generalized interstitial or mixed interstitial-alveolar pattern.

Box 18-1

Possible Causes of Pulmonary Edema

Decreased Plasma Oncotic Pressure

Hypoalbuminemia
- Gastrointestinal loss
- Glomerulopathy
- Liver disease
- Iatrogenic overhydration
- Starvation

Vascular Overload

Cardiogenic
- Left heart failure
- Left-to-right shunts
- Overhydration

Lymphatic Obstruction (Rare)

Neoplasia

Increased Vascular Permeability (Acute or Adult Respiratory Distress Syndrome)

Inhaled toxins
- Smoke inhalation
- Gastric acid aspiration
- Oxygen toxicity

Drug or toxins
- Snake venom
- Cisplatin in cats

Electrocution
Trauma
- Pulmonary
- Multisystemic

Sepsis
Pancreatitis
Uremia
Disseminated intravascular coagulation
Inflammation (infectious or noninfectious)*

Miscellaneous Causes

Thromboembolism
Severe upper airway obstruction
Near drowning
Neurogenic edema
- Seizures
- Head trauma

From Hawkins EC: Disorders of the pulmonary parenchyma. p. 311. In Nelson RW, Conto CG (eds): Small Animal Internal Medicine. 2nd Ed. Mosby, St. Louis, 1998.
*Inflammation is usually the prominent clinical abnormality, not edema.

Box 18-2

Radiographic Changes with Parenchymal Disease

Disease	Radiographic Signs
Pneumonia	
Bronchopneumonia	Alveolar or mixed alveolar–bronchial pattern Air bronchograms present Changes present in multiple lobes and throughout the lobes
Aspiration	Most commonly affects ventral portions of middle lobes May be unilateral or bilateral Mixed alveolar–interstitial pattern Air bronchograms present unless consolidated
Inhalation	Early changes confined to interstitial pattern with peribrochial infiltrates Late changes show mixed alveolar–interstitial pattern with air bronchograms present Early changes are widespread and diffuse Later changes may affect dependent portions of lungs, mirnicleing aspiration
Pulmonary contusion	Irregular, patchy areas of mixed alveolar–interstitial patterns or consolidation Often contain air bronchograms May be associated with rib fractures, pneumothorax, or atelectasis
Pulmonary edema	
Cardiogenic	
Dog	Hilar, mixed alveolar–interstitial densities
Cat	Diffuse, peripheral alveolar or mixed pattern
Electric shock, snakebite, inhalation	Generalized, severe mixed pattern Often most pronounced in diaphragmatic lobes Bilateral, symmetrical Air bronchograms present
Hypoproteinemia	Mixed pattern with air bronchograms late Often accompanied by hydrothorax
Feline asthma	Increased interstitial densities and peribronchial markings Increased thoracic size Straightening of diaphragm Hyperlucency of lungs ± Aerophagia Emphysematous bullae with chronic asthma

From Morgan RV: Manual of Small Animal Emergencies. p. 198. Churchill Livingstone, New York, 1985.

A. Pleural effusion may also be present.
B. Vascular congestion is absent.

V. Blood gas analysis often detects hypoxemia, hypocapnia, and widened A-a gradient (difference in oxygen tension between alveolar [A] and arteriolar [a] blood) (Lagutchik, 1997).
VI. Laboratory abnormalities are helpful in determining the cause, particularly in noncardiogenic edema.

Differential Diagnosis

I. Bronchopneumonia
II. Pulmonary contusions
III. Parenchymal neoplasia
IV. Pulmonary thromboembolic disease

Treatment

I. Improve oxygenation
   A. Minimize stressful handling.
   B. Administer oxygen through nasal cannula, face mask, or oxygen cage.
   C. Intubate and begin positive-pressure ventilation if necessary.
II. Diuretic therapy is particularly effective for vascular overload disorders, especially CHF.
   A. Administer furosemide 2 to 4 mg/kg IV every 4 to 12 hours for clinical pulmonary edema.
   B. Diuretics are less beneficial for increased vascular permeability disorders (e.g., ARDS).
   C. Caution is advised in hypovolemic animals.
III. Xanthine-derivative bronchodilators may be beneficial to combat bronchospasm, enhance mucociliary function, and diminish diaphragmatic fatigue.
   A. Aminophylline 6 to 11 mg/kg PO TID (dogs) and 4 to 6 mg/kg PO BID (cats)
   B. Theophylline 4 to 5 mg/kg PO TID
IV. Institute specific therapies for each cause.
   A. Hypoproteinemia
   B. Cardiac disease (see Chapter 9)
   C. Smoke inhalation (see Chapter 133)

Monitoring of Animal

I. Monitor pulmonary function and cardiac disease parameters every 1 to 8 hours.
   A. Evaluate mucous membrane color, respiratory rate, and character for progressive trends.
   B. Monitor oxygenation with arterial blood gases and/or pulse oximetry.
   C. Monitor heart rate, rhythm, and QRS morphology on electrocardiography.
   D. The appearance of ventricular ectopic beats, increasing heart rate, or ST segment depression may indicate worsening of a hypoxic state.
II. Thoracic radiographs are reevaluated every 24 to 48 hours, remembering that radiographic changes often lag behind clinical response.
III. Monitor hydration status and cardiac output using serial measures, including packed cell volume (PCV), total protein (TP), central venous pressure, daily body weight, arterial blood pressure, urine output, and pulmonary capillary wedge pressures.

INFECTIOUS DISEASES

Bacterial Pneumonia

Definition

I. Pneumonia is inflammation of the lung.
II. Pneumonia is considered bacterial when bacterial organisms are identified as the cause or a part of the inflammatory process.
III. Bacterial bronchitis is bacterial infection of the airways.
IV. Bronchopneumonia occurs from bacterial colonization of the airways and parenchymal tissues (alveoli, interstitium).
V. Interstitial pneumonia is infection or inflammation of the pulmonary interstitium.
VI. Lobar pneumonia is inflammation affecting a single lung lobe.

Causes

I. Primary bacterial pneumonia is uncommon, and typically a predisposing condition exists.
   A. Chronic bronchitis ± bronchiectasis
   B. Ciliary dyskinesia
   C. Viral and fungal diseases
   D. Diseases associated with aspiration: regurgitation, dysphagia
   E. Foreign body penetration
   F. Immunosuppressive drug therapy, severe metabolic compromise
   G. Endocrinopathies: diabetes mellitus, hyperadrenocorticism
   H. Prolonged recumbency: atelectasis and hypostatic congestion
   I. Trauma
   J. Neoplasia
II. *Staphylococcus* spp., *Streptococcus* spp., *Escherichia coli,* and *Mycoplasma* spp. are common organisms.

Pathophysiology

I. Bacteria may be inhaled (most common route).
   A. Organisms may extend from upper airway disease.
   B. Organisms may be opportunistic invaders in diseases with impaired clearance mechanisms, such as chronic bronchitis, ciliary dyskinesia, and immunosuppressive drugs or disease states.
II. Bacteria may enter the lung hematogenously.
   A. Pneumonia may be a consequence of sepsis from any cause (immunosuppressive drugs).
   B. Intravenous catheter use in critical patients can be associated with pneumonia.
III. Bacteria may enter the lung through direct extension.
   A. Wound penetrating the thoracic cavity
   B. Inhaled foreign objects: grass awns
   C. Perforating esophageal lesions
   D. Iatrogenic: diagnostic or surgical procedures

Clinical Signs

I. History
  A. A thorough history provides an important insight into potential underlying causes.
    1. Vaccine status and animal exposure
    2. Geographic area traveled
    3. Prior illness
      a. Medications administered
      b. Signs related to other underlying causes
  B. A history of chronic airway disease is common.
  C. A history of vomiting or regurgitation may be present.
  D. A history of anesthesia and prolonged recumbency may suggest aspiration.
II. Respiratory signs
  A. Cough, usually productive
  B. Tachypnea, respiratory distress
  C. Bilateral mucopurulent nasal discharge
  D. Exercise intolerance
  E. Expiratory wheeze
III. Systemic signs
  A. Lethargy, anorexia
  B. Fever (not a consistent finding)
  C. Weight loss
  D. Signs related to predisposing causes

Diagnosis

I. Auscultation on physical examination
  A. Inspiratory (if bronchial component) and expiratory (most common) crackles may be ausculted.
  B. Expiratory wheeze is an occasional finding.
  C. Abnormal sounds may be most prominent over the ventral lung fields.
  D. Diminished sounds are often noted over areas of consolidation.
  E. Auscultation is sometimes insensitive for detecting early pulmonary changes.
II. Laboratory tests
  A. Complete blood count (CBC)
    1. A neutrophilic leukocytosis with a left shift (60% of cases) may be present (Greene, 2006).
    2. A neutropenia with a degenerative left shift can sometimes be seen.
    3. A normal CBC does not rule out bacterial pneumonia.
  B. Biochemistry panel: abnormalities related to underlying diseases
III. Thoracic radiography (see Box 18-2).
  A. Bacterial bronchitis is characterized by a prominent bronchial pattern with peribronchial cuffing ("doughnuts").
  B. Bronchopneumonia can affect multiple pulmonary regions and is characterized by bronchial, interstitial, and especially alveolar changes (air bronchograms).
  C. Bronchopneumonia lesions are typically found in the cranioventral lung fields.
  D. Interstitial pneumonia often appears as a diffuse reticular increase in parenchymal opacity.
  E. Interstitial lesions that assume a more caudal pattern are seen with hematogenous pneumonia.
  F. Lobar pneumonia is usually localized to one region or lung lobe.
    1. Consolidation with air bronchograms is commonly observed.
    2. Lesions associated with foreign bodies are focal.
IV. Pulmonary specimens
  A. Bronchoalveolar lavage
    1. Specimens are collected before antibiotics are administered.
    2. Septic neutrophilic inflammation is typical on cytology.
    3. Intracellular bacteria are usually present.
  B. Transthoracic aspirates
    1. They are particularly helpful in consolidated lung lesions or prominent interstitial disease.
    2. Septic neutrophilic inflammation and intracellular bacteria are noted.
  C. Lung biopsy
    1. Allows histopathologic examination
    2. Important if surgery is planned, such as with focal lesions
V. Culture of pulmonary specimens
  A. Isolation of the organisms is essential to support the diagnosis and provide specific treatment.
  B. Aerobic and anaerobic cultures are submitted.
  C. *Bordetella* spp. and *Mycoplasma* spp. require special culture media.
  D. Culture results must be interpreted in light of the source and collection method.

Differential Diagnosis

I. Other forms of infectious pneumonia: viral, protozoal, mycotic
II. Aspiration pneumonia
III. Pulmonary edema
IV. Pulmonary contusion
V. Infiltrative neoplasia
VI. Chronic bronchial disease
VII. Parasitic and eosinophilic pulmonary disease

Treatment

I. Antibiotics are the mainstay of therapy for bacterial pneumonia.
  A. Infections with more than one organism are common.
  B. Antibacterial chosen depends on culture and sensitivity.
  C. Broad-spectrum antibiotics are given empirically pending the results of culture and sensitivity.
    1. Cephalexin 20 to 40 mg/kg PO TID
    2. Trimethoprim-sulfadiazine 15 to 30 mg/kg PO BID
    3. Doxycycline 5 to 10 mg/kg PO BID (dogs) and 5 mg/kg PO BID (cats)
    4. Amoxicillin-clavulanate 20 to 25 mg/kg PO TID

II. Airway hydration is recommended to help prevent drying with increased viscosity of airway secretions and to enhance clearance of bacterial organisms.
   A. Fluid therapy is warranted with evidence of dehydration or systemic hypotension.
   B. Humidification of air provides additional moisture to the airways.
      1. Humidification is recommended for animals with lung consolidation or chronic airway disease (chronic bronchitis).
      2. Place pet in a steamy bathroom three to four times per day.
      3. Commercially available air-humidifying units can be purchased.
      4. Nebulizers deliver moisture deeper into airways than humidifiers.
         a. Disposable units are attached to bottled oxygen.
         b. Antibiotics are sometimes added to the nebulizing fluid.
III. Bronchodilators may be beneficial with suggested bronchospasm.
   A. Expiratory wheeze may be noted on physical examination.
   B. Cats are especially prone to bronchospasm secondary to airway inflammation.
   C. Methylxanthines help to relax bronchioles, enhance mucociliary clearance, and decrease respiratory muscle fatigue.
      1. Aminophylline 6 to 11 mg/kg PO TID (dogs) and 4 to 6 mg/kg PO BID (cats)
      2. Theophylline 4 to 5 mg/kg PO TID
   D. Other bronchodilators may be empirically used.
      1. Terbutaline 1.25 to 5.0 mg PO BID (dogs) and 0.625 mg to 1.25 mg PO BID (cats)
      2. Albuterol 50 μg/kg PO TID or aerosolized and inhaled
      3. Ipratropium bromide aerosol
IV. Physiotherapy promotes deeper respirations and coughing, with clearance of mucous debris.
   A. Light activity is encouraged if the animal is capable of ambulation without discomfort or distress.
   B. If the animal is recumbent for long periods, rotate it every 2 hours to decrease the potential for lung consolidation.
   C. Coupage is performed by bluntly striking the chest wall with cupped hands.
      1. Coupage enhances coughing and clearance of mucus and airway debris.
      2. It is particularly useful after nebulization.
V. Oxygen supplementation is indicated if cyanosis, distress, or severe hypoxemia (partial pressure of alveolar oxygen <60 to 65) is documented.
VI. Oxygen therapy helps minimize hypoxic-induced pulmonary arterial vasoconstriction.
VII. Identify and treat predisposing causes.
VIII. Surgical intervention may be required in those cases of lung lobe consolidation that are not responsive to medical therapy, or in rare cases in which secondary pneumothorax occurs.
IX. In general, corticosteroids, diuretics, and cough suppressants are avoided.

Monitoring of Animal

I. Pulmonary function is monitored 2 to 10 times per day for signs of deterioration, depending upon clinical severity.
   A. Respiratory rate, effort, and coughing
   B. Mucous membrane color
   C. Arterial oxygenation: serial blood gases, pulse oximetry
II. Thoracic radiographs are evaluated every 24 to 72 hours initially.
   A. Radiographic changes frequently lag 24 to 48 hours behind clinical findings.
   B. Radiographs may be repeated every 7 to 10 days after animal is stable.
III. A CBC is assessed every 24 to 48 hours initially.
IV. If there is a poor response to therapy, consider the following:
   A. Inappropriate antibiotic choice or administration
   B. Development of complications: sepsis, abscessation, consolidation, thrombosis
   C. Superinfection with resistant organisms
   D. Poor owner compliance with medications
   E. Inappropriate treatment of underlying condition
   F. Incorrect diagnosis

Viral Lung Disease

See Chapters 112 and 114.

Mycotic Lung Disease

Definition

I. Mycotic lung disease is a pulmonary infection caused by fungal (mycotic) organisms.
II. Mycotic diseases are often part of systemic infections.

Causes

I. *Coccidioides immitis*
II. *Blastomyces dermatitidis*
III. *Histoplasma capsulatum*
IV. *Cryptococcus neoformans:* most common systemic fungal disease of the cat
V. *Aspergillus flavus*

Clinical Signs

I. Clinical signs depend on route of entry, localization, or dissemination.
II. Pulmonary signs are similar to other forms of pneumonia (see Bacterial Pneumonia).
   A. Pulmonary signs are common in dogs with blastomycosis and coccidioidomycosis.
   B. Pulmonary signs may also be seen in cats with histoplasmosis and coccidioidomycosis.
III. Nasal signs are the predominant complaint with cryptococcosis and aspergillosis, although pulmonary disease may be present with severe disseminated infection or with

immunosuppression from steroid administration or a concurrent disease.
IV. Central nervous system and ocular disease (chorioretinitis and uveitis) occur with many fungal organisms.
V. Bony involvement resulting in pain and lameness may be noted, particularly with blastomycosis and coccidioidomycosis.
VI. Systemic signs are also common (weight loss, fever, lymphadenopathy).

Diagnosis

I. Thoracic radiographs are often characteristic.
   A. Diffuse, nodular interstitial pattern
   B. Miliary nodular pattern
   C. Hilar lymphadenopathy (particularly histoplasmosis and coccidioidomycosis)
   D. Sometimes bronchointerstitial patterns and lung lobe consolidation
II. Cytological evaluation of bronchoalveolar lavage samples or transthoracic aspirations may identify the organisms.
III. Fungal cultures may be performed, but the organisms can be difficult to grow.
IV. Serology is diagnostic with certain types of fungal infection (see Chapter 111).

Differential Diagnosis

I. Neoplastic lung disease
II. Bacterial pneumonia
III. Parasitic pneumonia
IV. Eosinophilic lung disease
V. Complicated chronic airway diseases

Treatment and Monitoring

I. Long-term therapy is essential for most cases of mycotic pneumonia (see Chapter 111).
II. Frequent re-examinations (and thoracic radiographs) are necessary to determine resolution of the pneumonia and to monitor for recurrence of disease.

Protozoal Lung Disease

Toxoplasma Pneumonia

Definition and Cause

I. *Toxoplasma gondii* is one of the most prevalent multisystemic protozoal organisms affecting warm-blooded vertebrates.
II. Feline species are the definitive host.
III. Infection occurs by ingestion of organisms or transplacentally.
IV. Immunodeficiency disease predisposes animals to develop clinical toxoplasmosis.

Clinical Signs

I. Pneumonitis is most commonly associated with acute toxoplasmosis.
II. Pulmonary symptoms are similar to other forms of pneumonia (see under Bacterial Pneumonia).
III. Generalized lymph node enlargement may be detected.
IV. Cysts readily form in the central nervous system, muscular tissue, and visceral organs, so other systemic signs are common (anorexia, diarrhea, hyperesthesia).
V. Anterior or posterior uveitis is also common.

Diagnosis

I. Thoracic radiography demonstrates a variety of abnormalities.
   A. Diffuse interstitial pattern
   B. Mottled interstitial to alveolar pattern
   C. Pleural effusion
II. Cytological evaluation of bronchial washes or transthoracic aspirates is more likely to yield bradyzoites or tachyzoites than with tracheal washes (interstitial location of disease); however, definitive demonstration of the organism antemortem is uncommon.
III. Histopathologic testing of lung tissues may be beneficial.
IV. Serologic testing combined with organism detection by polymerase chain reaction may confirm the diagnosis (see Chapter 116).

Differential Diagnosis

I. Bacterial pneumonia
II. Parasitic pneumonia
III. Complicated viral pneumonia
IV. Eosinophilic lung disease
V. Complicated chronic airway diseases
VI. Neoplastic lung disease

Treatment and Monitoring

I. See Chapter 116 for treatment protocols.
II. Prognosis is generally poor in cats with severe pulmonary disease.
III. Long-term therapy is often required.
IV. Recurrence of clinical signs may be noted, particularly if the duration of therapy is <4 weeks.

Pneumocystis Pneumonia

See Table 116-2.

INFLAMMATORY DISORDERS

Aspiration Pneumonia

Definition

I. Inhalation of fluid, food particles, or bacteria from the oropharynx often results in profound pulmonary inflammation.
II. Aspiration pneumonia can present as an acute fulminant illness or a chronic and insidious process.

Causes

I. The materials usually aspirated are acidic stomach contents and food.
II. Normal laryngeal and pharyngeal function ordinarily prevents aspiration.
III. Some disorders alter normal laryngeal-pharyngeal function, thereby predisposing to aspiration.

A. Local or systemic neuromuscular disease
B. Irritation and inflammation of oropharynx secondary to chronic reflux or regurgitation (megaesophagus, esophageal obstruction, esophagus, chronic vomiting)
C. Anesthesia or depressed mental states resulting in prolonged recumbency, reflux, and impaired oropharyngeal function

IV. Accidental intubation of the airway when administering medications or food, or lack of patient cooperation when administering such products, can result in aspiration pneumonia.

Pathophysiology

I. The severity of lung injury is related to various factors.
A. The volume of the aspirate
B. The pH of the aspirate, with pH values <2.5 being the most troublesome
C. Toxicity related to the specific particulate matter

II. Aspirated material may cause several reactions.
A. Obstruction and collapse of alveoli
B. Pulmonary hemorrhage and edema
C. Influx of inflammatory cells
D. Necrosis of airway epithelial cells
E. Bronchoconstriction

III. Infection is a common sequela owing to aspiration of oropharyngeal bacteria or secondary to the lung injury and impaired clearance mechanisms.

Clinical Signs

I. Acute onset of respiratory distress, tachypnea, and cough are typical.
II. Chronic, progressive respiratory signs may also occur.
III. Systemic signs such as fever, inappetence, lethargy, and shock are also common.
IV. Inspiratory and expiratory crackles and wheezes are usually ausculted in the cranioventral lung lobes.

Diagnosis

I. A history of chronic regurgitation or possible aspiration allows a presumptive diagnosis.
II. CBC often reveals an inflammatory leukogram.
III. Thoracic radiography may support the diagnosis (see Box 18-2).
A. Opacities may be diffuse or focal, interstitial to alveolar.
B. Increased alveolar opacities and consolidated regions are more prominent in the cranioventral and middle lung lobes (dependent areas).
C. Nodular opacities may be noted in chronic cases, or cases in which large solid particles have been aspirated.
D. A miliary nodular pattern may be found with aspiration of mineral oil.

IV. Respiratory secretions are evaluated by cytology and culture.
A. Cytological evaluation usually shows a predominance of neutrophils and some hemorrhage.
B. Bacteria may or may not be present.
C. Particulate matter (food) may be seen.

V. Also investigate the potential underlying causes.

Differential Diagnosis

I. Bronchopneumonia
II. Other forms of infectious pneumonia: viral, protozoal, mycotic, etc.
III. Acute respiratory distress syndrome
IV. Pulmonary thromboembolic disease
V. Pulmonary edema

Treatment and Monitoring

I. Improve pulmonary function.
A. Administer oxygen via nasal cannula, mask, or oxygen cage.
B. Intubate and apply positive-pressure ventilation if necessary.
C. Bronchodilators may be beneficial for bronchospasm.
1. Expiratory wheeze may be noted on physical examination.
2. Cats are especially prone to bronchospasm secondary to airway inflammation.
3. Methylxanthines relax bronchioles, enhance mucociliary clearance, and decrease respiratory muscle fatigue.
a. Aminophylline 6 to 11 mg/kg PO TID (dogs) and 4 to 6 mg/kg PO BID (cats)
b. Theophylline 4 to 5 mg/kg PO TID
4. Other bronchodilators may be empirically used.
a. Terbutaline 1.25-5.0 mg PO BID (dogs) and 0.625 mg to 1.25 mg PO BID (cats)
b. Albuterol 50 µg/kg PO TID or aerosolized and inhaled
c. Ipratropium bromide aerosol

II. Administer antibiotics according to culture results (no evidence for prophylactic use).
III. Treat for shock as indicated (see Chapter 132)
IV. Avoid overhydration with fluid therapy as increased tissue permeability may contribute to translocation of fluid into diseased lung.
V. Prevent further aspiration.
A. Intubate if animal is anesthetized or has a depressed state of consciousness.
B. Reposition feeding tubes.
C. Institute "upright" feeding for esophageal or pharyngeal disorders.

VI. Monitoring is similar to that described for Bacterial Pneumonia earlier in this chapter.

IDIOPATHIC DISORDERS

Acute Respiratory Distress Syndrome

Definition

I. Acute respiratory distress syndrome causes acute hypoxemic respiratory failure as a result of lung injury and increased tissue permeability.
II. ARDS is not a disease entity by itself, but is a syndrome identified secondary to numerous, critical illnesses.
III. Although well described, it is not known why the syndrome develops.

Causes

I. Sepsis
II. Acid aspiration
III. Multiple transfusions
IV. Shock
V. Pancreatitis
VI. Pneumonia, inhalation injury
VII. Drug reaction or overdose
VIII. Major trauma or surgery

Pathophysiology

I. In the early phase of ARDS, exudation of proteinaceous fluid (low-pressure pulmonary edema) occurs as a direct result of lung capillary injury and increased permeability.
II. In the later phases (7 to 10 days post insult), increased numbers of inflammatory cells, hyaline membrane formation, and fibrosis with increased dead-space fraction develop.
III. Severe hypoxemia occurs from arteriovenous shunting and ventilation-perfusion irregularities.
IV. Pulmonary hypertension (PH) occurs as a result of hypoxic-induced vasoconstriction and microembolization with capillary obstruction.

Clinical Signs

I. Acute, severe respiratory distress and tachypnea
II. Tachycardia
III. Anxiety, agitation
IV. Crackles and wheezes, particularly on expiration
V. Lung sounds sometimes quieter than expected (associated with hypovolemia)

Diagnosis

I. Onset of clinical signs hours to days after a precipitating event is highly suspicious.
II. Thoracic radiography reveals generalized interstitial or mixed pattern, consistent with noncardiogenic pulmonary edema (see Box 18-2).
III. Echocardiography may provide supportive information.
   A. It may be used to rule out left atrial and ventricular abnormalities that can be associated with high-pressure (cardiogenic) pulmonary edema.
   B. Evidence of acute PH (right ventricular [RV] and atrial dilation, estimation of pulmonary pressures from pulmonic or tricuspid regurgitation) supports the diagnosis of ARDS.
IV. Pulmonary capillary wedge pressure is low (<18 mm Hg) with ARDS and elevated with cardiogenic pulmonary edema.
V. Edema fluid analysis provides useful information in the early stages of ARDS.
   A. Fluid may be suctioned from the airways via tubing passed through an endotracheal tube.
   B. The ratio of protein content of the edema fluid (E) to the protein content in plasma (P) in ARDS is 79% to 90%, whereas the E:P ratio in cardiogenic edema is <50% (Bhorade, 1999).

Differential Diagnosis

I. Cardiogenic pulmonary edema
II. Other causes of noncardiogenic pulmonary edema: neurogenic, etc.
III. Pulmonary thromboembolic disease
IV. Acute pneumonia
V. Pulmonary contusions
VI. Aspiration pneumonia without ARDS

Treatment

I. Treat any defined underlying condition.
II. Oxygen therapy is essential.
   A. Supplemental oxygen is provided with a nasal cannula, Elizabethan collar method, or oxygen cage.
   B. Intubation and mechanical ventilation are sometimes indicated.
   C. Positive end-expiratory pressure methods are ideal in severe cases.
III. Maintain low-normal circulatory volume with cautious fluid therapy.
   A. Administer the smallest volume of fluids that maintains cardiac output and arterial blood pressure.
   B. A Swan-Ganz or other hemodynamic measuring catheter may be used to monitor cardiac output, and pulmonary capillary wedge and right heart pressures.
   C. Central venous pressure measurements are misleading if significant PH exists.
   D. Serial measurements of arterial blood pressure, PCV, TP, electrolytes, and renal function tests are useful to estimate hydration status.
IV. Corticosteroids are of unconfirmed benefit.
V. Diuretics may be clinically helpful in the initial phases but are of no benefit in the later phase (>5 to 7 days).
VI. Careful attention to hydration status is required with diuretic therapy.
VII. Nitric oxide as an endogenous mediator of vascular smooth muscle relaxation is under investigation (Bhorade, 1999).
VIII. Unfortunately, clinical trials in humans have not demonstrated any beneficial drug combination in improving survival.

Monitoring of Animal

I. Monitor respiratory rate and effort every 1 to 8 hours.
II. Assess serial blood gas measurements SID to QID.
III. Monitor hydration status by evaluating volume-related changes.
   A. Cardiac output, arterial blood pressure
   B. Pulmonary capillary wedge pressure
   C. Serial PCV, TP, electrolyte assays
   D. Renal function tests, urine output
IV. Thoracic radiographs are repeated SID to QOD.
V. Prognosis with severe ARDS is poor to guarded.

Lung Lobe Torsion

Definition and Causes

I. Lung lobe torsion is rotation of a lung lobe around its long axis.

II. The exact mechanism that results in increased mobility of a lung lobe is unknown.
III. Lung lobe torsion may be idiopathic, particularly in deep-chested breeds of dogs.
IV. The torsion may be associated with several events.
  A. Pleural effusion of alternate etiology
  B. Thoracic surgery and manipulation of tissues
  C. Trauma causing sudden lung lobe compression

Pathophysiology

I. Rotation of the lung lobe at the hilus strangles the bronchus and vascular pedicle.
  A. There is obstruction to ventilation and venous drainage.
  B. The artery remains partially patent.
  C. Progressive lobar engorgement of blood occurs.
  D. The lobe becomes an expansile mass.
  E. Increased hydrostatic pressure (venous congestion) causes exudation of bloody fluid into the pleural space.
    1. Pleural effusion may further impair tidal volume.
    2. Mild blood loss anemia can be observed.
II. Necrosis, fibrosis, and shrinkage of the lung lobe may eventually occur.

Clinical Signs

I. Historically, signs of preexisting pulmonary or pleural space disease may present.
II. Signs are usually acute and progressive.
  A. Respiratory distress and tachypnea
  B. Cough, with or without hemoptysis
  C. Hypotension and collapse
  D. Fever and lethargy

Diagnosis

I. Signalment may provide helpful clues, because deep-chested breeds (especially sight hounds) appear to have an increased incidence.
II. Physical examination is compatible with pleural effusion (see Chapter 19).
III. Thoracic radiographic findings vary depending on the stage of the disease.
  A. Pleural effusion usually obscures parenchymal detail.
  B. The pleural effusion may be removed and the radiographs repeated.
  C. Lobar consolidation is typically noted.
  D. Air bronchograms may occur early, but air is reabsorbed later.
  E. Rounding of the lung lobe edges is noted as the lung becomes engorged.
  F. The bronchus may lie in an incorrect anatomical plane.
IV. Pleural fluid analysis is consistent with a hemorrhagic modified transudate (see Chapter 19).
V. Underlying conditions may produce other laboratory abnormalities (e.g., hypoproteinemia associated with protein-losing enteropathy resulting in pleural effusion).
VI. Bronchoscopy is sometimes needed to verify rotation of the bronchus.
VII. Surgical exploration is necessary to confirm the diagnosis in some cases.
VIII. Histopathologic examination of the excised lung lobe is performed to rule out an underlying disease.

Differential Diagnosis

I. Other causes of bloody pleural effusion (see Chapter 19)
II. Lung mass and/or neoplasia
III. Lobar pneumonia
IV. Pleural space mass and/or neoplasia
V. Diaphragmatic hernia

Treatment

I. Improve tissue oxygenation.
  A. Provide supplemental oxygen with nasal cannula, mask, or oxygen cage.
  B. Remove pleural fluid to enhance lung expansion.
  C. Consider an indwelling chest tube, if warranted.
II. Support circulatory function with IV fluid therapy to maintain hydration and systemic blood pressure.
III. Surgical resection of the affected lobe is typically curative.

Monitoring of Animal

I. Anesthesia must be monitored carefully, because these animals are severely compromised.
II. Postoperatively, an indwelling chest tube is usually placed for the first 12 to 48 hours.
III. Respiratory rate and effort and mucous membrane color are monitored every 1 to 6 hours for the first 24 to 48 hours postoperatively.
IV. Prognosis is good with lobectomy, but underlying conditions may require additional therapy and monitoring.

Cystic-Bullous Lung Disease

Definition

I. Circumscribed regions of air and fluid occur in the lung parenchyma.
II. They form cysts, bullae, or pneumatoceles.
  A. Cysts are fluid- or air-filled lesions surrounded by respiratory epithelium.
  B. Bullae are large areas of air accumulation formed by the loss of alveolar walls.
  C. Pneumatoceles result from air entry into a necrotic lesion, such as an abscess, granuloma, or tumor.

Causes and Pathophysiology

I. Cysts may be congenital or acquired.
II. Bullae occur as a result of emphysema (bullous emphysema), inflammation, trauma, or undefined reasons.
  A. Emphysema results from enlargement and destruction of bronchial and alveolar walls secondary to obstructive pulmonary diseases, such as chronic bronchitis.
  B. The loss of radial traction from the alveoli contributes to airway collapse, because alveoli may fill with air, but expiration is impaired by airway closure.
III. *Paragonimus kellicotti* (lung fluke) can cause granuloma and/or pneumatocele formation in dogs and cats.
IV. Any of these lesions may rupture, creating a pneumothorax.

V. Depending on the number and severity of lesions, significant functional lung parenchyma may be lost, and large lesions may compress airways.

Clinical Signs

I. Signs may relate to the primary disease processes, such as chronic bronchitis or traumatic insult.
II. Acute respiratory distress and tachypnea can occur when cysts or bullae rupture, creating a pneumothorax.
III. Occasionally cystic-bullous lung disease is an incidental finding on thoracic radiography, and no clinical signs are reported.

Diagnosis

I. Thoracic radiography reveals solitary nodules or visible margins of cavitary lesions in the peripheral lung fields.
   A. Initially these lesions may be obscured by soft-tissue opacity from primary disease processes.
   B. Pneumothorax is identified if a cavitary lesion has ruptured.
II. Cytology from any specimens obtained via thoracocentesis (for fluid or air) may be helpful.
   A. *Paragonimus* spp. ova might be found.
   B. Aspiration of a bullous lesion is not recommended, owing to the risk of pneumothorax.
III. Thoracotomy, excision of the lesion, and histopathologic evaluation are often required for definitive diagnosis.

Differential Diagnosis

I. Trauma or any other cause of pneumothorax
II. Pleural effusion
III. Chronic bronchial disease

Treatment

I. Identify and treat acute pneumothorax, as needed (see Chapter 19).
II. Surgical exploration and removal of cavitary lesions is warranted in those animals with recurrent pneumothorax.
   A. Removal of localized lesions has the best long-term prognosis.
   B. Bullous emphysematous disease is difficult to surgically correct, because the bullae are numerous and the disorder is usually progressive.
   C. Even though recurrence is common, survival of >2 years is reported postoperatively (Hawkins, 2000).
III. Successful treatment of underlying diseases, such as chronic bronchial disease or lung flukes, provides the best chance of success.

Monitoring of Animal

I. Monitor anesthesia carefully because these animals are severely compromised.
II. An indwelling chest tube is usually placed for the first 12 to 48 hours after surgery.
III. Monitor respiratory rate and effort and mucous membrane color every 1 to 6 hours for the first 24 to 48 hours postoperatively.
IV. Monitor thoracic radiographs frequently for recurrence of bulla or cysts.
V. If bulla(e) are found radiographically, treatment is generally not advised unless the animal becomes symptomatic (i.e., development of pneumothorax).

PARASITIC DISEASES

Aelurostrongylus abstrusus

Definition and Cause

Aelurostrongylus abstrusus is a nematode that resides in the small airways and pulmonary parenchyma of cats (definitive host).

Pathophysiology

I. Ingestion of the intermediate host (snails, slugs) or the transport hosts (birds, lizards) results in infection.
II. Larvae migrate to small airways, mature into adults, and result in inflammatory and hypersensitivity reactions.
   A. Eosinophilic infiltrate
   B. Bronchospasm
   C. Airway exudate
III. Interstitial granuloma formation is common.
IV. First-stage larvae are expelled from the airways, swallowed, and passed in the feces.
V. Fecal spread of larvae to intermediate hosts and secondary spread to transport hosts then occur.

Clinical Signs

I. Most cats are asymptomatic, but young cats may be more likely to develop clinical signs.
II. The symptoms are indistinguishable from those of feline allergic bronchitis (primarily cough).

Diagnosis

I. Identification of larvae on bronchial wash samples or fecal flotation using the Baermann technique is definitive.
II. Multiple fecal samples must usually be evaluated (intermittent larval shedding).
III. Thoracic radiography may reveal a diffuse bronchointerstitial or a miliary and/or nodular interstitial pattern, similar to feline allergic bronchitis.

Differential Diagnosis

I. Feline allergic bronchitis
II. Bronchopneumonia
III. Other eosinophilic lung disease
IV. Capillariasis

Treatment and Monitoring

I. Fenbendazole 25 to 50 mg/kg PO BID for 14 days
II. Ivermectin 400 μg/kg PO once (Kirkpatrick and Megella, 1987)
III. Possibly corticosteroids for short-term control of clinical signs
IV. Signs monitored with thoracic radiographs
V. Prognosis excellent

Capillaria aerophila

Definition and Cause

Capillaria aerophila is a small nematode that lives beneath the epithelial surfaces of the large airways of dogs and cats.

Pathophysiology

I. Infection is via ingestion of ova or the paratenic host (earthworm).
II. Larvae migrate to the large airways and live beneath the epithelial surface.
III. Hypersensitivity to the parasite appears important for clinical symptoms.

Clinical Signs

I. Signs are uncommon.
II. Occasionally, animals present with signs of allergic bronchitis (cough).

Diagnosis

I. Thoracic radiography may be normal or reveal a bronchial to bronchointerstitial lung pattern.
II. Peripheral eosinophilia may be found.
III. Airway secretions obtained via bronchoalveolar lavage or tracheal wash are examined for *C. aerophila* ova.
IV. Fecal flotation may contain parasite ova, which may be confused with those of *Trichuris vulpis.*

Differential Diagnosis

I. Chronic bronchitis
II. Bronchopneumonia
III. Eosinophilic lung disease (nonparasitic)
IV. *Aelurostrongylus* spp. in cats

Treatment and Monitoring

I. Fenbendazole is given at a dose of 25 to 50 mg/kg PO BID for 14 days for dogs and cats.
II. Levamisole is administered at 8 mg/kg PO SID for 10 to 20 days in dogs.
III. Ivermectin 400 μg/kg PO is used except in ivermectin-sensitive dog breeds.
IV. Monitor clinical signs closely, but expect a good prognosis.

Paragonimus kellicotti

Definition and Cause

I. *Paragonimus kellicotti* is a small fluke that normally resides in the lung tissue of mink and other wild carnivores.
II. Snails and crayfish are necessary intermediate hosts, and the disease is most common in the Great Lakes region of the Midwest and in the southern United States.

Pathophysiology

I. Adult flukes live primarily in the caudal lung lobes and are walled off by an inflammatory, granulomatous response.
II. A connection from the granuloma to the airway allows for the passage of eggs.
III. Pneumatoceles (leakage of air into the granuloma) may occur.
IV. Granulomas may rupture, creating a pneumothorax.

Clinical Signs

I. Most animals are presented for chronic cough not responsive to traditional therapies.
II. Infection is more common in cats than dogs.
III. Some animals show no clinical signs.
IV. Occasionally, animals have signs of pneumothorax.

Diagnosis

I. Thoracic radiography often reveals solitary or cavitary mass lesions in the caudal (especially right side) lung lobes.
II. A bronchointerstitial or mixed interstitial-alveolar pattern may also be present.
III. Identification of the large operculated ova in fecal specimens or airway washes confirms the diagnosis.
IV. Fecal sedimentation may be needed to find ova.

Differential Diagnosis

I. Chronic bronchitis
II. Bronchopneumonia
III. Eosinophilic lung disease (nonparasitic)
IV. *Aelurostrongylus* spp. in cats
V. Other causes of cystic-bullous lung disease
VI. Neoplasia

Treatment and Monitoring

I. Give fenbendazole at doses of 25 to 50 mg/kg PO BID for 14 days for dogs and cats.
II. Thoracocentesis may be necessary to stabilize any pneumothorax.
III. Place chest tubes initially for large-volume pneumothorax.
IV. Surgical intervention is rarely needed.
V. Assess response to treatment through thoracic radiographs and serial fecal exams.
   A. Repeat treatment may be necessary in some cases.
   B. Prognosis is excellent.

IMMUNE/HYPERSENSITIVITY DISORDERS

Pulmonary Infiltration with Eosinophilia

Definition

I. Profound eosinophilic inflammation of the interstitium is sometimes referred to as pulmonary infiltration with eosinophilia (PIE) or eosinophilic pulmonary granulomatosis (EPG).
II. These disorders are characterized by pronounced eosinophilic interstitial pulmonary inflammation.

Causes

I. Eosinophilic inflammation is a hypersensitivity response to an underlying antigen source.
II. Heartworm disease is commonly associated with PIE and granulomatosis.

III. Other causes may include pulmonary parasites, inhaled allergens, and drugs.
IV. Some cases appear idiopathic or as a part of a hypereosinophilic syndrome.

Pathophysiology

I. Immunological mechanisms are likely responsible for the pathogenesis and progression.
II. Inflammation may result from various factors.
  A. Hypersensitivity to an antigenic stimulus
  B. Immune complex deposition and complement activation
  C. Cell-mediated (delayed) hypersensitivity in chronic disease

Clinical Signs

I. Coughing is the most common clinical complaint; however, other respiratory symptoms may be noted.
II. Auscultation can reveal normal lung sounds or crackles and expiratory wheezes.
III. Systemic signs (anorexia, weight loss), if present, are usually mild.

Diagnosis

I. Complete blood count
  A. Peripheral eosinophilia is a common finding, but is not present in every case.
  B. Basophilia may occasionally be noted.
II. Thoracic radiography
  A. A diffuse, patchy interstitial pattern is typical.
  B. Eosinophilic granuloma formation may produce a nodular or nodular-interstitial pattern.
  C. Hilar lymphadenopathy may be found, particularly in cases of EPG.
  D. Right ventricular (± atrial) enlargement and dilated pulmonary arteries (especially proximally) may occur as a result of prolonged PH.
III. Cytology of pulmonary specimens usually diagnostic
  A. Sources include tracheal or bronchial wash and transthoracic aspirate.
  B. Eosinophils predominate.
  C. A smaller, mixed population of inflammatory cells is also common.
  D. Mast cells are occasionally found.
IV. Definitive diagnosis: histopathology of lung biopsy
V. Identification of underlying source of antigenic stimulation
  A. Heartworm testing
  B. Fecal flotation for parasites
  C. Serological testing and/or cultures for systemic mycoses
  D. Careful examination of biopsy specimens for infectious agents or neoplasia

Differential Diagnosis

I. Chronic allergic bronchitis
II. Parasitic lung disease
III. Diffuse pulmonary neoplasia
IV. Lymphomatoid granulomatosis
V. Severe bronchopneumonia: bacterial or mycotic

Treatment

I. Identification and elimination of the underlying source of antigen may be curative.
II. Corticosteroids are the primary medical therapy.
  A. Prednisone 1 to 2 mg/kg PO BID is the most common therapy.
  B. Inhalant corticosteroids have been empirically used with reasonable success.
  C. Incomplete responses are possible, especially in dogs with EPG.
III. Immunosuppressive medications can be added in dogs that do not respond to prednisone alone.
  A. Cyclophosphamide 50 mg/m^2 PO QOD
  B. Azathioprine 2 mg/kg PO SID for 7 to 10 days, then QOD
IV. Antibiotics are indicated if secondary infection is confirmed on initial evaluation.
V. Bronchodilators can be helpful to reduce bronchospasm, enhance mucociliary clearance, and decrease respiratory muscle fatigue.
  A. Methylxanthine-derivatives
    1. Aminophylline 6 to 11 mg/kg PO TID (dogs) and 4 to 6 mg/kg PO BID (cats)
    2. Theophylline 4 to 5 mg/kg PO TID
  B. Other bronchodilators
    1. Terbutaline 1.25 to 5.0 mg PO BID (dogs) and 0.625 mg to 1.25 mg PO BID (cats)
    2. Albuterol 50 µg/kg PO TID or aerosolized, inhaled
    3. Ipratropium bromide aerosolized, inhaled

Monitoring of Animal

I. Clinical signs are used to monitor response to therapy.
  A. The animal's response to therapy is reassessed at least weekly.
  B. After resolution of clinical signs, medications are gradually tapered to the lowest effective dose.
  C. After 3 months of remission of clinical signs, medications may be stopped in some cases.
II. Thoracic radiography is also used to assess response to therapy.
III. Radiographs are reevaluated initially at least once weekly.
IV. Monitor a CBC every 2 weeks to look for signs of bone marrow suppression if immunosuppressive agents are administered.
V. Medication adjustments are frequently required over time based on clinical response and appearance of adverse reactions.
VI. Many animals require lifelong drug therapy.

VASCULAR DISORDERS

Pulmonary Thromboembolism

Definition

I. Pulmonary thromboembolism (PTE) is occlusion of the pulmonary arterial system with thrombi.
II. The emboli may arise from a distant site.

III. PTE is often a secondary phenomenon, and the predisposing condition is usually identifiable.

Causes

I. Hypercoagulable states
   A. Protein-losing disorders: enteropathies, nephropathies
   B. Hyperadrenocorticism
II. Sepsis
III. Disseminated intravascular coagulation
IV. Immune-mediated disorders, including anemia and thrombocytopenia
V. Vascular diseases: heartworm, vasculitis
VI. Neoplasia, especially adenocarcinomas (Goldhaber, 2000)
VII. Other chronic pulmonary inflammation, particularly when associated with significant PH
VIII. Systemic inflammatory syndromes (without sepsis), such as pancreatitis
IX. Trauma or surgery with immobilization
X. Iatrogenic: indwelling catheters, transfusions

Pathophysiology

I. One or more alterations of the components of Virchow's triad lead to thrombi formation.
   A. Endothelial trauma or disease
   B. Hypercoagulability
   C. Blood stasis
II. Thrombi lodge in pulmonary arteries, creating several sequelae.
   A. Ventilation-perfusion abnormalities
   B. Hypoxemia, tachypnea, and hypocapnia (hypercapnia in severe cases)
   C. Reflex pulmonary arterial vasoconstriction
   D. Bronchoconstriction mediated by vasoactive substances
III. PH arises from several factors.
   A. Increased pulmonary vascular resistance
   B. Vasoconstriction
   C. Arterial wall hypertrophy and fibrosis in chronic cases
IV. Right heart failure may ensue.
V. Systemic hypotension may result from diminished filling of the left ventricle (LV) and poor cardiac output.

Clinical Signs

I. Respiratory distress, tachypnea
II. Coughing ± hemoptysis
III. Jugular distention and pulsations
IV. Symptoms of right heart failure: pleural, abdominal effusion
V. Auscultation findings suggestive of PH (see next section)
VI. Crackles or increased bronchial sounds, possibly normal lung sounds

Diagnosis

I. A history of predisposing factors combined with appropriate clinical signs help make the diagnosis.
II. Thoracic radiography may be normal or reveal one or more abnormalities.
   A. Enlargement of proximal pulmonary arteries
   B. Attenuation of peripheral pulmonary vessels
   C. Right atrial ± RV enlargement
   D. Mild pleural effusion
   E. Increased interstitial opacities, particularly in the caudodorsal lung fields
   F. Focal oligemia with massive central artery occlusion (Westermark's sign)
III. Blood gas analysis is not specific for PTE, but may reveal several abnormalities.
   A. Hypoxemia, hypocapnia (hypercapnia in severe disease)
   B. Metabolic acidosis
   C. Normal blood gases in early, mild disease
IV. Echocardiography helps support the diagnosis of PTE by identifying PH (see next section).
V. Plasma D-dimer assays support the diagnosis of PTE, because D-dimer concentrations >1000 ng/dL have a specificity of 94% (sensitivity 80%) and concentrations >2000 ng/dL have a specificity of 98.5% (sensitivity 36%) in predicting PTE.
VI. A ventilation-perfusion nuclear scan is most helpful if it is clearly normal or clearly abnormal; however, most scans are inconclusive (Kress, 1999).
VII. Pulmonary angiography is the most sensitive and specific test for PTE.
   A. Identifies filling defects in the arteries or cessation of blood flow
   B. Can detect emboli as small as 1 to 2 mm (Goldhaber, 2000)
   C. Heavy sedation or anesthesia required and usually a disadvantage in the compromised animal
VIII. High resolution helical computed tomography may be performed at some institutions.

Differential Diagnosis

I. Airway obstruction
II. Acute pneumonia
III. Acute respiratory distress syndrome
IV. Other pulmonary parenchymal disorders
V. Other causes of PH

Treatment

I. Improve tissue oxygenation with supplemental oxygen (nasal cannula, mask, or oxygen cage).
II. Positive end-expiratory pressure ventilation is sometimes required in severe cases.
III. Cautious use of parenteral fluid therapy is necessary.
   A. These animals may be hypotensive because of pulmonary arterial obstruction and diminished filling of the LV.
   B. Aggressive IV fluids may exacerbate RV pressure overload and displace the interventricular septum, further impairing LV filling.
IV. Anticoagulant therapy prevents further clot formation while allowing for endogenous fibrinolysis.
   A. Heparins are the cornerstone of therapy.
      1. Give unfractionated heparin at 200 U/kg IV, followed by 75 to 200 U/kg SC TID to QID.

2. Assess a partial thromboplastin time (aPTT) SID to QID if the higher dosing ranges are used.
3. Have protamine sulfate available to antagonize a heparin overdose.
   a. Give 1 mg protamine for each 100 U of heparin to be inactivated.
   b. Reduce dose by half for every 30 minutes lapsed since heparin was administered.
4. Low-molecular-weight heparin has been experimentally shown to provide safer and more effective anticoagulant coverage for dogs; however, the dose is not well established in clinical patients.

B. Warfarin or coumarin derivatives can be used.
1. They provide long-term antagonism of coagulation.
2. Coagulation times must be closely monitored and can be difficult to regulate.
3. Warfarin 0.1 mg/kg PO SID is the recommended dose.

C. Antiplatelet drugs, such as aspirin, ticlopidine and clopidogrel, are used primarily for prevention in high-risk disease states.

V. Fibrinolytic therapy includes agents such as streptokinase and tissue plasminogen activator.
A. The therapy is most effective in relatively acute states (<2 weeks).
B. Excessive bleeding can be a significant side effect.

VI. Embolectomy may be considered if the thrombus is centrally located, but the mortality rate with surgery is high.

VII. Identification and treatment of the predisposing condition is very important.

Monitoring of Animal

I. Detect response to therapy and resolution of thrombi by improvements in the following parameters:
A. Respiratory rate and effort
B. Serial blood gases or pulse oximetry
C. Pulmonary and systemic blood pressures
D. Thoracic radiography

II. Monitor coagulation times, such as aPTT or prothrombin time (PT) carefully.
A. With unfractionated heparin therapy, a 1.5-fold to twofold increase in the PT is desirable.
B. With warfarin therapy, a 1.5-fold to twofold rise in the PT is desirable.

III. Prognosis is variable depending on the size and location of the thrombi and their underlying cause.

IV. The prognosis is especially poor with large central pulmonary artery thrombi.

Pulmonary Hypertension

Definition

I. Pulmonary hypertension is an increase in pulmonary vascular resistance caused by vasoconstriction, vascular obstruction, vascular volume overload, or lung resection, and occurs secondary to many pulmonary parenchymal disorders.

II. PH can be acute or chronic.

III. PH is typically a secondary phenomenon; recognizing the existence of PH necessitates a search for the underlying condition.

Causes

I. Acute pressure overload
A. Pulmonary thromboembolism
B. Acute respiratory distress syndrome
C. Acute hypoxic pneumonia
D. Extensive lung resection

II. Chronic pressure overload
A. Chronic airway diseases: bronchitis, bronchiectasis, emphysema
B. Chronic parenchymal disorders: neoplasia, PIE, etc.
C. Restrictive lung disease: pleural and pleural space disease
D. Chronic PTE
E. Heartworm disease
F. Congenital heart disease
G. Occasionally idiopathic forms

Pathophysiology

I. Elevations in pulmonary arterial pressure are accompanied by elevations in RV preload, afterload, intraventricular pressure, and heart rate.

II. As RV pressure rises, the interventricular septum shifts to the left, impairing LV filling.

III. A vicious cycle ensues wherein increases in RV pressure promote RV ischemia and dilatation, worsen LV filling and myocardial ischemia, and exacerbate hypotension.

IV. Right heart failure can also occur.

Clinical Signs

I. Signs are usually referable to the underlying disease process.

II. Tachypnea, cough, and exercise intolerance (hypoxia and hypotension) are common.

III. A sudden onset of respiratory distress may be noted if the cause of PH is an acute process or involves acute decompensation of a chronic process.

IV. Jugular distention and pulsations suggest elevated right heart filling pressures.

V. The precordial impulse may feel stronger on the right hemithorax.

VI. Right heart failure may be present (pleural effusion, ascites).

VII. Auscultation may reveal one or more abnormalities.
A. Tricuspid regurgitation
B. Split S2 and/or loud, "snappy" S2 sounds
C. Right-sided S3 sound

Diagnosis

I. A history of predisposing factors combined with appropriate clinical signs help make the diagnosis.

II. Thoracic radiography may be normal or reveal one or more abnormalities.

A. Enlargement of proximal pulmonary arteries
B. Attenuation of peripheral pulmonary vessels
C. Right atrial ± RV enlargement
D. Mild pleural effusion
E. Radiographic pulmonary patterns consistent with underlying causes

III. Echocardiographic signs of PH include the following:
A. A poorly contracting RV
B. Tricuspid regurgitation
C. Leftward shifting of the interventricular septum
D. Pulmonary artery dilatation and pulmonic regurgitation
E. Possibly a thrombus in the right atrium, RV, or main pulmonary artery
F. Loss of the respiratory variation of the diameter of the caudal vena cava

IV. Catheterization of the right side of the heart and the pulmonary artery definitively documents hypertension in these chambers.

V. Laboratory evidence of other underlying disease states also may be present.

Differential Diagnosis

I. Acute or chronic respiratory conditions without PH
II. Other cardiac diseases

Treatment

I. Enhance arterial oxygen saturation and attempt to keep it >96%.
II. Minimize oxygen demands via sedation, treatment of fever, and assisted ventilation.
III. Finding the optimal circulatory volume can be challenging.
A. Aggressive IV fluids may exacerbate RV pressure overload and displace the interventricular septum, impairing LV filling and output.
B. If no benefit is noted in response to discrete fluid therapy, consider vasoactive drug therapy.
IV. Vasoactive drugs may be beneficial in increasing right-sided cardiac output.
A. Dobutamine 5 to 7 μg/kg/min IV
B. Dopamine 5 to 7 μg/kg/min IV
V. Pulmonary arterial dilator therapy has received much attention, but specific therapy is not well established.
A. Calcium channel blockers have been advocated.
B. Sildenafil (2 to 3 mg/kg PO BID to TID) has been empirically used with reasonable success.
C. Inhaled nitric oxide is a potent pulmonary vasodilator.
VI. Treatment of any underlying condition is of utmost importance.

Monitoring of Animal

I. Use response to therapy to guide treatment.
A. Respiratory rate and effort
B. Serial blood gases or pulse oximetry
C. Pulmonary and systemic blood pressures
D. Thoracic radiography

II. The underlying condition and the effectiveness of therapy require close monitoring.

NEOPLASIA

Definition

I. Tumors of the pulmonary parenchyma can be primary, metastatic, or multicentric in origin.
II. Metastatic and multicentric neoplasms are more common than primary ones.
III. Older animals are affected most often, although young animals may sometimes develop lymphoma and lymphomatoid granulomatosis (dogs).

Causes

I. Primary lung tumors are typically malignant.
A. Carcinomas are the most common neoplasm.
1. Adenocarcinoma
2. Bronchoalveolar carcinoma
3. Squamous cell carcinoma
4. Small-cell carcinoma
B. Primary sarcomas and benign neoplasms are uncommon.
C. Lymphomatoid granulomatosis is a disease akin to lymphosarcoma.
II. There are numerous metastatic neoplasms involving the lungs.
A. Carcinomas: nonpulmonary and pulmonary origin
B. Osteosarcoma, fibrosarcoma
C. Hemangiosarcoma
D. Melanoma
E. Other malignant tumors
III. Multicentric neoplasms can involve the lung.
A. Lymphosarcoma
B. Mast cell tumor
C. Malignant histiocytosis

Pathophysiology

I. Environmental factors, such as passive cigarette smoke, have been implicated.
II. Genetic factors may play a role in some neoplasms (e.g., malignant histiocytosis in Bernese mountain dogs).
III. Metastasis to the lungs is common via hematogenous or lymphatic systems.
IV. Tumor emboli may be trapped in the lung owing to its extensive capillary network.
V. Hypertrophic pulmonary osteopathy is the most common paraneoplastic syndrome in dogs (see Chapter 81).
VI. Neoplasms may cause clinical signs from ventilation-perfusion abnormalities, compression or obstruction of airways, or pleural space disease (mass affect or effusion).
VII. Inflammatory reactions to the tumors contribute to the pathology (e.g., secondary infections, hemorrhage, PTE).

Clinical Signs

I. Cough
II. Tachypnea ± respiratory distress

III. Weight loss, anorexia, lethargy
IV. Fever
V. Lameness from hypertrophic pulmonary osteopathy

Diagnosis

I. Thoracic radiography often provides a tentative diagnosis of neoplasia.
   A. Left and right lateral projections and a dorsoventral projection are needed to thoroughly assess the pulmonary parenchyma.
   B. Tumor margins may be distinct or indistinct if inflammation and edema are present.
   C. Some general radiographic patterns are noted.
      1. A solitary nodule may be associated with primary lung tumors.
         a. Right caudal lung lobes are the most common location in dogs.
         b. Left lung lobes are affected more commonly in cats.
      2. Multiple circumscribed nodules are often seen with metastatic neoplasia.
      3. An interstitial generalized, reticulonodular pattern can be noted with multicentric or metastatic neoplasia.
      4. A mixed, disseminated alveolar pattern may indicate a concurrent secondary inflammatory process.
      5. Lobar consolidation is found in some cases.
   D. Other radiographic findings may include pleural effusion and thoracic or hilar lymphadenopathy.
II. Cytological evaluation of a percutaneous fine-needle aspirate, bronchoalveolar lavage, or pleural fluid can yield a tumor type.
III. Histopathologic evaluation of samples obtained at exploratory thoracotomy is sometimes necessary for a definitive diagnosis.

Differential Diagnosis

I. Nonneoplastic solitary lung lesions: cysts, granulomas
II. Lobar pneumonia
III. Mycotic pneumonia
IV. Parasitic lung disease

Treatment

I. Surgical intervention (lobectomy) is the treatment of choice for solitary lung tumors.
II. Chemotherapy is often recommended for neoplasms that are incompletely resected.
III. Chemotherapy may be a beneficial adjunctive therapy to surgery or may be indicated as the sole treatment depending on the tumor type.
IV. Lymphomatoid granulomatosis and malignant histiocytosis may be treated with lymphosarcoma protocols (see Chapters 69 and 77).

Monitoring of Animal

I. Prognosis depends on the tumor type, the tumor burden, and the degree of metastasis.
II. Surgical resection of a solitary tumor without metastasis carries the best long-term prognosis (>1 year).
III. Monitor thoracic radiographs every 1 to 3 months post-treatment.

TRAUMA

Pulmonary Contusions

Definition and Causes

I. Hemorrhage into the pulmonary parenchyma
II. Most often caused by blunt chest trauma
   A. Animals that have been hit by motorized vehicles commonly present with pulmonary contusions.
   B. Pulmonary hemorrhage can occur even when external thoracic damage is not detected.

Pathophysiology

I. Hemorrhage occurs from traumatic rupture of parenchymal vessels.
II. Bleeding occurs into the interstitium and alveoli in the region of the insult.
III. Flooding of the lung tissue with blood impairs normal gas exchange and results in clinical signs.

Clinical Signs

I. Acute tachypnea and respiratory distress are noted with severe contusions.
II. Tachypnea may also occur from pain, pneumothorax, or cardiovascular shock, which are common with acute pulmonary trauma.
III. Crackles are often ausculted over the contused area.
IV. Minimal clinical signs may be noted if only mild hemorrhage has occurred.

Diagnosis

I. History and physical examination (fractures, abrasions) may suggest a traumatic episode.
II. Thoracic radiography reveals regional, irregular patches of mixed interstitial-alveolar patterns (see Box 18-2).
III. Pneumothorax, lung consolidation, or rib fractures are sometimes identified.

Differential Diagnosis

I. Acute pneumonia
II. Acute respiratory distress syndrome
III. Pulmonary thromboembolic disease
IV. Lung lobe torsion

Treatment

I. Improve oxygenation with supplementation via nasal, mask, or oxygen cage.
II. Specific therapy for the contusions is not usually necessary.
III. Treatment for the other trauma-related problems is often more critical.

A. Blood loss
B. Circulatory shock
C. Fracture stabilization

Monitoring of Animal

I. Serial thoracic radiographs are evaluated for resolution of the abnormalities.
II. Frequency of radiography (every 1 to 5 days) depends on the severity of abnormality noted and the clinical signs.
III. Secondary complications such as abscessation, lung consolidation, or the formation of cavitary lesions may occur but are unusual.
IV. Prognosis is excellent for recovery from mild to moderate pulmonary contusions, provided that other injuries sustained are stabilized and fluid therapy is monitored carefully.

Near-Drowning

Definition

I. Near-drowning is aspiration of water during submersion.
II. The result is severe pulmonary damage.

Cause and Pathophysiology

I. Normal reflexes cause cessation of ventilation under water.
II. Increased levels of carbon dioxide in the bloodstream subsequently stimulate breathing efforts.
III. Aspiration of water dilutes surfactant, collapses alveoli, and causes severe oxygenation impairment.
IV. Aspiration of salt water exacerbates fluid flux into the alveoli (hypertonic solution).
V. Laryngospasm occurs in about 10% of cases, preventing aspiration of water and resulting in a "dry drowning" form of the condition (Hawkins, 1995).
VI. Bacteria, vomitus, or chemicals in the water may predispose to a secondary pneumonia.
VII. Severe hypoxia causes profound neurological disturbances from cerebral edema or herniation.

Clinical Signs

I. Loss of consciousness and severe respiratory distress or arrest are typical.
II. Cardiovascular shock and hypothermia may be noted.
III. Auscultation usually reveals inspiratory and expiratory crackles and wheezes.
IV. Neurological abnormalities and altered mentation may indicate cerebral edema.

Diagnosis

I. Diagnosis is based on the history of rescuing the animal from the water.
II. Thoracic radiography reveals generalized, mixed interstitial–alveolar pulmonary patterns.
A. Radiographic changes often lag 24 to 48 hours behind clinical symptoms.
B. The presence of radiopaque material in the airways (sand bronchograms) is a poor prognostic indicator.
III. Bronchial wash and cultures are indicated if there is suspicion of secondary bacterial infection.

Treatment

I. Ventilation is provided as soon as possible.
A. Cardiopulmonary or mouth-to-muzzle resuscitation is indicated during the initial rescue.
B. Provide oxygen with a nasal cannula, mask, or oxygen cage.
C. Positive-pressure ventilation is often required.
II. If neurological symptoms are present after metabolic stabilization, treatment for cerebral edema may be warranted (see Chapter 23).

Monitoring of Animal

I. Respiratory function as well as metabolic and neurological status are followed closely.
II. A poor prognosis is associated with coma, blood pH <7.0, respiratory arrest, and the need for mechanical ventilation.

Smoke Inhalation

See Chapter 133.

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CHAPTER 19

Diseases of the Pleural Cavity

Graham Swinney

PLEURAL EFFUSION

Definition

I. Pleural effusion is the abnormal accumulation of fluid in the pleural space.
II. The pleura is a serosal surface that consists of a single layer of flattened mesothelial cells with an underlying thin layer of connective tissue that contains blood vessels and lymphatics (Forrester et al., 1991).
III. The pleura lining the thoracic walls, diaphragm, and mediastinum is the parietal pleura.
IV. The visceral pleura covers the serosal surface of the lungs.
V. The pleural space is the potential space between the parietal and visceral pleura.
VI. In normal animals, a small amount of fluid (2 to 3 mL) is present in the pleural space that serves as a lubricant for the lungs during respiration (Fossum, 2000).

Causes and Classification

I. Classification
   A. Based on physical characteristics (color, transparency, total protein, total nucleated cell count), effusions are classified as transudates, modified transudates, or exudates.
   B. Fluid can be further classified as pure transudates, hemorrhagic, inflammatory (nonseptic or septic), chylous, neoplastic, or pyogranulomatous types (Forrester et al., 1991).
II. Pure transudate (Table 19-1)
   A. Mechanism of production is usually reduced oncotic pressure from hypoalbuminemia.
   B. The cause of hypoalbuminemia can be reduced production (e.g., functional hepatic disease, portal vascular anomalies, malnutrition, malabsorption) or increased loss (e.g., protein-losing nephropathies, protein-losing enteropathies, vasculitis, inflammatory exudates, burns, wounds, hemorrhage, chronic gastrointestinal [GI] blood loss).
   C. Albumin is usually <1.5 g/dL, but a pure transudate can occur if albumin is >1.5 g/dL and there is also increased capillary hydrostatic pressure or lymphatic obstruction.
   D. With chronicity, a pure transudate may become modified from pleural irritation (Forrester et al., 1991).
III. Modified transudate
   A. It has a higher protein level and cellularity than a pure transudate.
   B. Factors increasing hydrostatic pressure or causing lymphatic obstruction can play a role (Forrester, 1988; Fossum, 2000).
      1. Heart failure in dogs: right-sided or combined right- and left-sided failure
      2. Heart failure in cats: right-sided failure, more commonly bilateral disease, or left-sided disease with pulmonary hypertension as pleural lymphatics drain into pulmonary veins (de Morais, 2000)
      3. Combined pleural and peritoneal effusions in cats: cardiac disease, neoplasia, hepatic or renal disease (Wright et al., 1999)
      4. Masses (usually neoplasms) obstructing pleural veins or lymphatics
      5. Pericardial effusion and cardiac tamponade or postpericardiectomy
      6. Lung lobe torsion
      7. Dirofilariasis
      8. Diaphragmatic hernia, especially with herniation of the liver into the thorax
      9. Pulmonary thromboembolism
IV. Exudate
   A. Mechanism of fluid production is often secondary to increased vascular or lymphatic permeability or to vessel obstruction.
   B. Inflammation of the pleural surface secondary to infection (pyothorax) is a potential cause.
      1. Obligate anaerobes are the most common isolates, especially in cats, followed by facultative organisms.
      2. Common organisms are listed in Table 19-2 (Walker et al., 2000).
      3. Unusual organisms may include *Mycoplasma* spp. and *Cryptococcus* spp. (Barrs et al., 2005).
      4. The source of infection can be extension from pneumonia (bacterial, viral, fungal, mycobacterial, parasitic); penetrating thoracic wounds; perforation of mediastinal structures, especially the esophagus; foreign bodies (e.g., grass awns); or hematogenous spread.
      5. Cats from multi-cat households are at a higher risk of pyothorax (Waddell et al., 2002).

TABLE 19-1

Characteristics of Pleural Effusions

TYPE OF EFFUSION	GROSS APPEARANCE	DIAGNOSTIC FEATURES	CYTOLOGY
Pure transudate	Clear, colorless No odor	Cell count <1000/μL Protein often <1.5 g/dL, s.g. <1.018 Low viscosity	Small lymphocytes, mesothelial cells, macrophages, neutrophils
Modified transudate	Serous serosanguineous Clear to moderately turbid	Cell count between 1000 and 5000/μL Protein variable, usually 2.5-3 g/dL s.g. 1.018-1.030	Variable: RBCs, neutrophils, lymphocytes ± eosinophils, macrophages, mesothelial cells May find neoplastic cells (e.g., lymphoblasts)
Exudate—nonseptic	Serous to serosanguineous to yellow Thick and viscous with FIP Hazy to turbid	Cell count >5000/mL Protein >3.0 g/dL s.g. >1.018	No bacteria Variable; if FIP: neutrophils, plasma cells, lymphocytes, macrophages, RBCs
Exudate—septic	Turbid or opaque White, yellow or red May have odor, especially if anaerobes involved ± Flocculent material or sulfur granules	Cell count >5000/μL Protein >3.0 g/dL s.g. >1.018	Neutrophils, may have degenerative changes, may see bacteria: intracellular ± extracellular
Chylothorax	Opaque, white, or pink	Cell count variable Protein 2.0-6.5 g/dL Fluid triglyceride concentration > serum triglyceride concentration Chylomicrons present	Lymphocytes perdominate but if chronic, neutrophils may be increased.
Hemothorax	Red	Cell counts similar to peripheral blood	RBCs, WBCs in similar proportions to peripheral blood May see erythrophagocytosis No platelets if present >45 min

s.g., Specific gravity; *RBC,* red blood cell; *FIP,* feline infectious peritonitis; *WBC,* white blood cell.

C. Other causes of exudative effusions include the following:
   1. Feline infectious peritonitis (FIP)
   2. Immune-mediated diseases: systemic lupus erythematosus, rheumatoid arthritis
   3. Uremia, pancreatitis
   4. Cardiac disease
   5. Neoplasia: chest wall or pulmonary (either primary or secondary) tumors, lymphosarcoma, mesothelioma
   6. Lymphomatoid or eosinophilic pulmonary granulomatosis (Bounous et al., 2000)

V. Hemorrhagic effusion
   A. Secondary to trauma, neoplasia, and coagulopathies (more likely coagulation system rather than platelet or vessel wall disease)
   B. Surgery, lung lobe torsion, dirofilariasis
   C. Pulmonary infarction

VI. Chylothorax effusion
   A. Idiopathic
   B. Thoracic lymphangiectasia
   C. Cardiac disease, pericardial effusion
   D. Trauma and rupture of the thoracic duct
   E. Neoplasia, thromboembolic disease
   F. Infectious causes: fungal granuloma and dirofilariasis
   G. Suspected breed predispositions for chylothorax: Afghan hound, Shiba inu, and purebred cats, particularly Asian breeds (Fossum et al., 1991; Fossum, 2000).
   H. Iatrogenic with cranial vena cava ligation or brachiocephalic vein ligation (Greenberg and Weisse, 2005)

VII. Other effusions
   A. Peritoneal fluid can cross the diaphragm via the lymphatics.
   B. Bile pleural effusion is reported in conjunction with biliary rupture (Barnhart and Rasmussen, 1996).
   C. Eosinophilic effusions occur with neoplasia, parasites, hypersensitivity reactions, and rarely pneumothorax (cat) (Fossum et al., 1993).
   D. Pseudochylous fluid is rare in small animals but can be associated with tuberculosis (Fossum, 2000).

TABLE 19-2

Characteristics of Common Bacterial Isolates with Pyothorax

BACTERIA	OXYGEN REQUIREMENT	GRAM'S STAIN	MORPHOLOGY	SENSITIVITY
Actinomyces spp.	Facultative or obligate anaerobe	Positive	Small bacillus, or filamentous with occasional branching, some sulfur granules	Penicillin, ampicillin, amoxicillin/clavulanate, erythromycin, doxycycline
Bacteroides spp.	Anaerobe	Negative	Bacillus, may stain poorly	Penicillin, metronidazole, amoxicillin/clavulanate, clindamycin, chloramphenicol
Escherichia coli	Facultative	Negative	Bacillus	Amikacin, gentamicin, ceftizoxime best; enrofloxacin possibly less effective
Fusobacterium spp.	Anaerobe	Negative	Bacillus—thin, may stain poorly	Penicillin, metronidazole, amoxicillin/clavulanate, clindamycin, chloramphenicol
Klebsiella spp.	Facultative	Negative	Bacillus, large capsule	Cefotaxime, amikacin, gentamicin, ticarcillin
Nocardia spp.	Aerobe	Positive, partially acid fast	Bacillus, filamentous, with beading from irregular staining, sulfur granules	Trimethoprim/sulphonamide, amikacin, ± imipenem, cephalosporin, ampicillin
Pasteurella spp.	Facultative	Negative	Bacillus, bipolar staining	Very susceptible to most drugs, including penicillin, amoxicillin/clavulanate
Peptostreptococcus spp.	Anerobe	Positive	Coccus	Penicillin, metronidazole, clindamycin, amoxicillin/clavulanate
Prophyromonas spp.	Anaerobe	Negative	Coccobacillus, pale staining	Penicillin, metronidazole, amoxicillin/clavulanate, clindamycin, chloramphenicol

Pathophysiology

I. Volume of pleural fluid is a result of a balance of fluid production by the parietal pleura and fluid absorption by the visceral pleura (Forrester et al., 1991).
II. Movement of pleural fluid is governed by Starling's forces (Forrester et al., 1991).
  A. The parietal pleura has a net force of approximately 9 cm H_2O, resulting in pleural fluid production.
  B. The visceral pleura has a net absorptive force of 10 cm H_2O.
III. The lymphatic drainage system removes fluid not absorbed by pleural capillaries (Forrester et al., 1991).
  A. Lymphatics are the only means for red blood cells (RBCs), proteins, and particulate matter to be absorbed.
  B. Lymphatic absorption is mainly via lower mediastinal pleura and costal parietal pleura.
  C. Hyperventilation increases lymphatic absorption, and hypoventilation reduces absorption of protein and RBCs.
IV. Mechanisms of pleural fluid production fall into one of four categories.
  A. Increased capillary hydrostatic pressure
  B. Reduced capillary oncotic pressure
  C. Lymphatic obstruction
  D. Increased vascular permeability

Clinical Signs

I. The severity of clinical signs varies with the underlying cause, the volume of the effusion, and the rate of fluid accumulation (Fossum, 2000).
II. A significant volume of fluid must be present before animals show signs of impaired ventilation.
III. Signs include a restrictive breathing pattern, increased inspiratory effort, tachypnea, shallow respiration, open-mouth breathing, cyanosis, lethargy, and coughing from irritation caused by the effusion.
IV. Depending on the cause, the signs also include a chronic cough, weight loss, inappetence, abdominal effusion, diarrhea, or concurrent signs of trauma.

Diagnosis and Differential Diagnosis

I. Physical examination
  A. Thoracic auscultation
    1. Muffled lung sounds ventrally, muffled heart sounds

2. Perhaps increased bronchovesicular lung sounds dorsally
3. Careful auscultation for cardiac murmurs, arrhythmias, and displacement of heart sounds to one side or caudally (suggesting a mass effect)

B. Thoracic percussion
1. In the presence of an adequate volume of fluid, thoracic percussion is hyporesonant (dull) ventrally.
2. Systematic percussion (with the animal standing or sternal) may detect a fluid line with normal resonance dorsally, and may determine if fluid accumulation is more severe on one side.

C. Thoracic compression
1. It is performed on the cranial thorax of all cats with an effusion.
2. Reduced compressibility occurs with a cranial mediastinal mass.

D. General physical examination
1. Abdominal fluid accumulation may occur with cardiac or hepatic disease, lymphosarcoma, or hypoalbuminemia.
2. In the presence of cardiac disease, jugular distension or pulses and/or altered peripheral pulse quality may be noted.
3. Other signs of systemic disease may be present, including pale mucous membranes, weight loss, lymphadenomegaly, signs of trauma, fever, and obtundation.

II. Thoracocentesis

A. Several methods have been described, but thoracocentesis is most commonly performed with the animal standing or in sternal recumbency (see Chapter 3).
1. Collect diagnostic samples using a 21- to 23-gauge butterfly needle connected to a three-way stopcock and a syringe, or by using a needle or an intravenous catheter with a three-way stopcock and an intravenous fluid extension set.
2. Place 5 mL of fluid into an ethylenediamine tetraacetic acid (EDTA) tube for cell analysis, and 5 mL into a plain tube for biochemical analysis.
3. Prepare four to six smears immediately and air dry these for cytological examination.
4. If fluid is of low cellularity, it can be centrifuged and smears made from the sediment (Forrester et al., 1991).

B. Also submit fluid for aerobic and anaerobic culture and sensitivity when cytological findings confirm the presence of an exudate.

III. Thoracic radiography

A. Ideally, pleural fluid is removed first, because more thorough evaluation of lung fields and other thoracic structures is then possible.

B. Take precautions not to stress the animal if significant fluid volume is still present, especially in cats.
1. Minimize handling.
2. Administer supplemental oxygen.
3. Perform dorsoventral rather than ventrodorsal views.
4. Standing lateral views may be taken.

C. Radiographic signs vary with the volume of fluid, but can include the following:
1. Increased number and thickness of interlobar fissures: seen with approximately ≥100 mL of fluid in a medium-sized dog (Thrall, 1998)
2. Decreased visualization of the heart, especially in the dorsoventral view
3. Retraction of lungs away from the thoracic wall, with a fluid density present between these two structures
   a. Lung retraction is typically uniform.
   b. If the pattern is not uniform, an underlying pulmonary disease may be present.
4. An increased radiopacity dorsal to the sternum on lateral views from fluid accumulation and scalloping of lungs ventrally
5. Blunting of lung margins at costophrenic angles on the ventrodorsal view
6. Obscured line of diaphragm on dorsoventral and lateral views
7. Widening of the mediastinum

D. Small-volume effusions are detected more readily on ventrodorsal views and expiratory films (Forrester et al., 1991).

E. Horizontal beam radiography can enhance detection of small fluid volumes, but it does not demonstrate a straight fluid line because fluid appearance is altered by the adjacent lung (Thrall, 1998).

F. Free pleural fluid is equally distributed between left and right pleural spaces, and its distribution is affected by changes in recumbency.

G. Fluid not affected by changes in recumbency suggests the following:
1. Encapsulation associated with pyothorax, chylothorax, or FIP
2. Altered lung compliance
3. Other intrathoracic pathology (Thrall, 1998).

H. Certain effusions (e.g., pyothorax, chylothorax) result in constrictive pleuritis, and the lungs do not fully expand after fluid drainage (Glennon et al., 1987).

IV. Ultrasonography

A. Ultrasound examination is often performed before drainage of the effusion.
1. Fluid provides an acoustic window.
2. Ultrasonography enhances the examination of the thoracic structures.

B. Ultrasonography is useful to examine the heart and pericardium for underlying diseases and the mediastinum for masses.

C. It may identify small-volume pleural effusion not detected radiographically (Reichle and Wisner, 2000).

D. It may also detect other pathology.
1. Consolidated lung lobe
2. Certain pulmonary abnormalities, such as masses or lung lobe torsion
3. Presence of abdominal contents in the thoracic cavity with diaphragmatic hernias (Reichle and Wisner, 2000)

E. It also helps guide drainage of loculated fluid or aspiration of mass lesions (Reichle and Wisner, 2000).
F. Echogenic fluid on ultrasound is more likely to be exudative in nature (Reichle and Wisner, 2000).

V. Physical and cytological examination of pleural fluid (see Table 19-1)
A. Pure transudates
1. Usually clear, colorless, and odorless, with low viscosity
2. Small lymphocytes, mesothelial cells, macrophages, and well-preserved neutrophils on cytology (Forrester et al., 1991)
B. Modified transudates
1. Serous to serosanguineous, clear to moderately turbid, low viscosity
2. Cytology variable: typically mesothelial cells, macrophages, well-preserved neutrophils, lymphocytes, sometimes eosinophils
3. Rarely neoplastic cells (lymphoblasts): many pulmonary neoplasms (primary or secondary) do not exfoliate
C. Exudates
1. Pyothorax fluids are often opaque, vary from white to yellow to blood-tinged, and may contain flocculent material or sulfur granules with *Nocardia* or *Actinomyces* spp. infections.
2. Chylothorax may be white or pink and opaque; it remains opaque after centrifugation (Fossum et al., 1991).
3. The effusion associated with FIP is often thick, tenacious, and straw colored; it also clots readily.
a. An albumin:globulin ratio >0.8 in effusion rules out FIP, and gamma globulin >32% is consistent with FIP (Shelly et al., 1988).
b. The protein electrophoretic pattern of an FIP effusion is the same as that of serum (Paltrinieri et al., 1998).
4. Viscosity is related to a high cell count and is manifested by a stringy or ropey appearance when fluid is manually pulled apart.
5. Inflammatory exudates typically have a majority of neutrophils, with some macrophages, lymphocytes, and mesothelial cells.
a. If the inflammation is septic, there may be degenerative changes in the neutrophils, such as karyolysis and karyorrhexis (Forrester et al., 1991).
b. The presence of intracellular bacteria is consistent with bacterial infection.
6. Neoplastic effusions contain macrophages, neutrophils, mesothelial cells, and possibly some lymphoblasts (Forrester et al., 1991).
7. Early chylothorax has a predominance of lymphocytes, and chronicity is characterized by increased numbers of nondegenerate neutrophils and some macrophages.
8. FIP effusions typically contain neutrophils, plasma cells, macrophages, and erythrocytes in a coarse, pink background.
9. Occasionally, neoplastic epithelial cells are seen in the effusion (Fossum, 2000).
a. Pulmonary carcinoma cells: rare, easily confused with reactive mesothelial cells
b. Mast cells
c. Melanoma cells
10. Hemorrhagic effusions may have a packed cell volume similar to peripheral blood, show erythrophagocytosis, and contain no platelets (Forrester, 1991).

VI. Culture and sensitivity testing of pleural fluid
A. It is always indicated if septic inflammation is suspected.
B. Submit fluid for both aerobic and anaerobic culture.
C. A negative culture in the face of apparent pyothorax indicates probable anaerobic infection.

VII. Pleural fluid triglyceride and cholesterol analyses
A. They are used to differentiate a true chylous effusion from a pseudochylous effusion.
B. In true chylous effusions, the triglyceride level is significantly higher than the serum triglyceride level (Fossum et al., 1991).
C. In true chylous effusions, the pleural fluid cholesterol: triglyceride ratio is ≤0.15 (Fossum et al., 1991).
D. In pseudochylous effusions, pleural fluid cholesterol is greater than serum cholesterol, and pleural fluid triglyceride is lower than or equal to the serum triglyceride level (Fossum, 2000).
E. In anorexic or fasted animals, the pleural fluid may not look milky and may have a triglyceride level below what is expected for chylous effusions.
F. Consider measuring pleural fluid and serum triglyceride levels postprandially.

VIII. Pleural fluid biochemical analysis
A. Pleural fluid pH, glucose, and white blood cell (WBC) differential counts help differentiate bacterial and nonbacterial causes of pleural effusion in cats (Stewart et al., 1990).
1. A pH <6.9, glucose <10 mg/dL, and neutrophils >85% of total WBC count are consistent with a pyothorax.
2. Malignant pleural effusions have pH >7.2 and neutrophils are <45% of total WBC count.
B. Pleural fluid is considered an exudate if the lactate dehydrogenase level is >200 IU/L (Stewart et al., 1990).
C. Fibronectin concentration in fluid (as compared with plasma concentration) also helps differentiate causes of pleural effusion (Hirschberger and Pusch, 1996).
1. Cardiogenic pleural effusions have a fibronectin level in the effusion of <31.5% of plasma level.
2. Malignant effusions have levels >31.5%.

IX. Biopsy
A. Open or thoracoscopic biopsy is often required for a diagnosis of mesothelioma.
B. Definitive diagnosis based on pleural fluid analysis alone is difficult, because reactive and neoplastic mesothelial cells are hard to differentiate (Fossum, 2000).

X. Thoracoscopy
   A. Provides adequate information to determine the underlying disease process
   B. Minimal morbidity and mortality
   C. Provides representative biopsy specimens in a large percentage of cases (Kovak et al., 2000)
   D. Pneumothorax is an uncommon but potential complication when combined with pulmonary biopsy (Kovak et al., 2002)

Treatment

I. General Recommendations
   A. If the effusion is causing significant compromise of ventilation, drainage of the effusion is warranted.
      1. Place a thoracic drain if continued fluid production is anticipated.
      2. An indwelling catheter drainage system, using a Seldinger technique is reportedly less traumatic and painful than thoracic drains (Frendin and Obel, 1997).
   B. Treatment of the underlying disorder may result in resolution of the effusion without necessitating drainage.

II. Pyothorax
   A. Place bilateral thoracic drains.
      1. Drain the effusion and lavage the pleural cavity with a warm isotonic physiologic solution (10 mL/kg).
      2. Repeat lavages until fluid withdrawn is relatively clear, then lavage BID to TID.
      3. The addition of heparin to the lavage solution (1500 U/100 mL lavage solution) appears to be of benefit, but proteolytic enzymes are of little value (Fossum, 2000).
      4. The addition of antibiotics to the lavage solution offers no advantage over systemic antibiotic therapy.
      5. The drains are left in place until minimal fluid is retrieved (<2 mL/kg daily), the effusion is clear, ventilation has improved, and there are no bacteria seen on Gram stains of drained materials (usually 5 to 7 days).
   B. Systemic antibiotics are chosen based on culture and sensitivity testing (see Table 19-2).
      1. Initial empirical choices are based on a Gram stain of the effusion.
      2. Antibiotics are continued for a minimum of 4 to 6 weeks.
   C. If an obvious underlying lesion is detected initially, or there is no response to therapy over 5 to 7 days, surgical intervention is indicated.
      1. Abnormal tissue is excised and submitted for microbiological and histopathologic examination, and the thoracic cavity is thoroughly lavaged.
      2. Thoracostomy tubes are placed at the time of surgery and left in place until the aforementioned criteria are met.
      3. Animals with a fibrosing pleuritis after pyothorax may have persistent restrictive respiratory signs, and require further treatment.
         a. Decortication techniques may be performed once the tissue is mature or becomes vascularized and adheres to the pleura (Fossum, 2000).
         b. Results on decortication are mixed: some attempts are successful, whereas others are not (Harpster, 1986; Fossum et al., 1992).
         c. Pulmonary edema may occur with reexpansion of the lungs.
   D. In cats, bradycardia or hypersalivation are indicators of poor outcome (Wadell et al., 2002).

III. Chylothorax
   A. Specific treatment of the underlying disease (e.g., cardiac disease, trauma), if identified, may be sufficient to resolve the condition.
   B. During the time the underlying disease is resolving, intermittent thoracocentesis may be required to manage ventilatory compromise.
   C. Medical management is indicated initially, unless there is rapid fluid accumulation or the underlying disease is correctable with surgery.
      1. Perform thoracocentesis, as required.
      2. Monitor electrolytes if frequent drainage is performed.
         a. Hyponatremia may occur from losses in pleural fluid.
         b. Hyperkalemia is associated with reduced renal excretion (Willard et al., 1991).
      3. A low-fat diet is given to help reduce the flow of chyle.
         a. The reduced fat in the effusion helps increase absorption from the pleural cavity (Fossum, 2000).
         b. Diets such as Hill's r/d or Eukanuba Restricted Calorie are recommended.
         c. If the animal refuses commercial diets, a homemade diet may be tried, but must be supplemented to make it a complete diet (Fossum, 1997).
            (1) Boiled rice or potato, oatmeal, or pasta (1 cup)
            (2) 1 cup low-fat cottage cheese
            (3) Appropriate vitamins and minerals
            (4) Calcium supplement: calcium carbonate
            (5) Can substitute skinless, boiled chicken breast or canned tuna in water
      4. Rutin (a benzopyrone drug used to treat lymphedema and that may stimulate macrophages to absorb chyle) may be tried.
         a. Dose: 50 mg/kg PO TID
         b. Questionable effect but some success reported (Thompson et al., 1999)
   D. If medical management is inadequate, surgical intervention may be indicated.
      1. Thoracic duct ligation in combination with mesenteric lymphangiography
         a. The technique involves cannulating a mesenteric lymphatic vessel (identified by feeding high-fat–content cream preoperatively) and injecting contrast.

b. Thoracic duct rupture is rarely identified.
c. Most dogs and cats have thoracic lymphangiectasia (Birchard et al., 1988; Kerpsack et al., 1994).
d. The thoracic duct and its branches are ligated via an intercostal thoracotomy or transdiaphragmatic approach using hemoclips or nonabsorbable suture (Birchard et al., 1988).
e. Lymphangiography is repeated after ligation to ensure that all branches of the thoracic duct have been ligated (Fossum, 2000).
f. Reported success rates for complete resolution of effusion in cats vary from 20% to 53% (Fossum et al., 1991; Kerpsack et al., 1994).
g. In dogs, the rate of resolution is around 53% (Birchard et al., 1988).
h. Successful thoracic duct ligation likely leads to formation of abdominal lymphaticovenous anastomoses to transport chyle to the venous system, therefore bypassing the thoracic duct (Fossum, 2000).

2. Passive pleuroperitoneal drainage (Peterson et al., 1989)
   a. Sections of the diaphragm are surgically resected, and fenestrated Silastic sheeting is sutured in place over the defects.
   b. An alternative is to place transdiaphragmatic Silastic tubes (Orton, 1993).
   c. The technique may be combined with thoracic duct ligation.
   d. The aim is to allow the pleural fluid to move into the peritoneal cavity to increase the potential surface area from which fluid can be resorbed.
   e. Documented success is limited (Jerram et al., 1999).
   f. Complications include obstruction of the shunts with fibrin or viscera, persistence of some chyle in the pleural cavity, and the potential long-term risk of fibrosing pleuritis.
3. Active pleuroperitoneal or pleurovenous shunting (Smeak et al., 1987; Wilauer and Breznock, 1987)
   a. Use a double-valve Denver shunt catheter (Denver Biomaterials Inc., Evergreen, Colo.).
   b. Place one end of the catheter in the thorax (via an intercostal thoracotomy), and the other end either into the peritoneal cavity through a subcutaneous tunnel (pleuroperitoneal) or into the azygous vein or caudal vena cava (pleural venous).
   c. With both techniques, place the pump chamber on the lateral aspect of a rib to facilitate pumping.
   d. Owners manually pump the chamber to move the fluid out of the pleural space, 100 to 300 times BID to QID.
   e. This technique is a more effective way of emptying the pleural space than with passive techniques.
   f. The pleurovenous technique alleviates the problem of fluid accumulation in the peritoneal cavity.
   g. Disadvantages include cost, thrombosis, obstruction of the catheter, air embolism, venous occlusion, sepsis, abdominal distention (if pleuroperitoneal), potential lack of owner compliance, and inability to resolve the underlying disease (Smeak et al., 1987; Wilauer and Breznock, 1987).
   h. Aspirin is recommended postoperatively to minimize risk of clot formation (Wilauer and Breznock, 1987).
4. Omentalization of the pleural space (Williams and Niles, 1999)
   a. A dorsal omental pedicle flap is brought through an incision in the pars costalis of the diaphragm and sutured to the mediastinum in the region of the lymphaticovenous anastomosis between the thoracic duct and cranial vena cava.
   b. The diaphragmatic incision is partially closed to avoid cranial displacement of abdominal contents.
   c. This technique exploits the large surface area of the omentum and its lymph-draining capability (Williams and Niles, 1999).

E. Thoracic duct ligation and pericardectomy (Fossum et al., 2004)
   1. Based on the theory that in some animals with chylothorax, chyle causes chronic irritation of the pericardium with resultant thickening.
   2. Thickened pericardium can increase right-sided venous pressure, which would impede drainage of chyle into lymphaticovenous communications after thoracic duct ligation.
   3. Success rates reported in one study are 100% in dogs and 80% in cats (Fossum et al., 2004).
F. Fibrosing pleuritis is a risk with chronic chylothorax.
   1. Pleura is thickened by diffuse fibrous tissue that restricts normal lung expansion.
   2. See preceding information on decortication under treatment of pyothorax.

IV. Hemothorax
A. Treatment depends on the severity of the hemorrhage.
   1. Therapeutic thoracocentesis is performed if there is significant respiratory compromise, but avoided if a coagulopathy is the cause.
   2. Most RBCs (70% to 100%) will be absorbed intact without hemolysis (Orton, 1993).
   3. If hemorrhage is severe, a blood transfusion or autotransfusion may be required.
B. Treatment of the underlying disease process must be addressed.
   1. Treat acquired coagulopathies (see Chapter 68).
   2. If a congenital coagulopathy is present, consider appropriate blood products to provide coagulation factors.
   3. Hemorrhage not responding to medical management necessitates surgical intervention.

V. Neoplastic effusions
A. Lymphosarcoma may respond to chemotherapy or radiotherapy if it is confined to the cranial mediastinum.

B. Thymoma, primary pulmonary neoplasms, cardiac neoplasms, or thoracic wall neoplasms may be resectable in some cases.
C. Chemotherapy may be tried for mesotheliomas and carcinomatosis (Moore et al., 1991).
1. Benefits have been reported with intracavitary administration of cisplatin, which reaches high concentrations in tissues within a few millimeters of the contact surface.
2. Combination therapy with systemic doxorubicin may also be tried (Hawkins and Fossum, 2000).
3. Cisplatin is administered intrapleurally at 50 mg/m^2 diluted in 0.9% NaCl at a rate of 250 mL/m^2 via a 16-gauge intravenous catheter.
D. If the underlying disease cannot be treated successfully, palliation is attempted.
1. Pleuroperitoneal shunting can be used, but there is a risk of seeding neoplasia in the peritoneal cavity.
2. Standard thoracocentesis is used for relieving symptoms of respiratory distress.

Monitoring of Animal

I. Monitor respiratory rate and effort, especially if respiratory distress is present.
II. Monitor mucous membrane color, thoracic percussion, heart rate and rhythm, thoracic auscultation (including air movement), and heart sounds.
III. Use pulse oximetry to assess oxygenation.
IV. Change fluid therapy as needed to maintain normal fluid, electrolyte, and acid-base status.
V. Monitor body weight and condition daily.

PNEUMOTHORAX

Definition

I. Pneumothorax is the accumulation of a gas (including air) in the pleural space, and may be traumatic or spontaneous in origin.
II. Sources of the air include the following:
A. Pleurocutaneous: air enters through a defect in the chest wall (open pneumothorax)
B. Pleuropulmonary: air enters from the lung (closed pneumothorax)
C. Mediastinal: air enters from mediastinal structures such as the trachea or esophagus
D. Pleurobronchial: air enters from an abnormal bronchus
E. Gas-producing organisms in the pleural space
III. Tension pneumothorax arises with very high positive intrapleural pressure during expiration (Holtsinger and Ellison, 1995).

Causes

I. Trauma
A. Most common cause: pneumothorax possible in nearly 50% of thoracic trauma cases (Holtsinger and Ellison, 1995)
B. Blunt trauma: automobile accidents, falling from heights, kick injuries
C. Penetrating injuries: bite wounds, penetrating foreign bodies, gunshot wounds, esophageal trauma
D. Rupture of pulmonary parenchyma or the bronchial tree with forceful compression of the thorax against a closed or open glottis (Fossum, 2000)
E. Torn pulmonary parenchyma by shearing forces (Fossum, 2000)
II. Spontaneous forms
A. A closed pneumothorax occurs from air leakage from the lung parenchyma with no history of trauma.
B. Primary pneumothorax occurs in the absence of any evidence of preexisting underlying pulmonary pathology.
1. It is associated with rupture of an air-containing space within or beneath visceral pleura (blebs or bullae) (Holtsinger and Ellison, 1995).
a. Blebs are contained entirely in the pleura (between the internal and external elastic laminae).
b. Bullae are lined partly by thickened fibrotic pleura, fibrous pulmonary tissue, and emphysematous lung (Holtsinger and Ellison, 1995).
2. Reported incidence in dogs varies from 0% to 50% (Holtsinger and Ellison, 1995; Valentine et al., 1996).
C. Secondary spontaneous pneumothorax occurs with recognizable underlying structural or functional pulmonary disease.
1. Most common cause in dogs
2. May arise with pneumonia, pulmonary abscesses, tuberculosis, parasitic infections (dirofilariasis, or *Paragonimus* spp., *Angiostrongylus* spp., *Aelurostrongylus* spp.), chronic obstructive pulmonary disease, pulmonary neoplasia, pulmonary thromboembolism, and congenital cysts
3. May occur with bullous emphysema
III. Iatrogenic pneumothorax
A. Diagnostic procedures such as venipuncture (Godfrey, 1997)
B. Transthoracic needle placement during pulmonary or cranial mediastinal aspiration or biopsy, and pericardiocentesis (Teske et al., 1991)
C. Placement of thoracostomy tubes
D. Endotracheal intubation
1. Overinflation of the tube cuff
2. Rotation of the animal without disconnecting it from the breathing circuit
3. Traumatic intubation with a stylet in place
4. Removal of the tube with the cuff inflated
E. Positive pressure ventilation with intraalveolar pressures greater than pressures within the perivascular sheath
F. Certain surgical procedures; circumcostal gastropexy, adrenalectomy, dorsolateral approaches to the thoracic spine

Pathophysiology

I. The entrance of air into the pleural space separates parietal and visceral pleura results in lung collapse and expansion of the thorax.
II. Pneumothorax is unilateral if the mediastinum is intact, but the free air is usually bilateral (Fossum, 2000).

III. Hypoventilation results in hypoxemia and respiratory acidosis when the pneumothorax is severe, especially if there is a large open chest wound (Orton, 1993).
IV. Ventilation-perfusion mismatching also plays a role in the hypoxemia.
V. The loss of negative intrapleural pressure reduces venous return to the right side of the heart, thereby decreasing cardiac output and compromising pulmonary perfusion.
VI. Tension pneumothorax may result from a pleuropulmonary or pleurocutaneous fistula acting as a one-way valve (Orton, 1993).
   A. Severely compromised ventilation from collapse of lungs
   B. Compresses the vena cava, adversely affecting cardiac function (Holtsinger and Ellison, 1995)
   C. Tends to be rapidly progressive

Clinical Signs

I. Animals with pneumothorax display a restrictive breathing pattern characterized by rapid, shallow ventilation.
II. Exercise intolerance is often apparent.
III. As pneumothorax progresses in severity, signs of respiratory distress become severe with extension of the head and neck, as well as elbow abduction.
IV. Signs of hypoxemia, such as cyanosis and recumbency, may be seen.
V. Pale mucous membranes and reduced amplitude of peripheral pulses often occur.
VI. Tension pneumothorax may cause a barrel-shaped thorax that appears to remain "fixed" in maximal expansion (Fossum, 2000).

Diagnosis

I. Historical evidence
   A. Known trauma or possibility of trauma
   B. Recent clinical signs of respiratory disease, such as coughing, dyspnea
   C. Recent thoracic diagnostic procedures, anesthesia, surgery, or pericardiocentesis
   D. Ingestion of foreign bodies or signs of regurgitation (suggestive of esophageal disease)
II. Physical examination
   A. Dyspnea, tachypnea, restrictive breathing pattern, possible "barrel" chest
   B. Pale mucous membrane color, poor pulse quality
   C. Evidence of trauma: lacerations, fractures, subcutaneous emphysema
   D. Auscultation
      1. Reduced ventilatory sounds dorsally and muffled heart sounds
      2. Possibly signs of pleural fluid
   E. Percussion
      1. May be hyperresonant dorsally
      2. Possibly tympanic with tension pneumothorax
III. Thoracocentesis
   A. Location of drainage is based on auscultation or radiographs, but the seventh through ninth intercostal spaces in the dorsal third of the thorax are recommended.
   B. Drainage of one side usually drains both hemithoraces.
   C. Consider removing some air before thoracic radiographs are taken.
IV. Thoracic radiography
   A. Radiographic changes depend on the volume of air in the pleural space and the views taken.
      1. Retraction of the lung away from the thoracic wall is seen on lateral, ventrodorsal, and dorsoventral views.
      2. As a result of lung collapse, there is an increase in the opacity of the lungs.
      3. The diaphragm is flattened and caudally displaced.
      4. Dorsoventral view is more sensitive than ventrodorsal for pneumothorax and less stressful for the animal.
      5. There is usually bilateral involvement because air easily diffuses across the mediastinum.
      6. If unilateral pneumothorax is suspected, it is better to have the affected hemithorax in a dependent position.
      7. Small volumes of air can be detected at the costophrenic angles on a dorsoventral view.
   B. In a recumbent lateral view, the heart appears to be displaced dorsally as it loses support from inflated lung (Thrall, 1998).
   C. With tension pneumothorax, the degree of lung collapse is greater.
      1. The lung may lose its normal shape and appear as an amorphous opacity compressed against the midline.
      2. If pneumothorax is unilateral, there is a contralateral mediastinal shift.
      3. There is also marked caudal displacement of the diaphragm.
   D. Also evaluate for evidence of trauma, such as fractured ribs, pulmonary contusions, diaphragmatic hernia, and other orthopedic injuries.
   E. Look for underlying pulmonary pathology, such as pneumonia, abscesses, and nodules, as well as for signs of esophageal disease, such as foreign bodies.
   F. Pulmonary blebs are rarely detected radiographically because they may have already ruptured, and larger bullae may be an incidental finding (Fossum, 2000).
V. Additional tests
   A. Arterial blood gas analysis to determine the severity of respiratory compromise
   B. Fecal parasitology
   C. Heartworm test
   D. Pulmonary cytology and microbiology (± bronchoscopy) for underlying pulmonary disease
   E. Esophagoscopy or contrast esophagography for suspected pleuroesophageal leakage
   F. Bronchography for suspected bronchopleural fistula
   G. Exploratory thoracotomy: lateral approach or median sternotomy (location of lesion unknown)
   H. Thoracoscopy: less invasive, allows direct visual examination of the pleural cavity

Differential Diagnosis

I. Pleural effusion
II. Diaphragmatic hernia
III. Pulmonary diseases: inflammation, neoplasia, thromboembolism, contusion, edema
IV. Pneumomediastinum

Treatment

I. Traumatic pneumothorax
  A. Cover open thoracic wounds immediately with an occlusive dressing.
    1. Once the wound is covered, perform thoracocentesis.
    2. Delay surgical closure of an open wound until the animal is clinically stable.
  B. If signs are mild, conservative management may be adequate.
    1. Cage rest alone may allow pleural air to resorb over 5 to 14 days (Kern et al., 1994).
    2. Closely monitor for respiratory distress or signs of cardiovascular compromise.
    3. If dyspnea is present, needle thoracocentesis is performed and repeated as necessary.
    4. Give oxygen therapy if the animal is hypoxemic, especially if there is concurrent pulmonary disease.
    5. If animals are in pain from rib fractures or soft-tissue trauma, use analgesics to help relieve respiratory signs.
  C. If dyspnea is severe or frequent needle thoracocenteses is required, tube thoracostomy is recommended (see Chapter 3).
  D. Surgery is rarely required in cases of traumatic pneumothorax, but is indicated if air accumulation fails to resolve after 5 days or esophageal perforation is suspected.
II. Spontaneous pneumothorax
  A. Conservative management of spontaneous pneumothorax is often unrewarding.
    1. Tube thoracostomy and continuous drainage is preferable to intermittent thoracocentesis.
    2. If the underlying pulmonary pathology (e.g., pneumonia, dirofilariasis) can be corrected, the pneumothorax may resolve.
    3. Conservative therapy is contraindicated if pulmonary abscessation is suspected.
    4. Recurrence rates are high.
  B. Surgical intervention is often required.
    1. If significant pneumothorax persists for more than 48 hours, surgery is indicated (Holtsinger et al., 1993).
    2. Median sternotomy is often the ideal approach because it allows thorough inspection of both hemithoraces, and provides good exposure of the lung apices, which are common sites of pathology (Holtsinger and Ellison, 1995).
    3. If an obvious lesion cannot be seen, filling the thorax with saline can aid in localizing the lesion.
    4. Treatment involves excision of diseased tissue via partial or complete lobectomy.
    5. With bullous emphysema, the rate of recurrence is significant (12.5%) (Valentine et al., 1996).
    6. Mechanical pleurodesis for bullous emphysema, while not obliterating the pleural space, may result in pleural fibrosis sufficient to limit air leakage from blebs or bullae (Jerram et al., 1999).

Monitoring of Animal

I. Respiratory rate and effort, lung sounds, heart rate, mucous membrane color, and refill time are monitored frequently.
II. Pulse oximetry can be used to assess oxygenation.
III. The volume of air drained from the thorax is measured and recorded.
IV. Commercial thoracostomy tubes have depth measurements and radiopaque markers allowing visual and radiographic monitoring of tube placement and position.
V. Animals with thoracostomy tubes are monitored closely to ensure that they do not damage the tube, with resultant air leakage into the thorax.
  A. Loosening of connectors and three-way stopcocks are additional sources of air leakage.
  B. Use clamps (such as a bulldog clamp) more proximally on the tube to minimize these risks.
  C. Suture or wire adaptors to the tube to help reduce leakage.
VI. Thoracostomy tubes must be monitored continuously.
VII. Thoracic radiography is an objective way to monitor resolution of the pneumothorax and any other pulmonary abnormalities.

DIAPHRAGMATIC HERNIA

Definition

I. Diaphragmatic hernia is a condition in which abdominal contents enter the thoracic cavity through an abnormal opening in the diaphragm.
II. Hernias may be congenital or acquired.
III. The abdominal contents may enter the pleural space (pleuroperitoneal hernia) or the pericardial sac (peritoneopericardial diaphragmatic hernia).
IV. A rare form is a hiatal hernia, which may be either paraesophageal or gastroesophageal (Wilson and Hayes, 1986).
V. True diaphragmatic hernias (or eventrations) are subtotal diaphragmatic tears in which the serosa on the thoracic surface of the diaphragm is intact (Voges et al., 1997).

Causes

I. Traumatic hernias
  A. Any trauma to the abdomen can potentially result in a diaphragmatic hernia.
  B. Usually there is a sudden increase in intraabdominal pressure, with resultant rapid deflation of the lungs when the glottis is open, causing a significant pleuroperitoneal pressure gradient.
  C. The diaphragm usually tears at its weakest point (i.e., the muscular portion).
  D. The location and size of the tear depend on the position of the animal during the episode of trauma.

II. Congenital hernias
  A. Pleuroperitoneal forms are infrequently reported in dogs and cats (Wilson and Hayes, 1986; Fossum, 2000).
  B. The peritoneopericardial form is more commonly recognized.
    1. Failure of the lateral pleuroperitoneal folds and the ventromedial pars sternalis to unite
    2. Faulty development of the dorsolateral septum transversum
    3. Prenatal injury to the septum transversum
    4. Heritability not known for this condition, but Weimaraners overrepresented (Evans and Biery, 1980)

Pathophysiology

I. Traumatic diaphragmatic hernia
  A. Presence of abdominal organs in the thoracic cavity restricts ventilation.
  B. Loss of diaphragmatic continuity results in loss of lung contact with parietal pleura, and negative intrathoracic pressure becomes continuous with pressure in the abdominal cavity.
  C. The thoracic and abdominal wall musculature must assume the workload of the diaphragm.
  D. Pain may reduce thoracic wall motion.
  E. Lung collapse and/or atelectasis may occur secondary to organ entrapment or the accumulation of pleural fluid or air.
  F. Pulmonary contusion often occurs as a direct result of trauma to the parenchyma.
  G. Myocardial contusion also may occur with trauma.
  H. Hypovolemia may be present, which may further exacerbate respiratory signs and ventilation-perfusion mismatch.
  I. Increased pulmonary capillary permeability and consequent pulmonary edema also play a role.
  J. Entrapment of part of the GI tract or other abdominal organs may produce signs related to specific organ systems other than the respiratory tract.
II. Congenital hernias
  A. Signs are related to the space-occupying effect of the abdominal contents in the thoracic cavity, and to the effects on the abdominal organs themselves.
  B. Other signs may relate to concurrent congenital defects such as cardiac anomalies, portosystemic shunts, or polycystic kidneys (Neiger, 1996).

Clinical Signs

I. Congenital diaphragmatic hernia
  A. There is wide variation in presentation and signs.
    1. Some animals are asymptomatic, whereas others may have severe clinical signs.
    2. Respiratory signs are the most common manifestation and (depending on the abdominal contents displaced into the thorax) may be exacerbated by ingestion of food.
    3. Gastrointestinal signs, such as vomiting and diarrhea, may occur in both dogs and cats (Evans and Biery, 1980; Neiger, 1996).
    4. Nonspecific signs of anorexia, weight loss, and lethargy may also be present, and are common with chronic hernias.
  B. The hernia may be diagnosed incidentally if the animal develops an unrelated illness that prompts diagnostic imaging of the thoracic or abdominal cavities.
II. Traumatic hernias
  A. It is more frequently recognized in young animals (1 to 2 years of age).
  B. It is more frequent in male dogs in some studies (Boudrieu and Muir, 1987; Fossum, 2000), but not others (Gibson et al., 2005).
  C. Duration varies from hours to years.
    1. There may be no specific signs of herniation even in animals with severe, life-threatening injuries.
    2. The hernia may have been present for years in animals presented with respiratory signs.
    3. In one study of chronic diaphragmatic hernias, only 38% of affected animals were dyspneic (Minihan et al., 2004).
  D. Clinical signs are variable.
    1. Shock with pale membranes, cyanosis, tachypnea, dyspnea, and tachycardia
    2. Cardiac arrhythmias: commonly ventricular, associated with significant mortality (Boudrieau and Muir, 1987)
    3. Other signs
      a. If the liver is displaced, hydrothorax is common.
      b. Icterus may occur if there is extrahepatic bile duct obstruction (Boudrieau and Muir, 1987).
      c. If the stomach is displaced, there is a risk of gastric dilatation.

Diagnosis

I. Physical examination
  A. Congenital hernias
    1. Possibly muffled heart sounds, displacement of the apex beat, and heart murmurs
    2. Possibly increased amplitude of heart sounds over the contralateral hemithorax
    3. Other abnormalities
      a. Ventral body wall defects, such as umbilical hernia or sternal abnormalities
      b. Concurrent congenital cardiac anomalies resulting in murmurs
  B. Traumatic hernias
    1. Respiratory distress, thoracic wall injury, muffled heart and lung sounds
    2. Altered lung sounds and cardiac arrhythmias if pulmonary contusions present
    3. Absence of normally palpated structures in abdomen
    4. Concurrent orthopedic injuries
II. Radiography
  A. Congenital hernias
    1. Plain radiographic findings may include some or all of the following:
      a. An enlarged, globoid, or spherical cardiac silhouette

b. Altered opacity within the pericardium (gas or fat)
c. Loss of distinct ventral border of the diaphragm in the absence of significant pleural fluid
d. Persistent dorsal mesothelial remnant detected between the cardiac silhouette and the diaphragm
e. Mesothelial remnant usually ventral to or superimposed on the caudal vena cava on a lateral radiograph
f. Mesothelial remnant representing the dorsal border of the hernia
g. Small liver or cranial displacement of the stomach
h. Soft-tissue mass in the caudal thorax in cats (Voges et al., 1997)

2. Contrast radiography is indicated if results of plain radiographs are equivocal, and include positive contrast studies of the GI tract and positive contrast celiography.

B. Traumatic hernias
1. Plain radiographic findings are frequently definitive.
a. Loss of continuous diaphragmatic outline, to which pleural fluid is often a contributing factor
b. Presence of abdominal contents in the thorax
c. Displacement of the lung fields and heart cranially and/or laterally
d. Cranial displacement of abdominal viscera, especially stomach and intestines
e. Displacement of bronchial structures (Hyun, 2004)
f. Other signs of trauma, including rib, orthopedic, or soft-tissue injuries (Williams et al., 1998)

2. On positional radiography, look for gravitational shifting of herniated viscera compared to survey films (e.g., reduction of hernia with erect ventrodorsal view).
3. Contrast radiography may be helpful.
a. An upper GI series determines whether the stomach or intestines are herniated.
b. Positive contrast celiography may be of value in some cases.
(1) Inject 1 to 2 mL/kg of warmed water-soluble iodinated contrast medium via a catheter placed into the peritoneal cavity to the right of midline and cranial to the umbilicus to avoid the spleen.
(2) Roll the animal from side to side or around the long axis with the pelvis elevated.
(3) Herniation is confirmed if contrast appears in the pleural cavity and there is roughening or irregularity of the abdominal surface of the diaphragm.
(4) If no hepatic outline is present, a hernia is likely.
(5) False negatives occur with injection into the falciform fat, if large volumes of free peritoneal or pleural fluid dilute the contrast, or if there is plugging of the diaphragmatic defect by falciform fat, omentum, or adhesions (Williams et al., 1998).

III. Ultrasonography
A. With a congenital peritoneopericardial hernia, echocardiography potentially demonstrates the presence of fat, intestine, or liver in the pericardial sac.
B. Traumatic hernias may be recognized either by discontinuity of the diaphragm (with transhepatic evaluation of the diaphragm) or if abdominal soft tissues are seen adjacent to the cardiac silhouette.
1. Care must be taken to avoid mistaking mirror-image artifact as an indication of a hernia, because the liver may appear on both sides of the diaphragm (Williams et al., 1998).
2. Ultrasonography has an advantage over radiography, because it is not affected by the presence of pleural fluid.

IV. Other tests
A. Computed tomography or magnetic resonance imaging is preferable to celiography.
B. Thoracoscopy detects herniation of abdominal contents.
C. Exploratory laparotomy and careful examination of the diaphragm are also options.
D. Electrocardiography may be normal or reveal axis deviation, but these findings are nonspecific (Neiger, 1996).
E. Serum biochemistries in animals with gastric outflow obstruction may reveal metabolic alkalosis, hypochloremia, and hypokalemia (Roe et al., 1986).

Treatment

I. Congenital hernias
A. Repair hernias as they are detected and when the animal is old enough to cope with the anesthesia.
B. If the hernia is detected in a young animal, early correction minimizes the risk of adhesion formation (Johnson, 1993).
C. A ventral midline approach is preferred because the hernias are usually ventral (Johnson, 1993; Neiger, 1996).

II. Traumatic hernias
A. Perform surgical correction of the hernia as early as possible once the animal has been stabilized.
1. Surgery undertaken within 24 hours of trauma has the highest mortality rate in one study (Boudrieau and Muir, 1987), but in another study was low at 10.3% (Gibson et al., 2005).
2. Surgery may need to be performed early on an emergency basis if there is life-threatening hypoventilation related to lung compression by abdominal viscera, and/or if there is significant gastric distention (Roe et al., 1986).
3. If surgery is to be delayed, monitor closely for worsening of respiratory signs.
B. The surgical techniques used are similar to those for congenital hernias (Wilson and Hayes, 1986; Johnson, 1993).
C. With a long-standing traumatic hernia, surgical correction is potentially risky because of the presence of adhesions (with potential for pneumothorax and

hemorrhage when they are broken down) and long-term lung atelectasis.
D. A recent study showed similar mortality for acute and chronic hernias (Minihan et al., 2004).
E. Median sternotomy may be required for chronic hernia correction (Minihan et al., 2004).

Monitoring of Animal

I. Monitor cardiorespiratory status closely after surgery.
A. Pneumothorax may occur from incomplete removal of air after surgery or continued leakage of air.
B. After closure of a large, chronic hernia, there is a significant rise in intraperitoneal pressure, which can compromise venous return and necessitate aggressive fluid therapy.
II. Reexpansion pulmonary edema can develop after rapid lung reexpansion in chronic cases.
A. The condition occurs most frequently in cats (Soderstrom et al., 1995; Stampley and Waldron, 1993).
B. The edema is associated with accumulation of a protein-rich fluid in the alveoli.
C. Reperfusion injury is considered the most likely cause.
D. The edema may develop immediately postoperatively, or up to a few hours later.
E. The respiratory compromise is progressive, with worsening hypoxia that is poorly responsive to oxygen supplementation.
F. Recommendations to minimize risks of reexpansion pulmonary edema include the following:
1. Reinflate atelectatic lungs gradually.
2. If lung expansion does not occur with pressures of 20 to 30 cm H_2O, place a chest drain to allow for spontaneous reexpansion.
3. The pleural space is drained with continuous low-pressure suction at <10 cm H_2O (Johnson, 1993; Stampley and Waldron, 1993).
G. Positive end-expiratory pressure ventilation may be necessary to maintain alveolar patency and adequate oxygenation, but the mortality is still significant.
H. Potential future therapy includes the use of free radical scavengers and glucocorticoids (Soderstrom et al., 1995).

FLAIL CHEST

Definition and Cause

I. Flail chest is thoracic wall instability with paradoxical movement of the flail segment that is the consequence of trauma.
II. Flail chest occurs when two or more ribs are fractured dorsally and ventrally, resulting in loss of continuity with adjacent tissues (Fossum, 2000).

Pathophysiology

I. The flail segment results in pendulous movement of air in the thorax, causing a functional increase in dead space.
II. Concurrent injury to lung parenchyma, such as pulmonary edema or contusions, contributes to the severity of signs.
III. Additional factors include reduced pulmonary compliance, hypoventilation, pulmonary arterial-to-venous shunting, increased airway resistance, and increased work of breathing (Anderson et al., 1993; Fossum, 2000).
IV. Pain also contributes to hypoventilation.
V. The trauma may be severe enough to result in concurrent pneumothorax, pleural effusion, diaphragmatic hernia, and cardiac dysfunction.

Clinical Signs

I. Paradoxical movement of the flail segment
II. Reluctance to move from pain
III. Dyspnea, cyanosis, open-mouth breathing

Diagnosis

I. Clinical signs, particularly the paradoxical thoracic movement, are supportive.
II. Radiography confirms the diagnosis.
A. Examine for a rib fracture pattern consistent with flail segment.
B. Pulmonary contusions, pulmonary edema, pneumothorax, pleural fluid, and diaphragmatic hernia may be noted.
III. Arterial blood gas analysis is consistent with hypoxemia.

Treatment

I. Initial treatment is directed at stabilizing the cardiovascular system with fluid therapy.
II. Temporary limitation of motion of the flail segment is achieved by placing the animal in lateral recumbency with the flail segment in a dependent position.
A. This is undertaken only for short periods to prevent the development of atelectasis in the dependent lung.
B. Some animals may have too much pain to lay on the injured side.
III. A simple surgical technique to stabilize the flail segment may be performed (McAnulty, 1995).
A. Place a nonabsorbable suture around the center of each free-floating rib in the flail segment, and tie the suture to the middle of an external splint (wooden tongue depressors or a stiff plastic splint) that lies parallel to the ribs.
B. Place dorsal and ventral countertraction splints perpendicular to the rib axis between the skin and the traction splints. Be sure they extend at least one undamaged rib beyond the flail segment both cranially and caudally.
C. Place material such as gauze sponges between the traction and countertraction splints until the free ends of the flail segment are retracted and compressed against the underside of the countertraction splints.
D. The flail segment is stabilized relative to adjacent, unfractured ribs and moves with them during respiration.
E. Tape splints and gauze together, and cover with a light bandage.
IV. Occasionally, open surgical techniques to stabilize the ribs are required.

A. Intramedullary pins
B. Removal of the fracture segments with repair of the defect with a muscle flap or mesh
C. Suturing ribs to adjacent ribs

V. A more recent study showed no difference in outcome between patients treated with fracture stabilization and those not stabilized (Olsen et al, 2002).
VI. Analgesia is important to minimize pain-related hypoventilation.
A. Narcotics can be used so long as depression of the respiratory center is avoided.
B. Intercostal nerve blocks using 0.5% bupivacaine (maximum, 2 mg/kg) are helpful.
C. Intrapleural administration of 0.25% bupivacaine solution is followed by placement of the animal in lateral recumbency for 20 minutes with the affected side down (Anderson et al., 1993).
VII. Provide oxygen supplementation as needed.
VIII. Mechanical ventilation may be necessary in animals with severe respiratory compromise.

Monitoring of Animal

I. Closely monitor respiratory and cardiovascular function until the animal is stable.
II. Monitor serial arterial blood gases or utilize continuous pulse oximetry.
III. Repeat thoracic radiographs every 24 to 72 hours to monitor resolution of underlying pulmonary parenchymal disease.
IV. Cats with flail chest are significantly more likely to die than those with simple rib fractures (Kraje et al., 2000).

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CHAPTER 20

Diseases of the Mediastinum and Chest Wall

Graham Swinney | Trevor N. Bebchuk

PNEUMOMEDIASTINUM

Graham Swinney

Definition

I. Pneumomediastinum is the accumulation of free air or gas in the mediastinal space.
II. The mediastinum is the anatomic region that divides the thorax into the left and right pleural cavities.
III. The mediastinum is lined by parietal pleura.

Causes

I. Air may enter the mediastinum from the head, pharynx, and cervical region because it is contiguous with the cervical fascia cranially.
   A. Penetrating wounds caused by bites and foreign bodies, including injuries, such as stick penetration in the pharynx (White and Lane, 1988)
   B. Jugular venipuncture or central venous catheter placement (Biller, 2000)
II. Pulmonary and airway disease and/or rupture can lead to pneumomediastinum.
   A. Secondary to severe parenchymal disease
      1. Inflammation, neoplasia
      2. Fibrosis, such as that seen in paraquat toxicity
   B. Trauma
   C. Iatrogenic sources
      1. Tracheal rupture associated with intubation
         a. Cuff overinflation
         b. Change in the position of the animal without disconnection from the breathing circuit
         c. Damage from a stylet used for intubation
         d. Direct trauma from the tube during placement
         e. Removal of the endotracheal tube with the cuff inflated (Mitchell et al., 2000)
      2. Transtracheal wash
      3. Mechanical ventilation
         a. It is most likely related to marginal alveolar rupture (Brown and Holt, 1995).
         b. Air migrates into the mediastinum via the perivascular connective tissue sheaths (Brown and Holt, 1995).
      4. Tracheostomy tube placement
      5. Pericardiocentesis (Van den Broek, 1986)
III. Esophageal rupture and/or leakage can be a cause of pneumomediastinum.
   A. Foreign bodies, or associated with removal of foreign bodies
   B. Esophagitis and ulceration
   C. Esophageal dilatation procedures
   D. External trauma
   E. Perforation secondary to neoplasia
IV. Air may enter from the retroperitoneal space following surgery or gastrointestinal (GI) rupture because the mediastinum communicates directly with this space via the aortic and esophageal hiatuses (Van den Broek, 1986).
V. Gas-producing infections in the mediastinum are potential causes.
VI. Spontaneous pneumomediastinum has been reported in a racing greyhound (Jones et al., 1975).

Pathophysiology

I. Typically, pneumomediastinum is a benign condition with no obvious clinical signs, other than those related to the causative condition.
II. Subcutaneous emphysema may occur from communication between the mediastinum and cervical fascia.
III. If mediastinal pressure increases abruptly, the mediastinal pleura may rupture and result in pneumothorax (usually pressures >20 mm Hg) (Brown and Holt, 1995).
IV. If mediastinal pressures becomes very high and air cannot escape from the mediastinal space, there can be circulatory complications (Rudloff et al., 1996).
   A. The increased mediastinal pressure results in compression of the vena cava, azygos vein, and pulmonary artery, causing congestive signs (Rudloff et al., 1996; Biller, 2000).
   B. Cardiac output may be reduced (Rudloff et al., 1996).
   C. An "airlock" has been proposed as a cause of circulatory collapse with pneumomediastinum.
   D. Bubbles in perivascular sheaths may compress pulmonary arteries and veins, reducing venous return (Brown and Holt, 1995).
V. High pressures in the mediastinum may also compromise ventilation.

Clinical Signs

I. The clinical signs vary with the severity of the pneumomediastinum and with the underlying etiology.
II. Some animals are clinically normal.
III. Subcutaneous emphysema may be present and can vary from mild, localized emphysema to severe and generalized changes.
IV. Signs relating to underlying disease vary depending on organ involvement.
V. In cases of very high mediastinal pressures or an extension to a severe pneumothorax, additional respiratory and circulatory signs can be expected.
   A. Severe dyspnea
   B. Jugular venous distention
   C. Signs of hypotension: tachycardia, weak pulse, pale mucous membranes, delayed capillary refill time
   D. Cyanosis with significant respiratory compromise
VI. Horner's syndrome occurs if the sympathetic trunk is affected.

Diagnosis

I. History of trauma, foreign body ingestion, respiratory disease, GI-related illness, abdominal procedures, toxin exposure (paraquat), or diagnostic procedures involving cervical region, respiratory tract, or esophagus
II. Physical examination findings, as discussed previously
III. Thoracic radiographic findings
   A. The entrance of free air into the mediastinum provides a negative contrast, allowing increased visibility of the left subclavian artery, brachycephalic trunk, cranial vena cava, and azygos vein (Van den Broek, 1986; Fagin, 1988).
   B. The changes are most readily visible on lateral views of the thorax.
   C. Subcutaneous emphysema may also be apparent.
   D. Radiographs are also evaluated for concurrent pulmonary or tracheal disease, esophageal foreign bodies, pneumothorax, pleural effusion, and pneumopericardium (rare).
   E. Take care not to interpret a dilated esophagus or pulmonary overinflation as pneumomediastinum.
   F. In cases of suspected esophageal perforation, contrast radiography using water-soluble contrast agents may be indicated (see Chapter 4).
IV. Abdominal radiographs: ± pneumoretroperitoneum
V. Tracheoscopy, bronchoscopy to search for underlying etiology
   A. Check for airway damage.
      1. Tracheal perforations may not be detected.
      2. The tracheal membrane may obscure a lesion (Mitchell et al., 2000).
   B. Use esophagoscopy to search for perforation secondary to foreign bodies, esophagitis, or neoplasia.
VI. Bronchoalveolar lavage, bronchial wash, or pulmonary fine-needle aspiration
   A. Helps define underlying pulmonary disease
   B. May worsen pneumomediastinum
VII. Arterial blood gas measurement to assess ventilatory function and gas exchange

Treatment

I. If the animal is asymptomatic or the signs are mild, the disease is usually self-limiting.
   A. Specific therapy not required
   B. Resolution within 2 weeks with no ongoing leakage of air (Biller, 2000)
II. Subcutaneous emphysema spontaneously resolves and only requires drainage (using a needle) if it is causing discomfort.
III. Deep cervical wounds are sutured, and bandages may help limit further air leakage.
IV. If pneumothorax is causing dyspnea, treat with thoracocentesis (see Chapter 19).
V. Treatment of tracheal laceration depends on the severity of clinical signs and endoscopic findings (Brown and Holt, 1995; Mitchell et al., 2000).
   A. Medical therapy is indicated if dyspnea is mild to moderate, and subcutaneous emphysema is not progressive.
      1. Cage rest
      2. Oxygen supplementation
      3. Sedation
   B. Surgical intervention to suture the defect is indicated with severe dyspnea or tears that involve greater than one third of the airway diameter (Brown and Holt, 1995; Mitchell et al., 2000).
VI. If pneumomediastinum is associated with positive pressure ventilation, discontinue mechanical ventilation.
VII. If pneumomediastinum is secondary to pulmonary parenchymal disease, treatment is directed at the underlying problem.

Monitoring of Animal

I. Regular monitoring of respiratory rate and effort, mucous membrane color, capillary refill time, and heart rate is recommended.
II. In more critical animals, monitoring of pulse oximetry or blood gas measurements may be indicated.
III. Thoracic radiographs are used to monitor resolution or progression of pneumomediastinum and any associated underlying pathology.

MEDIASTINAL FLUID

Graham Swinney

Definition and Causes

I. Any accumulation of fluid in the mediastinal space
II. Mediastinal edema secondary to any disease process that can cause edema
III. Mediastinal hemorrhage
   A. Trauma
   B. Coagulopathy
   C. Neoplasia

D. Spontaneous aortic dissection (Boulineau et al., 2005)
E. Idiopathic thymic hemorrhage (Coolman et al., 1994)

Pathophysiology

I. Mediastinal edema: signs usually related to underlying disease
II. Mediastinal hemorrhage
  A. With severe hemorrhage, signs of acute blood loss
  B. May progress to hemothorax
  C. Respiratory signs with airway compression or hemothorax

Clinical Signs

I. Mediastinal edema is often asymptomatic.
II. Mediastinal hemorrhage may produce signs of blood loss.
  A. Pale mucous membranes
  B. Tachycardia, tachypnea
  C. Weakness, collapse
  D. Signs of pleural effusion with extension to hemothorax (see Chapter 19)

Diagnosis

I. Mediastinal edema: often an incidental finding of a widened mediastinum on thoracic radiographs
II. Mediastinal hemorrhage
  A. History of trauma or potential rodenticide exposure
  B. Physical examination findings of blood loss, anemia
  C. Thoracic radiographs: mediastinal widening, possible pleural effusion
  D. Ultrasonography: mediastinal fluid, possible mass(es)
  E. Hematology: low hematocrit, platelet count
  F. Possible coagulation abnormalities

Treatment

I. Mediastinal edema: treatment of underlying disease
II. Mediastinal hemorrhage
  A. Supportive care
  B. Transfusion if required
  C. Vitamin K therapy for rodenticide toxicity
  D. Treatment of hemothorax (see Chapter 19)

Monitoring of Animal

I. Mediastinal edema: rarely requires monitoring
II. Mediastinal hemorrhage: respiratory rate and effort, hematocrit, total solids

MEDIASTINITIS

Graham Swinney

Definition

I. Inflammation within the mediastinal space
II. Can be acute or chronic in nature
III. Typically the result of infection

Causes

I. Extension from esophageal leakage
  A. Foreign bodies causing perforation
  B. Esophagitis from ingested irritants, gastric reflux, or persistent vomiting resulting in ulceration and perforation
  C. Trauma
  D. Iatrogenic sources
    1. Diagnostic endoscopy
    2. Therapeutic procedures: foreign body removal, balloon dilatation
  E. Neoplasia resulting in esophageal wall necrosis
  F. Postesophageal surgery
II. Extension from tracheal or large airway rupture
  A. Trauma
  B. Iatrogenic causes: endoscopy, intubation
III. Extension from adjacent tissues
  A. Fascial planes from neck, axilla, and thoracic inlet
  B. Pleura, pericardium, lungs, and lymph nodes
IV. Penetrating thoracic injury
  A. Bite or bullet wounds
  B. Migrating foreign bodies: plant material
V. Following certain procedures
  A. Following thoracic surgery
  B. Thoracostomy tubes
  C. Mediastinal fine-needle aspiration or percutaneous needle biopsy
VI. Hematogenous or lymphatic spread of infections to the mediastinum
  A. Agents involved are usually bacterial or fungal.
  B. Acute mediastinitis is most commonly bacterial in nature.
    1. Organisms include *Staphylococcus* spp., *Streptococcus* spp., *Escherichia coli,* and *Corynebacterium* spp. (Dunn, 1994; Rogers, 1997).
    2. If esophageal perforation is the inciting agent, anaerobes may be involved.
  C. Chronic mediastinitis may be bacterial or fungal in nature.
    1. Bacterial agents include *Nocardia* spp., *Actinomyces* spp., *Corynebacterium* spp., and *Staphylococcus* spp., with granuloma formation (Lemire and Hoover, 1995; Biller, 2000).
    2. Fungal agents include *Histoplasma* spp., *Blastomyces* spp., *Cryptococcus* spp., and *Coccidioides* spp.

Pathophysiology

I. Systemic signs arise if sepsis is present.
II. Pleural effusion may develop secondarily.
  A. Extension of infection into pleural space
  B. Contributes to the respiratory manifestations of the disease
III. Chronic mediastinitis may result in a mass lesion.
  A. Compresses blood vessels and lymphatics
  B. Compresses the trachea or large airways
  C. Alters esophageal function
  D. Predisposes to recurrent laryngeal nerve dysfunction (Biller, 2000)

Clinical Signs

I. Animals with acute mediastinitis may have severe systemic signs related to sepsis, such as fever and/or obtundation.

II. Animals with chronic mediastinitis may have more insidious signs or signs related to a mass lesion in the thorax.
  A. Dyspnea, tachypnea
  B. Head, neck, and thoracic edema consistent with cranial vena cava syndrome
  C. Dysphagia or regurgitation from esophageal compression
III. Coughing may be present.
IV. Thoracic pain may be detected if the inflammation is acute.
V. Stridor, dyspnea, or dysphonia are often present if there is recurrent laryngeal nerve dysfunction.
VI. Dull thoracic percussion is noted with concurrent pleural fluid.
VII. If a granuloma is present, there may be reduced cranial thoracic compressibility.
VIII. Some signs relate to the underlying disease, such as with tracheal or esophageal perforation.

Diagnosis

I. History of inciting causes, respiratory or esophageal disease, and prior diagnostic or therapeutic procedures
II. Compatible clinical signs
III. Thoracic radiographic findings
  A. In acute mediastinitis, radiographs are normal early in the course of disease.
  B. Increased mediastinal width, either localized (suggesting a mass) or diffuse, may be apparent on dorsoventral or ventrodorsal views.
    1. Mediastinal fluid and masses can also cause widening.
    2. Pleural fluid may result in apparent widening of the mediastinum.
  C. Dorsal displacement of the trachea may be present on the lateral views, but this appearance can also occur with pleural fluid.
  D. In some cases of mediastinitis, pleural fluid is present concurrently.
  E. If mediastinitis is secondary to esophageal or tracheal perforation, pneumomediastinum and cervical subcutaneous emphysema may also be present.
  F. Mediastinal lymphadenomegaly may be detected (Thrall, 1998).
  G. Pulmonary pathology may also be seen.
IV. Contrast radiography sometimes helpful
  A. Esophagogram for suspected perforation using an iodine based contrast agent
  B. Angiography if cranial vena cava syndrome present
V. Computed tomography (CT) or magnetic resonance imaging (MRI) to provide more detailed structural information
VI. Fine-needle aspiration of cranial mediastinal pathology followed by cytology and microbiology
VII. Thoracoscopy for visual examination and biopsy
VIII. Endoscopy of the esophagus or trachea if perforation suspected
IX. Thoracotomy to explore the chest and obtain biopsies

Differential Diagnosis

I. Mediastinal fluid: hemorrhage, edema
II. Mediastinal masses: lymphosarcoma, thymoma
III. Mediastinal fat accumulation
IV. Pleural fluid

Treatment

I. Initial therapy: treat the underlying cause
II. Antimicrobial therapy
  A. Empirically, broad-spectrum antibiotics that have anti-anaerobic activity may be tried.
  B. It is best to obtain samples for cytology and microbiology before instituting therapy.
  C. Choose an appropriate drug based on culture and sensitivity testing.
    1. If the infection is bacterial, continue therapy for at least 4 to 6 weeks.
    2. If the infection is fungal, several months of treatment are usually necessary.
III. Supportive therapy
  A. Possible fluid therapy
  B. Thoracostomy tube if pleural fluid present
  C. Rest, analgesia
IV. Surgical therapy
  A. Repair esophageal or tracheal perforations surgically.
  B. Cranial vena cava syndrome arising from a large granuloma usually requires surgery and may be very challenging to treat.
  C. Abscesses are surgically drained.
  D. Thoracostomy tubes are inserted at the end of surgery.

Monitoring of Animal

I. With the acute form, monitor body temperature, respiratory rate and effort, and hydration status.
II. Serial thoracic radiographs are used to monitor resolution of the disease.
III. Monitoring the leukogram is not specific for resolution of mediastinitis, but may indicate decreased inflammation.
IV. Close monitoring of any thoracostomy tube and resolution of any infection is mandatory (see Chapter 19).
V. Renal function is monitored closely if an aminoglycoside antibiotic or amphotericin B is administered.

MEDIASTINAL MASSES

Definition

I. A space-occupying lesion in the mediastinum
II. Includes tumors, cysts, granulomas, and hematomas

Causes

I. Neoplasia
  A. May arise from a number of different tissue origins
    1. Lymph nodes, thymus, great vessels, trachea, esophagus, paravertebral tissue (Biller, 2000)
    2. Ectopic thyroid or parathyroid tissue, ectopic tissue of third and fourth branchial pouches (Rogers, 1997)
    3. Extension from adjacent tissues: lung, mesothelium

4. Metastatic lesions

B. Lymphosarcoma
1. In dogs, lymphosarcoma may occur alone (approximately 3% of cases) or as part of the multicentric form of the disease (Vail, 2000).
2. In cats, it may be part of a multicentric form or occur alone.
a. The incidence is higher and there is a strong association with feline leukemia virus in young cats, but overall the prevalence is decreasing (Vail, 2000).
b. In one study, most cats with mediastinal lymphosarcoma were young and Siamese (Court et al., 1997).
3. Three groups of lymph nodes are present in the cranial mediastinum.
a. Cranial mediastinal: lying along major vessels just ventral to trachea
b. Sternal: just dorsal to sternum, cranioventral to internal thoracic vessels, medial to second costal cartilage
c. Tracheobronchial or hilar nodes: at tracheal bifurcation (Biller, 2000)
4. Lymphosarcoma of the thymus is also possible (Day, 1997).

C. Thymoma
1. Rare tumors in dogs and cats that originate from epithelial cells of the thymus (Biller, 2000)
2. Classified as noninvasive or invasive rather than benign or malignant, because classification is difficult histologically (Bellah et al., 1983)
3. Rarely metastasizes

D. Other less commonly reported neoplasms
1. Lymphangioma, lymphangiosarcoma
2. Histiocytic neoplasms
3. Chemodectoma

II. Thymic cysts
A. Branchial cysts that arise from remnants of branchial pouch epithelium, usually in older dogs (Biller, 2000)
B. Other cysts of pleural, lymphatic, bronchogenic, and thymic origin (Day, 1997; Biller, 2000)

III. Lymphadenopathy (nonneoplastic)
A. Bacterial origin: often associated with mediastinitis or pyothorax
B. Fungal: usually with mediastinitis or pulmonary involvement (see previous section)
C. Mycobacteriosis: rare
D. Secondary to lymphatic drainage from abdominal pathology, such as pancreatitis
E. Granulomatosis disorders
1. Lymphomatoid: either inflammatory or neoplastic
2. Eosinophilic: likely related to hypersensitivity (Biller, 2000)

IV. Thymic enlargement in young animals before thymic involution

V. Esophageal diseases with a secondary mediastinal mass
A. Neoplasia, granuloma
B. Hiatal hernia, gastroesophageal intussusception

Pathophysiology

I. Respiratory signs occur secondary to a number of potential causes.
A. Space-occupying mediastinal mass
B. Compression of trachea or primary bronchi
C. Pleural fluid accumulation

II. Gastrointestinal signs occur from compression of the esophagus, or because the primary disease involves the esophagus.

III. Other signs are related to the space-occupying nature of some mediastinal masses, and include the following:
A. Swelling of the head, neck, and forelimbs can occur with vascular or lymphatic compression and/or invasion, or with secondary venous thrombosis (Sottiaux and Franck, 1998).
B. If there is entrapment of peripheral nerves, laryngeal paralysis or Horner's syndrome may result (Biller, 2000).
C. Neurological signs are related to thoracolumbar vertebral or spinal involvement (Day, 1997).

IV. A number of systemic consequences may develop from cranial mediastinal masses (paraneoplastic syndromes).
A. Immune-mediated diseases
1. Myasthenia gravis occurs secondarily with thymoma and may be localized or generalized in nature.
2. Myasthenia gravis arises rarely with mediastinal cysts in cats (Malik and Gabor, 1997).
3. Polymyositis has also been recognized.
4. Immune-mediated skin disease, sometimes exfoliative in nature, may occur in cats with thymomas (Day, 1997) (see Chapters 73 and 93).
B. Hypercalcemia: lymphosarcoma (primarily), thymoma
C. Monoclonal gammopathy secondary to lymphosarcoma, with possible consequences of hyperviscosity

V. Metastasis of thymomas is uncommon, but they may spread to the lungs, central nervous system, and heart (Aronsohn et al., 1984; Sorde et al., 1994).

Clinical Signs

I. Clinical signs often reflect an underlying disease process (e.g., granuloma secondary to esophageal perforation).

II. Some animals are asymptomatic if the lesion is small or growing slowly.

III. Nonspecific signs of lethargy, inappetence, and weight loss may be present.

IV. Signs relating to the mass include one or more of the following:
A. Respiratory signs
1. Dyspnea, tachypnea
2. Cough, stridor
3. Reduced air movement on auscultation and dullness ventrally if pleural effusion present
B. Gastrointestinal signs
1. Dysphagia, regurgitation

2. Hypersalivation
C. Possibly edema of the head, neck, and thoracic area
D. Laryngeal paralysis or Horner's syndrome

V. Paraneoplastic signs may include the following:
A. Weakness secondary to myasthenia gravis, polymyositis, or hypercalcemia
B. Regurgitation, cranial nerve deficits with myasthenia gravis
C. Polyuria, polydipsia, vomiting, diarrhea, cardiac arrhythmia with hypercalcemia
D. Mucocutaneous skin disease in cats
E. Hyperviscosity syndrome (rare) with lymphosarcoma and monoclonal gammopathy (see Chapter 73)

Diagnosis

I. Signalment
A. Young Siamese cats: lymphosarcoma
B. Labrador retrievers and German shepherd dogs: thymoma (Day, 1997)
C. Older animals: thymoma

II. Historical signs and physical findings consistent with a cranial mediastinal mass

III. Thoracic radiography
A. Elevation or compression of the trachea on a lateral radiograph
B. Widening of the mediastinum on dorsoventral or ventrodorsal projections
1. With thymoma, the widening may be more left sided.
2. Mass may displace the heart and lungs caudodorsally and to the right (Bellah et al., 1983).
C. Complete or partial collapse of cranial lung lobes
D. Possibly pleural fluid
E. Displacement of trachea, lungs, and heart
F. Metastasis to lungs or interstitial infiltration with lymphosarcoma
G. Lymphadenomegaly
H. Esophageal dilatation from obstruction or secondary to myasthenia gravis

IV. Contrast radiography: esophageal, angiographic studies (see Chapter 4)

V. Ultrasonography
A. Determines size and internal structure of mediastinal lesion(s)
B. Helps detect vascular invasion of the mass
C. Determines vascularity of mass
D. Helps guide aspiration or biopsy sampling

VI. Advanced imaging
A. CT can be compromised by the presence of pleural fluid.
B. CT appearance does not help differentiate the different histological types of lesions (Yoon et al., 2004).
C. MRI is difficult because of movement associated with respiration.
D. Scintigraphy is indicated if the mass is suspected of being thyroid in origin.

VII. Laboratory tests
A. Hematology for neoplastic-related cytopenias
B. Biochemistry profile to assess calcium levels, presence of organ dysfunction secondary to neoplasia, or paraneoplastic syndromes
C. Acetylcholine receptor antibody assay for suspected myasthenia gravis (see Chapter 25)
D. Serological evaluation for possible fungal diseases

VIII. Cytological examination of transthoracically collected aspirates
A. Lymphosarcoma: malignant lymphocytes predominate
B. Thymoma
1. Many lymphocytes may be detected.
2. If mast cells are present, the diagnosis is unclear, and primary mast cell tumor must be ruled out (Day, 1997).
3. Small numbers of epithelial cells are suggestive of thymoma (Biller, 2000).
C. Inflammatory cells: granuloma, abscess

IX. Culture and sensitivity testing of aspirates if infection suspected

X. Bronchoscopy with bronchoalveolar lavage, bronchial wash, or transtracheal wash for underlying pulmonary pathology

XI. Biopsy and histopathology
A. Transthoracic: ultrasound-guided, CT-guided (Zekas et al., 2005)
B. Via thoracoscopy
C. Via thoracotomy

Differential Diagnosis

I. Other mediastinal diseases that cause widening, such as mediastinitis

II. Mediastinal fluid or fat

III. Other causes of pleural effusion (see Chapter 19)

IV. Pulmonary consolidation in the cranial thorax

Treatment

I. Lymphosarcoma
A. Chemotherapy is the treatment of choice (see Chapter 69).
B. Chemotherapy also helps control paraneoplastic syndromes.
C. Radiotherapy is rarely used as an adjunct to chemotherapy.
1. Both normal and malignant lymphocytes are extremely radiosensitive (Maleo, 1997).
2. Radiotherapy can be used to reduce dyspnea early in the course of treatment.
3. It may help decrease the need for repeated thoracocenteses to drain pleural fluid.
4. It can be useful if the tumor is resistant to chemotherapy (Maleo, 1997).

II. Thymoma
A. Surgical excision is the treatment of choice.
1. Complete excision is more difficult if the thymoma is invasive (Hunt et al., 1997).
2. Paraneoplastic syndromes may improve after excision.

3. Complication rates for surgery are higher if there is concurrent megaesophagus.
4. If excision is incomplete, recurrence is likely.

B. Radiation is an option for nonresectable lesions, but complete resolution is unlikely, and survival over 12 months is rare (Maleo, 1997).
C. Treat severe hypercalcemia medically with fluids, furosemide, and glucocorticoids (see Chapters 48 and 73).
D. See Chapter 25 for treatment of myasthenia gravis.

III. Other neoplasms: surgical excision
IV. Mediastinal cysts
A. Transthoracic aspiration may relieve signs.
B. If they recur following aspiration, consider excision.
V. Inflammatory diseases: see Mediastinitis

Monitoring of Animal

I. Animals with mediastinal masses are monitored for deterioration in respiratory function, development or exacerbation of cranial vena cava syndrome, or GI signs.
II. Animals with myasthenia gravis and megaesophagus are monitored closely for the development of aspiration pneumonia.
III. If surgery is performed, close monitoring of respiratory and cardiovascular function postoperatively is important.
IV. Appropriate, postoperative thoracostomy tube care is necessary (see Chapter 19).
V. Follow-up thoracic radiography is recommended after thymectomy.
VI. If hypercalcemia is present, monitor serum calcium levels following medical therapy or surgery (see Chapter 73).

CHEST WALL NEOPLASIA

Trevor N. Bebchuk

Definition

I. Most tumors of the chest wall are malignant.
II. Benign lesions include tumors, exostoses, and cysts.

Causes

I. Primary malignant rib tumors (Montgomery et al., 1993; Pirkey-Ehrhart et al., 1995)
A. Osteosarcoma
1. It comprises 54% to 63% of all rib tumors.
2. Rib form comprises 4% to 13% of all osteosarcomas.

B. Chondrosarcoma
1. It comprises 28% to 40% of all rib tumors.
2. Rib form comprises up to 33% of all chondrosarcomas.

C. Hemangiosarcoma: 0 to 22% of all rib tumors
D. Fibrosarcoma: 0 to 4% of all rib tumors

II. Metastatic rib tumors
A. Much less common than primary tumors
B. Often a result of local extension
C. Usually osteosarcoma or hemangiosarcoma

III. Benign lesions
A. Multiple cartilaginous exostoses
1. Also known as *osteochondromatosis*
2. May undergo malignant transformation to chondrosarcoma

B. Chondroma
C. Osteoma
D. Hemangioma
E. Bone cyst

Clinical Signs

I. Signalment
A. Dogs: age 2 to 14 years
B. Rare in cats
C. No sex or breed predilection
D. Usually medium- to large-breed dogs (4 to 55 kg)

II. May be asymptomatic (Montgomery et al., 1993; Pirkey-Ehrhart et al., 1995)
A. The tumor may have extensive intrathoracic expansion, with only a small externally palpable mass.
B. Osteosarcomas are often present for up to 12 weeks before detection.
C. Chondrosarcomas may be present for up to 33 weeks before diagnosis.
D. Hemangiosarcomas are usually detected within 2 to 4 weeks.

III. Weight loss, lethargy
IV. Dyspnea
V. Thoracic limb lameness
VI. Chylothorax (Watine et al., 2003)

Diagnosis

I. Thoracic radiography
A. Take three views, including right lateral, left lateral, and ventrodorsal.
B. Frequently there is a mixed proliferative and/or osteolytic lesion of the affected rib.
C. The tumor is usually at or near the costochondral junction.
D. There is no predilection for the side or specific rib involved.
E. Pulmonary metastases may be noted in up to 50% of the cases.

II. Fine-needle aspiration of mass for cytological evaluation
A. Results often indicate malignancy.
B. The definitive tumor type may not be identified.

III. Incisional or excisional biopsy with histopathology
IV. CT or MRI
A. Advanced imaging may provide more information on the extent of the tumor.
B. MRI is hampered by movement of the thoracic wall with respiration.

V. Nuclear scintigraphy: bone scan to define extent of tumor and presence of metastases
VI. Laboratory tests
A. Complete blood count, serum chemistry, and urinalysis are indicated, especially before surgery.
B. Results may reflect geriatric changes rather than specific tumor-induced abnormalities.

TABLE 20-1

Types of Chest Wall Tumors

TUMOR TYPE	INCIDENCE	BEHAVIOR	METASTATIC POTENTIAL	TREATMENT	PROGNOSIS
Osteosarcoma	Common	Malignant	High	Complete excision and adjunctive chemotherapy	Poor: 240-day median survival time with treatment
Chondrosarcoma	Common	Malignant	Low	Complete excision	Fair: 320-day to 1080-day median survival time
Hemangiosarcoma	Rare	Malignant	High	Complete excision	Poor: 30- to 210-day median survival time
Fibrosarcoma	Rare	Malignant	Moderate	Complete excision	Fair
Multiple cartilaginous exostoses	Rare	Benign, but can undergo malignant transformation	None	Generally none required	Good
Chondroma	Uncommon	Benign	None	Complete excision	Good

Differential Diagnosis

I. Osteomyelitis
II. Healed or nonunion rib fractures
III. Pulmonary pathology adjacent to the chest wall

Treatment

I. Aggressive en bloc resection of the tumor with extensive tissue margins is recommended for most lesions (Table 20-1).
   A. Excise all affected ribs and soft tissue, because rib tumors are locally aggressive.
   B. Repair the resulting chest wall defect using local muscle flaps and/or diaphragmatic advancement procedures.
   C. Very large or cranial defects require reconstruction using polypropylene mesh.
II. Adjunctive chemotherapy may be considered for some tumors.
   A. Improves survival times with osteosarcoma
      1. Cisplatin: dogs, not cats
      2. Carboplatin
      3. Doxorubicin
      4. Combination cisplatin and doxorubicin
   B. Not effective for hemangiosarcoma, chondrosarcoma, fibrosarcoma
III. The effectiveness of radiation therapy is unknown, but it may be useful for palliation.

Monitoring of Animal

I. Monitor for postoperative complications, such as blood loss, pain, hypoventilation, and increased risk of infection with use of polypropylene mesh.
II. Prognosis varies depending on the tumor type (Montgomery et al., 1993; Pirkey-Ehrhart et al., 1995).
   A. Osteosarcoma in dogs
      1. High metastatic potential
      2. Surgical excision alone: 90-day median survival and 60-day disease-free interval
      3. Surgical excision plus chemotherapy: 240-day median survival and 225-day disease-free interval
   B. Chondrosarcoma
      1. Low metastatic potential
      2. Surgical excision alone: 320- to 1080-day median survival and up to 1080-day disease-free interval
      3. Local recurrence common
   C. Hemangiosarcoma
      1. High metastatic potential
      2. Surgical excision alone: 30- to 210-day median survival and 30- to 150-day disease-free interval
III. Other factors also affect the prognosis.
   A. Complete resection on histopathologic examination is a good prognostic factor.
   B. Mark surgical margins with ink to improve the accuracy of histological evaluation.
   C. Prognosis is poor if the tumor has invaded through the parietal pleura into the thoracic cavity.
   D. The number of ribs resected has no bearing on the prognosis.

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CHAPTER 21

Introduction

Marc Kent

ANATOMICAL ORGANIZATION

Gross Anatomical Divisions

I. The nervous system is divided into the central and the peripheral nervous system.
II. The central nervous system (CNS) includes the brain and spinal cord.
  A. Divisions of the brain based on embryology (deLahunta, 1983; Jenkins, 1978)
    1. Prosencephalon
      a. Telencephalon (cerebrum): paired hemispheres containing the lateral ventricles
      b. Diencephalon: contains the thalamus and the third ventricle
      c. Mesencephalon: midbrain containing the narrow mesencephalic aqueduct
    2. Rhombencephalon
      a. Divides into two segments and contains the fourth ventricle
      b. Metencephalon: contains the pons ventrally and the cerebellum dorsally
      c. Myelencephalon: medulla oblongata
  B. Divisions of the spinal cord
    1. The spinal cord is divided into numbered segments in each region of the vertebral column, namely cervical (C), thoracic (T), lumbar (L), sacral (S), coccygeal or caudal (Cd).
    2. The spinal cord segments are also divided into functional segments, such as C1-C5, C6-T2, T3-L3, L4-S1, and S1-S3.
III. The peripheral nervous system includes motor, sensory, and autonomic nerves.
  A. The motor aspect of the peripheral nervous system is the lower motor neuron (LMN) system or neuromuscular system.
    1. The LMN unit is composed of the motor neuron cell body in the spinal cord or brainstem, the spinal or cranial nerve, the peripheral nerve, the neuromuscular junction, and the muscle.
    2. The motor neuron cell bodies for the nerves of the limbs reside in the C6-T2 and L4-S1 segments of the spinal cord for the thoracic and the pelvic limbs, respectively.
    3. Spinal nerves coalesce to form the brachial plexus and lumbosacral plexus before forming specific peripheral nerves of the thoracic and pelvic limbs respectively.
  B. The sensory nervous system consists of sensory nerves, their receptors, peripheral nerves, spinal or cranial nerves, cell bodies located in craniospinal ganglia, and projections in the CNS.
  C. The autonomic nervous system is divided into the sympathetic and parasympathetic branches.
    1. The preganglionic (first order) neuron cell body is located in the CNS, whereas the postganglionic (second order) neuron cell body is located outside the CNS.
    2. Preganglionic sympathetic neuron cell bodies are distributed in the thoracolumbar spinal cord.
    3. Preganglionic parasympathetic neuron cell bodies are located in the sacral spinal cord segments and within the nuclei of cranial nerves (CN) III, VII, IX, and X.
  D. Innervation of the head is supplied by 12 CN, which are referred to by either Roman numerals or their common names.

NEUROLOGICAL EXAMINATION

Components to Evaluate

I. Evaluation of the sensorium (mentation or mental status)
  A. *Sensorium* refers to an animal's behavior and how it interacts with individuals and responds to various environmental stimuli.

1. Commonly used qualifiers include obtunded, quiet, dull, depressed, hyperactive, and aggressive.
2. Stupor is used to describe animals that appear unconscious, but a noxious stimulus rouses them.
3. Comatose animals appear to be unconscious and cannot be aroused with a noxious stimulus.
4. The sensorium is also affected by sedatives, pain, analgesic medications, anticonvulsants, and during the postictal period.

B. Mentation is determined by the activity of the cerebrum and the ascending reticular activating system (ARAS) located in the brainstem.
C. Any intracranial lesion can alter the sensorium.
D. In general, structural lesions affecting the ARAS tend to result in more severe alterations in the sensorium than similar structural lesions in the cerebrum (deLahunta, 1983; Lorenz and Kornegay, 2004).

II. Evaluation of gait
A. Proper evaluation of gait is an important aspect of the neurological examination.
B. Evaluate gait by observing the animal walking away from and toward the examiner, as well as from the side, with the animal on a surface with good traction.
C. Gait can be divided into three broad categories, namely normal, ataxia, or consistent with LMN (neuromuscular).
1. Ataxia simply implies incoordination.
a. Vestibular ataxia is characterized by leaning, listing, and falling to one side with the animal appearing to be off balance, often having an altered head position (head tilt) or abnormal nystagmus.
b. Cerebellar ataxia is characterized as a dysmetria, as there is an alteration in the rate, range, and force of motion of the limbs (deLahunta, 1983).
c. Proprioceptive ataxia is characterized by a long-strided, often hypermetric gait in which there can be crossing of the limbs under the body and walking on the dorsum of the paw.
2. A gait consistent with LMN disease (neuromuscular) is characterized by a short-strided, choppy gait, and overflexion of the joints, which gives the animal a crouched appearance.

III. Evaluation of postural reactions
A. Postural reaction tests are designed to uncover deficits not apparent by gait observation alone (deLahunta, 1983).
B. Postural reaction tests require normal function of the sensory nerves; ascending general proprioceptive (GP) tracts that project to the ipsilateral cerebellum, contralateral thalamus, and cerebrum; descending upper motor neuron (UMN) tracts; and LMN units.
C. Postural reaction tests include hopping, proprioceptive placing, hemiwalking, wheelbarrowing with the head up, and extensor postural thrust (Lorenz and Kornegay, 2004).

IV. Evaluation of segmental spinal reflexes
A. Spinal reflexes test the integrity of a specific segment of the spinal cord that contains the reflex arc (Table 21-1), and do not rely on spinal cord function cranial to that segment.
B. Reflexes are graded as absent/areflexia (0), reduced/hyporeflexia (+1), normal (+2), increased/hyperreflexia (+3), and hyperreflexia with clonus (+4).
C. Evaluation of the spinal reflexes allows differentiation between LMN and UMN lesions.
1. Lesions affecting the spinal cord that contain the reflex arc result in hypo- to areflexia (LMN).
2. Lesions affecting the spinal cord cranial to the reflex arc result in normal to hyperreflexia (UMN, GP/UMN).
D. In addition to reflexes, strength, muscle tone, and muscle mass are assessed.
1. Decreased tone (hypotonia) and severe atrophy are consistent with LMN lesions.
2. Normal to increased tone (hypertonia), with little to no atrophy is consistent with UMN lesions.

V. Evaluation of CN function
A. Like spinal reflexes, CN reflex arcs are contained within a specific region of the brain (Table 21-2).
B. Exceptions to this rule are the menace response and the evaluation of nasal sensation, which require the integrity of the contralateral thalamus and somesthetic cerebral cortex.

VI. Sensory evaluation
A. A specific cutaneous area innervated by a single sensory nerve is an autonomous zone.
B. Testing autonomous zones provides functional information about specific sensory nerves (Table 21-3).

VII. Establishing the neuroanatomic diagnosis
A. Lesions affecting GP/UMN tracts are detected through postural reaction testing and provide the examiner with evidence of a neurological disorder affecting this pathway.
B. The exact location of the lesion along this long pathway is identified through the evaluation of spinal and CN reflexes.

Brain

I. Prosencephalic lesions
A. Clinical signs include seizures and changes in sensorium with preservation of a normal gait.
B. Contralateral postural reaction and menace deficits, and hypalgesia of the face can be seen.
C. Lesions affecting the diencephalon can also cause abnormal thermal regulation, autonomic, metabolic (e.g., animal loses weight despite normal caloric intake), and endocrine function.

II. Mesencephalic lesions
A. Lesions can affect the sensorium and cause gait (proprioceptive ataxia), GP/UMN, and postural reaction deficits, which are generally ipsilateral to the lesion.
B. Clinical signs relate to dysfunction of CN III and IV.

III. Metencephalon lesions
A. Abnormalities of the pons may occur.
1. Lesions can affect the sensorium and cause gait deficits (i.e., proprioceptive ataxia).

TABLE 21-1

Segmental Reflexes

REFLEX	METHOD OF TESTING	RESPONSE	NERVES	SPINAL CORD SEGMENT	VERTEBRAL SEGMENT
Thoracic Limb					
Withdrawal reflex*	Noxious stimulus is applied to the digit	Flexion of limb	S: Dorsal surface radial = palmar surface = ulnar/median M: All nerves of the brachial plexus	C6-T2	C5-T1
Biceps reflex	With elbow in slight extension, percuss biceps tendon at its insertion	Elbow flexion	S, M: Musculocutaneous	C6-C8	C5-C7
Triceps reflex	With elbow in slight flexion, percuss the triceps tendon at its insertion	Elbow extension	S, M: Radial	C7-T2	C6-T1
Extensor carpi radialis	Percuss the proximal muscle belly	Carpal extension	S, M: Radial	C7-T2	C6-T1
Pelvic Limb					
Patellar reflex*	With stifle in neutral position, percuss patellar tendon	Stifle extension	S, M: Femoral	L4-L6	L3-L4
Withdrawal reflex*	Noxious stimulus is applied to the digit	Flexion of limb	Dorsal surface = peroneal branch of sciatic, palmar surface = tibial branch, 5th digit = femoral (S), sciatic (M)	L6-S1	L4-L5
Cranial tibial reflex	Percuss the proximal muscle belly	Hock flexion	S, M: Peroneal branch of sciatic	L6-L7	L4-L5
Gastrocnemius reflex*	With hock in flexion, percuss the gastrocnemius tendon at its insertion	Hock extension	S, M: Tibial branch of sciatic	L7-S1	L4-L5
Other Sites					
Perineal reflex	Noxious stimulus is applied to the perianal region	Anal sphincter contraction	S, M: Perineal branch of pudendal	S1-S3	L5
Cutaneous trunci reflex	Noxious stimulus is applied to skin dorsal of midline	Skin twitch over thorax	S: Segmental M: Lateral thoracic	C8-T1(M)	C7-T1

S, Sensory; *M,* motor.
*Reflex is reliable.

2. GP/UMN and postural reaction deficits, ipsilateral to the lesion.

B. Clinical signs dysfunction of CN V may occur.
C. Cerebellar signs may develop.
1. Unilateral lesions can affect gait (cerebellar ataxia) and cause mild postural reaction deficits.
2. Menace deficits, despite normal vision and intention tremors of the head, are also possible.

IV. Myelencephalon lesions
A. Lesions can affect the sensorium, cause gait deficits (i.e., proprioceptive ataxia), GP/UMN, and postural reaction deficits ipsilateral to the lesion.
B. Deficits involving the function of CN VI through XII.
C. Specifically, deficits in CN VIII function cause a head tilt, vestibular ataxia, and abnormal nystagmus.

TABLE 21-2

Cranial Nerve Function and Testing

CRANIAL NERVE NUMBER AND NAME	RELATIONSHIP TO THE BRAIN	ANATOMIC COURSE	FUNCTION	METHOD OF TESTING	DEFICIT
I—Olfactory	Rostral aspect of cerebrum and piriform lobe	Enters cribriform plate	Smell (SVA)	Not usually performed Avoidance of noxious smell (alcohol)	Difficult to appreciate
II—Optic	Diencephalon (thalamus)	Enters the optic canal, decussates at the chiasm and projects via the optic tract to thalamus and then to the occipital cortex of cerebrum	Vision (SSA) Carries afferent information for pupil response to light	Menace response PLR	Blindness Bumping into objects Mydriasis
III—Oculomotor	Mesencephalon (midbrain)	Exits the midbrain ventrally to leave cranial cavity via orbital fissure	Adjusts pupil diameter in response to light (SVE-parasympathetic) Motor to the medial, dorsal, and ventral rectus and ventral oblique muscles (GSE)	PLR Detection of strabismus, physiological nystagmus	Mydriasis Resting strabismus (ventrolateral)
IV—Trochlear	Mesencephalon (midbrain)	Projects dorsally over the midline of the midbrain to exit cranial cavity ventrally via orbital fissure	Motor to the dorsal oblique extraocular eye muscle (GSE)	Detection of strabismus, physiological nystagmus	Resting strabismus (dorsolateral)
V—Trigeminal	Pons	Mandibular branch exits the pons to leave cranial cavity via oval foramen Maxillary branch exits the round foramen Ophthalmic branch exits the orbital fissure All three branches have GSA and mandibular contains SVE	Cutaneous sensation and proprioception of the head (GSA) Motor to the muscles of mastication (SVE)	Palpebral reflex Response to noxious stimulation of the nasal septum and face Palpation of the muscle of mastication Testing jaw tone	Absent palpebral reflex Hypalgesia to analgesia to the face Muscle atrophy of the muscles of mastication Reduced jaw tone Dropped jaw with bilateral deficit
VI—Abducens	Rostral medulla oblongata	Exits the cranial cavity via the orbital fissure	Motor to the lateral rectus and retractor bulbi muscles (GSE)	Detection of strabismus, physiological nystagmus	Resting strabismus (ventromedial)

SVA, Special visceral afferent; *SSA,* special somatic afferent; *PLR,* pupillary light reflex; *SVE,* special visceral efferent; *GSE,* general somatic efferent.

TABLE 21-2

Cranial Nerve Function and Testing—*cont'd*

VII—Facial	Rostral medulla oblongata	Exits the cranial cavity via internal acoustic meatus, petrosal bone (middle ear), and stylomastoid foramen	Motor to the muscles of facial expression (SVE) Cutaneous innervation of the concave surface of the ear (GSA) Innervation of the lacrimal gland (GVE-parasympathetic) Taste (SVA)	Menace response Palpebral reflex Observing facial muscle movements (ears, lips, eyelids)	Inability to blink Absence of facial expression Drooping of lip Drooling/dropping food from mouth Absent tear production Cutaneous sensation is difficult to test (overlapped by other nerves)
VIII—Vestibulocochlear	Rostral medulla oblongata	Exits the cranial cavity via the internal acoustic meatus	Hearing and balance Special proprioception (SSA)	Detection of physiological nystagmus Observing balance problems Behavioral responses to noise (hearing)	Head tilt Abnormal nystagmus Vestibular strabismus Vestibular ataxia (generally directed toward the affected side)
IX—Glossopharyngeal	Caudal medulla oblongata	Exits the cranial cavity internally via the jugular foramen and leaves via the tympanooccipital fissure	Motor and sensory to the pharynx (SVE, GSA) Innervation of the parotid and zygomatic salivary glands (GVE-parasympathetic) Taste (SVA)	Gag reflex	Dysphagia
X—Vagus	Caudal medulla oblongata	Exits the cranial cavity internally via the jugular foramen and leaves via the tympanooccipital fissure	Motor and sensory to the pharynx (SVE, GSA) Innervation of the viscera (GVE-parasympathetic) Taste (SVA)	Gag reflex	Dysphagia Laryngeal paresis/paralysis
XI—Accessory	Caudal medulla oblongata	Exits the cranial cavity internally via the jugular foramen and leaves via the tympanooccipital fissure	Motor to the trapezius, sternocephalicus, and portions of the brachiocephalicus muscles (SVE)	Palpation of neck and shoulder muscle mass	Atrophy of the neck and shoulder muscles
XII—Hypoglossal	Caudal medulla oblongata	Exits the cranial cavity via the hypoglossal canal	Motor to the tongue muscles (GSE)	Observation of tongue movements	Atrophy of the tongue musculature

GVE, General visceral efferent.

TABLE 21-3

Autonomous Zones of Cutaneous Innervation

NERVES	SPINAL NERVE ROOTS	CUTANEOUS SITE OF TESTING
Thoracic Limb		
Radial	C7-T1	Dorsal aspect of 3rd or 4th digit
Ulnar/median*	C8-T2	Palmar surface of paw
Musculocutaneous	C6-C8	Distal (2 cm) to medial epicondyle of humerus
Pelvic Limb		
Saphenous-femoral†	L4-L6	Distal (4 cm) to medial epicondyle of femur
Peroneal-sciatic	L6-L7	Dorsal surface between 2nd and 3rd digits
Tibial-sciatic	L7-S1	Proximal to metatarsal pad

*Both the median and ulnar nerves innervate the palmar aspect of the paw.
†The femoral nerve cutaneous area is overlapped by the peroneal nerve.

D. Lesions involving the caudal cerebellar peduncle, flocculonodular lobe, or fastigial nucleus of the cerebellum can cause paradoxical vestibular disease, which involves signs that are opposite the side of the lesion.

Spinal Cord

I. C1-C5 myelopathies
   A. Clinical signs include GP/UMN deficits and proprioceptive ataxia in all four limbs.
   B. Severe lesions can cause respiratory failure from paralysis of the diaphragm and intercostal muscles.
II. C6-T2 myelopathies
   A. Clinical signs include LMN deficits in the thoracic limbs, with GP/UMN deficits in the pelvic limb.
   B. The T1-T3 spinal cord segments contain the preganglionic neurons of the sympathetic nervous system that innervate the eye; therefore, ipsilateral Horner's syndrome may be seen.
III. T3-L3 myelopathies
   A. Clinical signs include GP/UMN deficits in the pelvic limbs.
   B. A more precise lesion location within the T3-L3 vertebral column can be identified by detecting a painful area (region of hyperesthesia), point of absence of the cutaneous trunci reflex, or a line caudal to which the animal is analgesic.
IV. L4-S1 myelopathy
   A. Clinical signs consist of LMN signs to the pelvic limbs.
   B. It can be difficult to separate spinal cord lesions involving the L4-S1 segments from diseases of the accompanying peripheral nerves.
V. Lesions affecting spinal cord segments S1-S3 cause urinary and fecal incontinence owing to decreased to absent anal and urethral sphincter tone (LMN bladder).

DIAGNOSTIC EVALUATION

I. A minimum database consists of a complete blood count (CBC), biochemistry profile, and urinalysis.
II. Magnetic resonance imaging (MRI) provides superior contrast of soft-tissue structures (Tidwell and Jones, 1999).
   A. Standard sequences include T1-weighted (T1), T2-weighted (T2), and post-contrast T1-weighted images (Thomson et al., 1993).
   B. Additional sequences (e.g., fluid attenuated inversion recovery, short tau inversion recovery, fat suppression T1 and T2, and plain T2) can provide information regarding the characteristic of lesions.
   C. Gadolinium containing contrast media is utilized to better identify lesions (Thomson, 1993).
   D. MRI characteristics and topographic features can often provide an accurate antemortem diagnosis.
III. Computed tomography (CT) images are constructed from the attenuation of an x-ray beam that is passed through the animal (Bailey, 1990).
   A. Images can be reconstructed in different planes and manipulated to better visualize bony or soft-tissue structures (Tidwell and Jones, 1999).
   B. Iodinated contrast media are used to enhance visualization of lesions and normal anatomic structures.
IV. Cerebrospinal fluid (CSF) analysis is a sensitive test for CNS pathology, but rarely provides a specific etiology.
   A. CSF can be obtained from the cisterna magnum or from the lumbar subarachnoid space (Cook and Denicola, 1988).
   B. CSF is examined for color, clarity, white and red blood cells, and protein content.
   C. Normally, CSF is clear and colorless.
      1. Normal CSF contains 0 to 5 white blood cells (WBC)/μL in the dog and 0 to 3 WBC/μL in the cat.
      2. Most cells are mononuclear.
      3. Protein content is normally <24 mg/μL (Bailey and Higgins, 1985; Rand et al., 1990).
V. Electromyography (EMG) provides information regarding the function of the LMN unit.
   A. EMG evaluates the electrical activity of the muscle through the measurement of the electrical potential of the extracellular fluid at the recording site (muscle) (Kimura, 2001).
   B. Abnormalities are generally nonspecific and can arise with disease of the nerve or muscle (Farnbach, 1980).
VI. Several types of evoked potentials may be measured.
   A. Motor nerve studies involve the stimulation of a motor nerve and recording the muscle action potential and they provide information regarding axons and myelination (Farnbach, 1980).
   B. Sensory nerve studies involve the stimulation of sensory or mixed sensory–motor nerves and recording latency

and they provide information regarding the integrity of the sensory nervous system (Holliday et al., 1977).

C. The F-waves are generated by the antidromic depolarization of a motor neuron, and F-wave evaluation provides information regarding the function of the proximal portion of the motor nerve (Knecht et al., 1983; Kimura, 2001).

D. Repetitive nerve stimulation consists of a series of consecutive stimulations in which decremental measurements are suggestive neuromuscular junction disease (myasthenia gravis) (Malik and Cook, 1989; Sims and McLean, 1990).

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CHAPTER 22

Seizures and Sleep Disorders

Fredrik Gruenenfelder

SEIZURES

Definition

I. A seizure is a nonspecifical, paroxysmal event or episode that may have a neurological or nonneurological etiology.
II. An epileptic seizure implies a neural cause.
III. An epileptic seizure is the clinical manifestation of involuntary alterations in behavior and locomotion caused by hypersynchronous, abnormal, neuronal activity in the cerebral cortex.
IV. Partial seizures arise from events in focal areas of the cerebral cortex.
  A. Paroxysmal alterations in motor function involve certain muscle groups, resulting in facial-muscle twitching, single-limb movements, or twisting of the head or neck.
  B. Paroxysmal alterations in vegetative or sensory functions cause abnormal behaviors, such as fly biting, excessive unmotivated vocalization, restlessness, unprovoked aggressiveness, drooling, or rapid running.
  C. No alteration in consciousness occurs during simple partial seizures, but consciousness is altered during complex partial seizures.
V. Generalized seizures originate from the cerebral hemispheres or thalamus and may begin with a focal event that progresses to involve the entire prosencephalon.
  A. Generalized seizures may be classified as tonic-clonic, clonic, atonic, or myoclonic.
  B. Autonomic disturbances, such as urination, defecation and hypersalivation, are common.
  C. Generalized seizures are often accompanied by alterations in consciousness.
VI. Unclassified seizures cannot be classified because of incomplete or inconsistent data.
VII. Certain events or phases may occur with seizures.
  A. The prodrome is the period before the onset of seizure activity.
    1. Prodromal signs include changes in behavior, such as anxiousness, increased attentiveness, or hiding.
    2. This phase can last for several days.
  B. The aura is the initial manifestation of a seizure.
    1. Signs include drooling, vomiting, pacing, or barking.
    2. The aura can last from seconds to minutes.
  C. Ictus is the actual seizure event and may include involuntary motor movements, abnormal muscle tone, abnormal sensation and behaviors; ictus usually lasts from seconds to minutes.
  D. The postictal phase is characterized by abnormal behavior, disorientation, weakness, blindness, and sensory or motor dysfunction that can last from minutes to 48 hours.
  E. The interictal period is the time between seizures, during which the animal is clinically and neurologically normal.
  F. Status epilepticus is a seizure lasting >5 minutes or repeated seizures without a return to consciousness between them (Thomas, 2003).
  G. Cluster seizures are defined as ≥2 seizures within 24 hours.
VIII. Epilepsy is defined as recurrent seizure activity caused by a chronic brain disorder (Berendt and Gram, 1999).
  A. Strictly defined, epilepsy does not imply an underlying cause of recurrent seizures.
  B. Epilepsy is commonly applied to situations in which an underlying cause is not defined and there may be a possible inheritance of the seizures.
    1. There is a familial predisposition for idiopathic epilepsy in certain breeds of dogs.
    2. In dogs, the age at onset is 1 to 5 years.
    3. Often the seizures are generalized, but they can be partial.
    4. Seizures occur spontaneously, often during rest or sleep.
    5. Seizure frequency initially is every 4 to 6 weeks.
    6. There is a tendency for frequency to increase if left untreated.
  C. Refractory epilepsy is frequent or severe seizure activity despite appropriate therapy.

Causes

I. Epilepsy can be classified based on the underlying etiology (Table 22-1).
II. Symptomatic epileptic seizures are caused by structural brain disorders.
III. Reactive epileptic seizures arise from disturbances in systemic metabolism or from toxicoses (no structural brain abnormalities).
IV. Cryptogenic epileptic seizures may occur from metabolic or structural brain disorders that are undetectable.

TABLE 22-1

Potential Causes of Seizures

CLASS OF DISORDERS	EXAMPLES
Degenerative diseases	Storage diseases: gangliosidosis, glucocerebrosidosis, glycoproteinosis, mucopolysaccharidosis glycogenosis, ceroid lipofuscinosis, leukodystrophy
	Diseases affecting intermediate metabolism
Anatomical anomalies	Hydrocephalus (primary, secondary), lissencephaly, hydranencephaly, porenecphaly
	Vascular malformations
Metabolic disturbances	Hepatic encephalopathy: portosystemic shunt, acquired liver disease
	Uremic encephalopathy
	Hypoglycemia: see Chapters 36 and 73
	Hypocalcemia: puerperal tetany, hypoparathyroidism
	Hypercalcemia, hypernatremia, hyponatremia, hyperlipoproteinemia
	Hypoxia, acid-base disturbances, polycythemia vera
Neoplasia	
Primary	Meningioma, meningiosarcoma, astrocytoma, glioblastoma multiforme
	Oligodendroglioma, oligoastrocytoma, gliomatosis cerebri
	Primitive neuroectodermal tumors, ependymoma, chorioid plexus papilloma
Secondary	Metastatic neoplasia, lymphoma
	Pituitary macroadenoma, hamartoma, suprasellar germ cell tumor
Inflammatory conditions	
Infections	
Bacterial	*Streptococcus* spp., *Staphylococcus* spp., *Escherichia coli, Pasteurella* spp., *Listeria monocytogenes*
Rickettsial	Rocky Mountain spotted fever, ehrlichiosis
Viral	Rabies, canine distemper virus, canine herpesvirus
	Feline infectious peritonitis, leukemia virus, immunodeficiency virus
Fungal	Cryptococcosis, blastomycosis, histoplasmosis, coccidiomycosis, phaeohyphomycosis
Protozoal	Neosporosis, toxoplasmosis
Parasitic	Dirofilariasis, toxascariasis, ancylostomiasis
Noninfectious causes	Granulomatous meningoencephalitis, necrotizing meningoencephalitis
	Necrotizing leukoencephalitis, eosinophilic meningoencephalitis
	Feline polioencephalomyelitis
Trauma	Head trauma: automobile crashes, high-rise building syndrome, bite wounds
Toxins	Organophosphates, carbamates, metaldehyde, pyrethrin (cats), ethylene glycol, bromethalin, lead
Vascular disorders	Hemorrhagic or ischemic infarction
	Feline ischemic encephalopathy from intracranial *Cuterebra* spp. larval migration

V. Idiopathic epileptic seizures have no recognized underlying metabolic or structural cause, and may be genetic in origin.

Pathophysiology

I. A seizure develops from transient, paroxysmal, uncontrolled, synchronized electrical discharge of neurons (Gandini et al., 2005).
II. The activity disperses to different areas of the brain over thalamocortical pathways, intrahemispheric association or commissural pathways (Podell, 2004).
III. The cause of the excessive electrical discharge may be an increased excitability of neurons (Gandini et al., 2005).
IV. A common mechanism may involve changes in equilibrium between the main inhibitory neurotransmitter (gamma aminobutyric acid [GABA]), and the main excitatory neurotransmitter (glutamate), with greater concentrations of glutamate (Fenner and Hass, 1989).
V. If the epileptic focus activates a critical number of areas, a generalized seizure occurs (March, 1998).
VI. Theoretically, the more new seizure foci that are recruited, the more difficult the seizures are to control medically (Podell, 2004).
VII. The end of the seizure is normally caused by active inhibition (Gandini et al., 2005).
VIII. Seizures can result in various secondary intracranial consequences.
   A. Accumulation of excitatory neurotransmitters (glutamate) can lead to neurotoxicity and neuronal cell death (Fujikawa, 2005).
   B. The disruption of neuronal function and integrity can lead to cerebral edema with increased intracranial

pressure and generalized, reduced perfusion of the brain (Podell, 2004).
C. Neurons have a much higher demand for energy during a seizure, which leads to anaerobic glycolysis, cerebral acidosis, and further neuronal dysfunction and death.

IX. Extracranial changes include hyperthermia, hypoventilation, hypoxia, and systemic hypertension.

Clinical Signs

I. Simple partial seizures
   A. Motor movements in a single group of muscles: facial muscle or one leg twitching
   B. No changes in consciousness
II. Complex partial seizures
   A. Altered consciousness
   B. Abnormal psychomotor function: fly biting, restlessness, barking, chasing of extremities
III. Generalized seizures
   A. Impairment of consciousness
   B. Excessive motor movements of the body and head (tonic/clonic movements)
      1. In the tonic phase, the animal is in a rigid, hyperextended posture.
      2. The clonic phase includes strong, jerky movements of the extremities, jaw, and neck muscles.
   C. Autonomic disturbances: hypersalivation, urination, defecation
IV. Atonic, myoclonic, and absent seizures: difficult to recognize, poorly defined in animals
V. Other signs: pacing, transient loss of vision, disorientation, changes in personality

Diagnosis

I. Ultimate goal: determine the cause of the seizures
II. Important historical information
   A. Vaccination status and travel history
   B. Potential of trauma and exposure to toxins
   C. Breed and familial history of seizures
   D. Previous medical and surgical history
   E. Onset and frequency of seizures
   F. Duration of ictus
   G. Duration and characteristics of the postictal phase
III. Physical examination
   A. Detection of systemic illness that may result in reactive epilepsy
   B. Identification of episodic nonneurological and neurological disorders easily confused with epileptic seizures
IV. Neurological examination
   A. Perform a complete neurological examination to identify interictal deficits (see Chapter 21).
   B. Asymmetrical, interictal deficits unrelated to postictal changes are suggestive of structural brain disease.
V. Minimal laboratory database
   A. Complete blood count (CBC)
   B. Serum biochemistry profile
   C. Urinalysis
VI. Advanced clinicopathologic testing based on initial laboratory results
   A. Liver function testing: bile acids, fasting serum ammonia, ammonia tolerance test
   B. Simultaneous serum glucose and insulin levels in hypoglycemic animals
   C. Serial blood glucose measurements in animals with suspected hypoglycemia
   D. Endocrine assays: hyperadrenocorticism, hypoadrenocorticism, hypothyroidism
   E. Toxicology testing: blood lead, acetylcholinesterase activity for organophosphate toxicities
   F. Systemic blood pressure measurement
VII. Specific testing for intracranial disorders
   A. Cerebrospinal fluid (CSF) analysis
   B. Measurement of serum and CSF antibody or antigen titers
      1. Feline enteric coronavirus/feline infectious peritonitis (FIP) virus
      2. Canine distemper virus, *Neospora caninum*, *Toxoplasma gondii*
      3. *Cryptococcus neoformans*, other fungal organisms
VIII. Imaging studies
   A. Thoracic and abdominal radiography
   B. Abdominal ultrasonography
   C. Transcolonic portal scintigraphy
   D. Magnetic resonance imaging (MRI) of the brain
IX. Establishing the type of seizures present
   A. Idiopathic epilepsy (Table 22-2)
      1. To classify the seizures as idiopathic epilepsy, the animal must have normal physical and neurological examinations and remain normal interictally.
      2. Ultimately, the diagnosis of idiopathic epilepsy is made through the exclusion of other causes of epilepsy (i.e., symptomatic or reactive).
      3. Clinicopathologic data are normal.
   B. Symptomatic epilepsy
      1. Hallmark findings are asymmetrical, neurological deficits or the persistence of any neurological deficit during the interictal period.
      2. Age of onset is often <1 or >6 years.
      3. Animals often have partial seizures, which may be generalized.
      4. Clinicopathologic test results are usually normal.
      5. Most cats have symptomatic or reactive epilepsy (Barnes et al., 2004; Quesnel et al., 1997).
   C. Reactive epilepsy
      1. Classic features are signs of systemic illness from metabolic disorders or toxicities (e.g., fever, lethargy, weight loss, anorexia, vomiting, diarrhea).
      2. If present, interictal neurological deficits are symmetrical.
      3. Seizures are often generalized.
      4. Abnormalities are often found in clinicopathologic tests.
   D. Cryptogenic epilepsy
      1. Physical and neurological examination findings may be normal or abnormal.

TABLE 22-2

Clinical Features of Idiopathic Epilepsy

CLINICAL PARAMETER	DOGS	CATS
Cause	Genetic defects causing abnormalities in neuronal ion channels are suspected	Unknown
Incidence	50% to 60% of seizure disorders	10% to 20% of seizure disorders
Age of onset	1 to 5 years	Unknown
Affected breeds	Proven genetic factor: Keeshond Multiple factors (genetic and environmental): beagle, German shepherd dog, golden retriever, Belgian tervuren, Labrador retriever, Bernese mountain dog, boxer, Shetland sheep dog, viszla, Irish wolfhound High incidence: cocker spaniels, poodles, St. Bernard, Irish setter, miniature schnauzer, collie, wiredhaired fox terrier, dachshund, Greater Swiss mountain dog, Horaks laborhound, border collie	No breed predilection identified
Clinical signs	Sudden onset Seizures often generalized (tonic-clonic) Commonly occur at night or during rest/sleeping	Sudden onset Seizures often generalized: excessive activity, vocalizing, hypersalivation, defecation, urination

2. Clinicopathologic data may be normal or abnormal.
3. Despite lack of evidence or identification of an underlying etiology, cryptogenic epilepsy is often presumed in dogs <1 year or >5 years and in most cats with seizures.

X. Age relationship to causes in dogs (see Table 22-2)
   A. Age <1 year
      1. Dogs often have symptomatic or reactive epilepsy.
      2. Seizure activity often arises from congenital anomalies or inflammatory diseases of the central nervous system.
         a. Hydrocephalus: Chihuahua, Maltese, Yorkshire terrier, potentially any breed
         b. Canine distemper virus
         c. Noninfectious inflammatory diseases: necrotizing meningoencephalitis in the pug, necrotizing leukoencephalomyelitis in the Yorkshire terrier, Maltese, Chihuahua, and other small breeds
      3. Portosystemic shunts must always be ruled out in this age group.
   B. Age 1 to 5 years
      1. Most common cause: idiopathic epilepsy
      2. Later onset of seizure possible with congenital anomalies
   C. Age >5 years
      1. Intracranial neoplasia is a common cause.
      2. Cryptogenic epilepsy is suspected when an underlying etiology cannot be found.

XI. Age relationship to causes in cats
   A. Age <1 year
      1. Infectious inflammatory diseases: FIP, protozoal diseases
      2. Congenital anomalies of the brain
      3. Metabolic disorders, portosystemic shunts
   B. Age 1 to 7 years
      1. Infectious, inflammatory diseases
      2. Trauma
      3. Vascular insults: feline ischemic encephalopathy from *Cuterebra* spp. larval migration
      4. Neoplasia
   C. Age >7 years
      1. Neoplasia
      2. Metabolic diseases: renal encephalopathy
      3. Vascular insults: feline ischemic encephalopathy

Differential Diagnosis

I. Nonneurological disorders
   A. Syncope
   B. Stereotypy with abnormal behavior
   C. Strychnine intoxication

II. Neurological disorders
   A. Vestibular disorders
   B. Myasthenia gravis
   C. Narcolepsy, cataplexy
   D. Involuntary motor movements: myoclonus, generalized tremors, dyskinesia

Treatment

I. The goal of emergency treatment is to stop the seizure activity without causing any harm to the animal.
   A. Emergency treatment is required for isolated seizures lasting >3 minutes, seizures occurring hourly, three or more seizures within 12 hours, cluster seizures, and status epilepticus (Box 22-1).
   B. Initial emergency treatment involves controlling the seizure with short-acting anticonvulsants and initiating treatment with long-acting anticonvulsants.
      1. Benzodiazepines are used for initial treatment.

Box 22-1

Emergency Treatment of Status Epilepticus or Cluster Seizures in Dogs and Cats

1. Give diazepam 0.5 to 2 mg/kg IV or midazolam 0.07 to 0.22 mg/kg IV, IM and phenobarbital 2 mg/kg IV.
2. If seizures continue or recur within 2 hours, give an additional dose of diazepam or midazolam.
   a. A loading dosage of phenobarbital can also be given.
   b. The loading dosage of phenobarbital is 12 to 15 mg/kg IV divided into 2 to 4 mg/kg dosages every 1 to 2 hours over 24 hours until seizures are controlled or the animal is extremely sedated.
3. If seizures continue or recur within 2 hours, then consider propofol 4 to 8 mg/kg IV bolus and start constant rate infusion (CRI) of diazepam or midazolam at 0.5 mg/kg/hr IV.
4. If seizures do not stop, increase the CRI to 2 mg/kg/hr IV in 0.5 mg/kg/hr increments; at higher dosages animals can develop apnea.
5. If seizures stop, continue CRI of diazepam or midazolam for 4 to 6 hours, then gradually discontinue the CRI over 4 to 6 hours.
6. If seizures recur after stopping the CRI, restart a diazepam or midazolam CRI for another 6 hours and continue phenobarbital 2 mg/kg IV, IM, PO BID.
7. If seizures do not stop with repeated diazepam or midazolam, then give propofol 4 to 8 mg/kg IV and start a propofol CRI at 0.1 to 0.6 mg/kg/min IV for 4 to 6 hours.
8. If seizures stop, then gradually discontinue propofol CRI over 4 to 6 hours.
9. If seizures do not stop with diazepam, midazolam, or propofol, then consider pentobarbital 2 to 15 mg/kg IV over several minutes, then a pentobarbital CRI of 0.5 mg/kg/hr IV for 4 to 6 hours.
   Caution:
   a. Severe cardiopulmonary depression can occur.
   b. Endotracheal intubation may be necessary.
   c. Intensive monitoring is essential.
   d. Animal may be neurologically abnormal for up to 1 week after pentobarbital CRI.

   2. Diazepam is the drug of choice.
      a. It can be used for seizures or during the postictal phase.
      b. It may be administered IV, rectally, or intranasally.
   3. Midazolam can be used as an alternative.
C. In reactive epilepsy, treatment of the underlying etiology is undertaken.
D. With cryptogenic or idiopathic epileptic seizures, long-term anticonvulsive drugs are initiated simultaneously with benzodiazepine administration.
E. If seizures stop after emergency treatment, then continue with long-term anticonvulsants.

II. The goal of long-term treatment is to provide chronic control of seizure activity.
A. Theoretically, the goal is complete control of seizure activity (without side effects); however, this is rarely achieved.
B. A more realistic goal is to decrease the severity and frequency of seizures, and to prevent cluster seizures and status epilepticus while maintaining a good quality of life.
C. Successful long-term treatment requires dedication and understanding of realistic goals by the owners.
   1. Treatment is lifelong.
   2. Anticonvulsants must be given on a regular, daily basis.
   3. Seizure emergencies may occur despite appropriate treatment.
   4. Good knowledge of the potential side effects of anticonvulsants is imperative.
D. Reasons to initiate long-term anticonvulsive therapy include the following:
   1. After status epilepticus or cluster seizures
   2. After the occurrence of two or more isolated seizure events within a 6- to 8-week period
   3. After prolonged postictal periods
   4. In cases where an identifiable structural lesion is causing seizures
   5. Delayed onset of seizure activity after head trauma

III. Long-term anticonvulsants are initiated after emergency control of seizures (Table 22-3).
A. Phenobarbital is the anticonvulsant of choice and can be used in both dogs and cats.
   1. After emergency treatment, start phenobarbital at 2 to 5 mg/kg PO, IM, IV BID.
   2. If seizures persist despite initial emergency treatment, a loading dosage of phenobarbital can be administered (See Box 23-1).
   3. Alternatively, a loading dose can be calculated as follows:

$$\textbf{Loading dose (mg)} = \textbf{desired serum level } (\mu\text{g/mL}) \times \textbf{body weight (kg)} \times 0.8\ \text{L/kg}$$
$$(\textbf{volume of distribution [Vd]})$$

   4. Animals are often heavily sedated for ≥24 hours when using the loading dose.
B. Potassium bromide (KBr) is a good second choice.
   1. It can be used in animals already receiving phenobarbital.
   2. In an emergency, KBr is administered as a loading dose because of its long half-life.
   3. Loading dosage is 400 to 600 mg/kg PO divided into six equal doses given over 1 to 5 days, depending on the severity of the seizures.
   4. Alternatively, a target steady state can be achieved based on the following formula:

$$\textbf{Target steady state concentration (Css)} \times 0.45\ \text{L/kg}$$
$$(\textbf{[Vd]}) = \textbf{total dose administered}$$

   5. Target serum concentration for KBr as monotherapy is 1 to 3 mg/mL, and as adjunctive therapy with phenobarbital is 1 to 2 mg/mL.

TABLE 22-3

Anticonvulsant Drugs Available for Use in Dogs and Cats

DRUG	USE AND MECHANISM OF ACTION	PHARMACOLOGY	DOSAGES	SIDE EFFECTS AND CAUTIONS
Diazepam	Prolongs opening of GABA receptors; used for short-term control of seizures; drug of choice for emergency treatment of status epilepticus/cluster seizures; can be used for long-term management in cats	Metabolized in liver, excreted by kidneys (90%) and in feces (10%) Bioavailability: 80% $t_{1/2}$ (dogs): 3 hours $t_{1/2}$ (cats): 5 hours $t_{1/2}$ of active metabolite nordiazepam in cats = 21-hour maximum CNS concentration reached 1 minute after IV administration	*Dogs, cats:* 0.5-2 mg/kg IV, rectally CRI: 0.5-2 mg/kg/hr IV in 0.9% NaCl *Cats:* 0.5-2 mg/kg PO BID for long-term use	Sedation CRI can cause apnea Dogs develop tolerance Acute fulminant hepatic necrosis in cats (idiosyncratic) Used cautiously in animals with liver dysfunction
Midazolam	Prolongs opening of GABA receptors; used for short-term control of seizures; drug of choice for emergency treatment of seizures	Metabolized in liver, excreted by kidneys (>90%) and in feces (<10%) Bioavailability: 90% $t_{1/2}$ (dogs): 77 minutes	*Dogs:* 0.07-0.22 mg/kg IV, IM, intranasally, rectally CRI: 0.5-2 mg/kg/hr IV	Sedation CRI can cause apnea Used cautiously in animals with liver dysfunction No data for cats
Propofol	Effects GABA receptor ionophor complex; used for short-term control of seizures; drug of choice for emergency treatment of seizures not controlled with benzodiazepines; used for hepatopathy-induced seizures	Metabolized via extrahepatic routes; rapidly distributed to whole body; effects seen within 1 minute; anesthesia lasts 5 minutes after single bolus	*Dogs, cats:* 4-8 mg/kg IV to effect CRI: 0.1-0.6 mg/kg/min IV	Induces anesthesia (intubation necessary) Apnea and hypoxemia Myocardial depression
Phenobarbital	Increases neuronal response to GABA; prevents glutamate-induced postsypnatic decrease in neuronal calcium influx; used for generalize seizures	Metabolized in liver Bioavailability: 90% $t_{1/2}$ (dogs): 24-40 hours Tss: 10-14 days	*Dogs, cats:* 2-5 mg/kg PO BID	Transient: ataxia, lethargy, behavioral changes Persistent: PU/PD polyphagia, obesity, lethargy, splenomegaly, hepatomegaly, increased ALT and ALP, decreased serum thyroxine Severe side effects: hepatotoxicity, myelofibrosis, necrotizing superficial dermatitis
Potassium bromide	Hyperpolarization of neuronal membranes through chloride channels; used for generalized seizures	Excreted unmetabolized by kidneys Bioavailability: 60% $t_{1/2}$ (dogs): 25 days $t_{1/2}$ (cats): 10 days Tss (dogs): 90-120 days Tss (cats): 50 days	*Dogs, cats:* 30-60 mg/kg PO SID	Transient: ataxia, sedation, hyperactivity, vomiting Persistent: PU/PD Rare: aggression, dermatitis, pancreatitis Increased risk of asthma in cats; impaired renal function elevates blood levels; high salt diet increases bromide secretion

GABA, Gamma-aminobutyric acid; $t_{1/2}$, half-life time; *CNS,* central nervous system; *CRI,* constant rate infustion; *Tss,* time-to-steady rate; *PU/PD,* polyuria/polydipsia; *ALT,* alanine aminotransferase; *ALP,* alkaline phosphatase.

Continued

TABLE 22-3

Anticonvulsant Drugs Available for Use in Dogs and Cats—*cont'd*

Felbamate	Inhibition of NMDA receptors; potentiation of GABA receptors; used for partial seizures; added to phenobarbital and potassium bromide	Metabolized in liver (30%), excreted by kidneys (70%) Bioavailability: 85% $t_{1/2}$: 5-6 hours Tss: 24-30 hours	*Dogs:* 15-70 mg/kg PO BID-TID, increased in 15-mg/kg increments up to 70 mg/kg/day PO	Rare: nervousness, hyperexcitability, liver toxicity, bone marrow suppression No data for cats
Gabapentin	Mechanism of action not completely understood; may enhance effects of phenobarbital, diazepam, felbamate; added to phenobarbital and potassium bromide; also used for neurogenic pain management	Minimally metabolized in liver, excreted by kidneys Bioavailability: 80% $t_{1/2}$: 3-4 hours	*Dogs:* 25-60 mg/kg PO BID-TID	Rare: sedation Questionable efficacy in dogs, owing to short $t_{1/2}$ Can be used in cats, but no data available
Levetiracetam	Mechanism of action unknown; added to phenobarbital and potassium bromide; potentially a monodrug therapy; used for generalized seizures and hepatopathy-related seizures	Excreted unchanged or hydrolyzed by kidneys Bioavailability: ≈100% $t_{1/2}$: 4 hours Anticonvulsant effects last longer despite short $t_{1/2}$	*Dogs:* 25-60 mg/kg PO BID-TID	Rare: salivation, restlessness, vomiting, ataxia
Zonisamide	Blocks voltage-dependent sodium channels and t-type calcium channels; enhances dopaminergic and serotonergic neurotransmission; inhibits glutamate-induced excitation; added to phenobarbital and potassium bromide; used for generalized seizures	Metabolized in liver Bioavailability: 80% $t_{1/2}$: 15 hours Tss: 3 days	*Dogs:* 10 mg/kg PO BID	Rare: drowsiness, ataxia, gastrointestinal upset

NMDA, N-methyl-D-aspartic acid.

6. In animals already receiving KBr, the formula for a new oral dose for recurrent seizures is (Podell, 2004):

(Target Css) − actual Css × Vd L/kg = (target desired Css − actual Css) × 0.45 L/kg = mg/kg divided into 4 equal doses QID

7. KBr can be given PO or per rectum, but not IV.
8. Rectal administration can lead to severe diarrhea.
9. Maintenance dose is 30 to 40 mg/kg PO SID.
10. KBr is slowly increased to effect, to a maximum dose of 60 mg/kg/day PO.
11. KBr can be used safely in dogs.
12. KBr should be used with caution in cats, because it can result in tachypnea, dyspnea, and coughing (Boothe et al., 2002).
    a. Dosage is the same as in the dog.
    b. The half-life is 10 days, with steady-state serum concentrations being reached in 50 days (Boothe et al., 2002).
    c. KBr is avoided in cats because it may increase the risk of asthma.
    d. Discontinued if respiratory signs or radiographic changes develop.

C. Sodium bromide (NaBr; 3%) can be given IV.
1. It is dissolved in sterile water (0.375 mEq Br/mL + 1.3 mEq Na/mL)
2. An IV loading dose is calculated using the following formula:

Steady-state concentration (Css) × Vd = total dose administered by constant rate infusion (CRI) in a central vein

D. In cats, the pharmacokinetics of diazepam supports its use as a long-term anticonvulsant.
   1. Diazepam is given at 0.25 to 1 mg/kg PO BID.
   2. Side effects include sedation and polyphagia.
   3. In cats, oral administration can cause fulminant hepatic failure (idiosyncratic reaction), so it is only used as a last choice.
   4. Diazepam is not used as a long-term anticonvulsant in dogs.
      a. Dogs develop tolerance to long-term therapy.
      b. In dogs, the half-life is very short (3 hours).

E. Felbamate can be used in dogs if seizure control is insufficient with phenobarbital and KBr.
   1. Felbamate is given at 15 to 70 mg/kg PO BID to TID.
   2. Rare side effects include nervousness, hyperexcitability, liver toxicity, and bone marrow suppression.
   3. Felbamate may be useful for partial seizures (Ruehlmann et al., 2001).
   4. No data are available on its use in cats.

F. Gabapentin can be used in dogs if seizure control is insufficient with phenobarbital and KBr.
   1. Gabapentin is given at 25 to 60 mg/kg PO TID to QID.
   2. Short-term side effects include sedation; long-term side effects are unknown.
   3. No data are available on its use in cats, but administration of up to 30 mg/kg PO TID is anecdotally well tolerated in cats.

G. Levetiracetam can be used as a second-choice anticonvulsant in dogs if seizure control is insufficient with phenobarbital and KBr.
   1. Levetiracetam is given at 5 to 30 mg/kg PO BID to TID.
   2. It can be used in animals with hepatic dysfunction.
   3. Rare side effects include salivation, restlessness, vomiting, and ataxia.

H. Zonisamide can be used in dogs if seizure control is insufficient with phenobarbital and KBr.
   1. Zonisamide is given at 10 mg/kg PO BID (Dewey et al., 2004).
   2. Animals concurrently receiving phenobarbital may require higher dosages of zonisamide.
   3. Rare side effects include drowsiness, ataxia, and gastrointestinal irritation.
   4. Minimal side effects are seen at dosages up to 75 mg/kg/day.

IV. Recommendations for long-term management of seizures is as follows:
   A. Phenobarbital is the first-choice anticonvulsant because of its faster onset of action, shorter half-life, and more predictable anticonvulsant effects.
      1. Animals are initially started on phenobarbital at 2 mg/kg PO BID.
      2. If seizure control is poor after reaching the steady state, the dosage of phenobarbital is gradually increased to approximately 5 mg/kg PO BID.
   B. If seizure control remains poor or severe side effects occur, KBr therapy is initiated at 30 mg/kg PO SID.
   C. If seizure control remains poor despite the addition of KBr, the dosage of KBr is gradually increased to a maximum of 60 mg/kg PO SID.
   D. If the animal does not tolerate phenobarbital well, monotherapy with KBr is initiated.
   E. In animals experiencing side effects or in those that are seizure-free for >1 year, the dosage of anticonvulsants can be gradually decreased.
   F. Second-choice anticonvulsants are typically used if seizures cannot be controlled with a combination of phenobarbital and KBr, or if side effects are intolerable.

Monitoring of Animal

I. Animals undergoing emergency treatment for seizures require intensive supportive care and monitoring.
   A. IV fluid therapy is administered for maintenance needs and any ongoing losses.
   B. Fluid input and output are closely monitored to maintain hydration.
   C. Supplementation with thiamine 25 to 50 mg IM, IV may be helpful, as thiamine is essential for glucose metabolism in the brain.
   D. Periodic monitoring of packed cell volume, total solids, blood glucose, serum calcium, and blood urea nitrogen is done.
   E. Monitor body temperature to avoid hyperthermia or hypothermia.
   F. Recumbent animals are turned every 4 to 6 hours.
   G. Animals receiving anticonvulsants by CRI are monitored as follows:
      1. Heart rate, respiratory rate, and temperature are measured every hour.
      2. Blood pressure and oxygenation via pulse oximetry or arterial blood gas analysis are monitored every 4 hours
      3. Monitor for slowing of respiratory rate, hypoventilation, and apnea, which may necessitate mechanical ventilation.
      4. Tracheal intubation may be necessary.
      5. Supplemental oxygen may be needed for hypoxemia.
      6. Change endotracheal tubes every 6 hours.

II. Owners may be taught to provide emergency treatment at home for seizures lasting >5 minutes, status epilepticus, cluster seizures, or postictal phases >2 hours.
   A. Diazepam can be administered rectally in dogs at 1 to 2 mg/kg (Podell, 1995).
      1. Use parenteral diazepam solution or commercially available rectal compounds.
      2. Diazepam is absorbed quickly across the rectal mucosa, reaching peak plasma concentration within 15 minutes.
      3. The first-pass effect is avoided with rectal application.
      4. Effects of rectal diazepam last for about 1 hour.
   B. Diazepam can be administered rectally in cats at 0.5 to 1 mg/kg.
      1. Pharmacokinetics are unknown, but may be similar to the dog.

2. Effects are seen within 10 to 15 minutes.
3. Diazepam may be less effective if the cat is also receiving long-term treatment with diazepam.

III. Monitoring of long-term anticonvulsant therapy is done through evaluations of clinical signs, seizure frequency, and measurement of serum drug levels.
   A. If an anticonvulsant is used within the recommended dosage range and the seizures are under control, serum levels may not be needed.
   B. Avoid under- or overdosing of drugs.
   C. Note that an animal can develop severe side effects despite having normal to low serum levels.
   D. Serum monitoring is recommended if seizure control is poor, the animal shows signs of toxicity, or severe side effects occur after initial adaptation to the drug.
   E. Monitoring serum levels allows for individualized treatment and minimizes the potential for side effects.
   F. Phenobarbital or KBr dosages can be incrementally increased when seizure control is poor or decreased to reduce side effects or toxicity.

IV. Dose adjustment of phenobarbital is initially based on the degree of seizure control.
   A. If the high end of the dosage range is needed to control seizures, serum phenobarbital levels are measured to prevent toxicity.
      1. Levels can be checked at any time during the day after steady state has been reached.
      2. Avoid serum separator tubes, because silicon binds phenobarbital and results in artificially low serum levels.
      3. Therapeutic serum phenobarbital levels (dependent on laboratory) are as follows:
         a. Dogs: 20 to 40 μg/mL
         b. Cats: 10 to 30 μg/mL
   B. Side effects of phenobarbital are listed in Table 22-3.
   C. A CBC, biochemistry profile, and urinalysis are performed every 6 months.
   D. When using serum phenobarbital levels to change dosages, a formula can be used:

(Desired concentration ÷ actual concentration) × total mg/day = new total mg dose phenobarbital/day

V. Serum KBr levels are evaluated if seizure control is poor or if toxicity is suspected.
   A. Serum levels can be checked at any time during the day after steady state has been reached.
   B. If used as monotherapy, therapeutic levels in dogs are 2 to 3 mg/mL.
   C. If used in combination with phenobarbital, therapeutic levels in dogs are 1 to 2 mg/mL (March et al., 2002).
   D. KBr can be adjusted using the following formula (Podell, 2004):

(Target Css – actual Css) × (0.02 × clearance/bioavailability) = new maintenance dose (added mg/kg/day)

   E. Side effects are listed in Table 22-3.
   F. Monitor CBC, serum biochemical profile, and urinalysis every 6 months.

VI. Optimizing seizure control involves several steps.
   A. It is imperative that an underlying cause be established, if possible.
      1. The earlier proper treatment is initiated, the better the chance for optimal control.
      2. In idiopathic epilepsy, anticonvulsive treatment is lifelong.
   B. Underdosing anticonvulsant drugs can lead to poor seizure control.
   C. Client education regarding realistic goals of seizure control and anticonvulsant side effects is required.
   D. If the animal is seizure free for >1 year, a slow, incremental reduction of the drugs may be tried over 6 months.

SLEEP DISORDERS

Definition

I. Narcolepsy is an abnormality in the sleep–wake cycle that manifests as excessive sleepiness and uncontrollable episodes of sleep.
II. Cataplexy is a short episode of complete loss of muscle tone, usually provoked by excitement and emotion.
   A. Loss of muscle tone is caused by central-mediated inhibition of α-motor neurons.
   B. Episodes are reversible.
   C. Consciousness is not altered in pure cataplexy.
   D. Cataplexy occurs often together with narcolepsy.

Causes

I. In dogs, narcolepsy can be caused by an inherited, autosomal, recessive defect of the hypocretin-receptor-2 gene (Lin et al., 1999).
II. Affected breeds include the Doberman pinscher, Labrador retriever, dachshund, and poodle.
III. Narcolepsy can also result from a decreased level of hypocretin-1 protein.
   A. Although the cause remains unknown, an autoimmune process is suspected.
   B. Affected breeds include the Airedale terrier, Afghan hound, Irish setter, malamute, St. Bernard, rottweiler, English springer spaniel, Weimaraner, Welsh corgi, and giant schnauzer.
IV. Inflammatory, neoplastic, or vascular lesions involving the hypothalamus may also be causes.
V. Narcolepsy is rare in cats.

Pathophysiology

I. Hypocretin-1 protein and the hypocretin-receptor-2 play important roles in the sleep–wake cycle and in control of α-motor neurons in the spinal cord (Yamuy et al., 2004).
II. Neurons containing hypocretin-1 are located predominantly in the posterior hypothalamus.
III. Fibers from these neurons are distributed to the locus coeruleus, nucleus raphe, and cerebral cortex.
   A. Binding of hypocretin-1 to the hypocretin-receptor-2 has a rousing effect and increases motor activity.

B. Deficiency in the numbers of functional hypocretin-receptor-2 leads to decreased effects of hypocretin-1 protein.
C. Similarly, a deficiency in the amount of hypocretin-1 protein also leads to diminished effects.
D. The result is an abnormal sleep–wake cycle regulation, leading to excessive sleepiness and episodes of sleep.
E. A loss of hypothalamic hypocretinergic control of α-motor neuron leads to loss of muscle tone and cataplexy.

Clinical Signs

I. Affected animals are typically <6 months; however, onset can occur in young adult animals.
II. Episodes are often provoked by excitement (e.g., feeding, drinking, playing).
III. Episodes consist of immediate onset of active sleep with rapid eye movement followed by a sudden return to a normal awake state (narcolepsy).
IV. Generalized muscle atonia (cataplexy) may also occur.
V. Affected animals often have prolonged sleep periods, as well as marked drowsiness during the day.
VI. Onset and termination of the episodes are abrupt.
VII. Duration of episodes ranges from seconds to 30 minutes.
VIII. External stimuli can often interrupt the episode.

Diagnosis

I. Presumptive diagnosis is made by observing an episode.
II. Breed, history, and clinical signs are supportive.
III. Episodes can be induced.
  A. Food-elicited cataplexy test (FECT)
    1. Line up about 10 small treats, 30 cm apart.
    2. Observe the animal for loss of muscle tone or sleep episodes.
    3. Record the time it takes for the animal to eat all the treats.
    4. A normal dog can eat the food within 1 minute without an episode occurring.
    5. A positive test result involves the following observations:
      a. The animal has two or more episodes and takes >2 minutes to eat all the treats.
      b. The animal falls completely asleep.
      c. The dog drops to the floor, but the head stays in a normal position.
  B. Pharmacological tests
    1. Yohimbine response test
      a. Yohimbine is administered at 50 μg/kg IV.
      b. A positive response is a 75% reduction in number or duration of episodes.
      c. The effect of yohimbine lasts 30 to 240 minutes.
    2. Anticholinergic drugs
      a. They can increase the duration and/or frequency of the episodes.
      b. The FECT is performed after administration of atropine 0.1 mg/kg IV or physostigmine 0.025 to 0.1 mg/kg IV.
      c. Affected animals have increased frequency and/or duration of episodes.
    3. Imipramine challenge
      a. Imipramine is administered at 0.5 mg/kg IV.
      b. A positive response consists of a decrease in episodes, but is not specific for narcolepsy and/or cataplexy.
IV. CSF analysis may be helpful (Mignot et al., 2002).
  A. Hypocretin-1 concentration can be measured in CSF by the Center for Narcolepsy, Department of Psychiatry, Stanford University School of Medicine.
    1. A level <100 pg/mL is consistent with narcolepsy from hypocretin-1 deficiency.
    2. A level of 101 to 200 pg/mL is suspicious for narcolepsy from hypocretin-1 insufficiency.
    3. Levels of 200 to 350 pg/mL are normal (Ripley et al., 2001).
  B. CSF analysis can help establish an underlying cause or rule out other disorders.
V. Genetic analysis also can be performed at Stanford University School of Medicine.

Differential Diagnosis

I. Myasthenia gravis
II. Syncope
III. Seizures
IV. Metabolic disturbances: hypoglycemia, hypocalcemia, hypokalemia, hyperkalemia, hypoadrenocorticism

Treatment

I. Cataplexy is usually treated with tricyclic antidepressants or selective serotonin reuptake inhibitors (Thomas, 2003).
  A. Imipramine 0.5 to 1 mg/kg PO BID to TID
  B. Desipramine 3 mg/kg PO BID
  C. Amitriptyline 1 to 2 mg/kg PO BID
  D. Protriptyline 5 to 10 mg/kg PO SID
II. Excessive sleepiness and sleep attacks are treated with sympathomimetics or monoamine oxidase-B inhibitors.
  A. Methylphenidate 0.25 mg/kg PO BID to TID
  B. Dextroamphetamine 5 to 10 mg PO BID to TID
  C. Selegiline 1 mg/kg PO SID (Thomas, 2003)
III. If an underlying etiology is identified, treatment is directed at the cause.
IV. Side effects of medical therapy include the following:
  A. Amphetamines can cause behavioral changes.
  B. If a combination of amphetamine and imipramine is used, severe catecholamine accumulation may occur from increased release and inhibition of reuptake.

Monitoring of Animal

I. Prognosis for a good quality of life is moderate to good.
II. Some animals improve with age.
III. Lifelong therapy is often required.
IV. Lifestyle changes that decrease triggering events help to improve the quality of life.

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CHAPTER 23

Disorders of the Brain

Scott J. Schatzberg

CONGENITAL/DEVELOPMENTAL DISORDERS

Congenital Vestibular Disease

Definition and Causes

I. Dysfunction of the peripheral vestibular system is seen in young dogs and cats, possibly from a congenital defect.
II. The disorder is presumed to be inherited.
III. It has been reported in the following breeds:
  A. Dogs: Doberman pinscher, American cocker spaniel, German shepherd dog, Akita, beagle
  B. Cats: Siamese, Burmese
IV. Aggregates of lymphocytes occur within the inner ear of affected Doberman puppies, but the significance of these lesions is unclear.

Clinical Signs and Diagnosis

I. Onset of signs is usually 3 to 12 weeks of age.
II. Head tilt, vestibular ataxia, circling, and deafness may be seen.
III. Nystagmus is not a feature of this disorder.
IV. Diagnosis is one of exclusion: rule out other causes of vestibular signs.

Differential Diagnosis

I. Otitis media/interna
II. Ototoxicity: aminoglycoside antibiotics, topical antiseptics (iodophors, chlorhexidine)

Treatment and Monitoring

I. No treatment is available.
II. Compensation for the vestibular signs may occur over several weeks.
III. Deafness (if present) is typically permanent.

Hydrocephalus

Definition

I. It is an increase in the volume of cerebrospinal fluid (CSF) within the ventricular system or subarachnoid space of the brain (de Lahunta, 1983).
II. In compensatory hydrocephalus, CSF accumulates in spaces within the cranial cavity not occupied by brain parenchyma.
III. In obstructive hydrocephalus, obstruction to flow or absorption of CSF causes ventricular dilation (especially of the lateral ventricles) with subsequent loss of brain parenchyma.

Causes

I. Compensatory hydrocephalus may result from the following:
  A. Developmental malformations: cerebral hypoplasia or aplasia
  B. Destruction of brain parenchyma from in utero viral infections: feline panleukopenia
  C. Cerebral necrosis secondary to cerebrovascular accidents: acquired hydrocephalus
II. Obstructive hydrocephalus may result from the following:
  A. Fusion of rostral colliculi (midbrain) with CSF outflow obstruction at the mesencephalic aqueduct
  B. Dysfunction of the arachnoid villi with poor reabsorption of CSF through the dorsal sagittal venous sinus
III. Acquired hydrocephalus may result from the following:
  A. Mass lesions blocking CSF flow: neoplasia, abscess, granuloma
  B. Neoplasia preventing CSF absorption by the arachnoid villi
  C. Infections (viral, bacterial) or inflammation of the ependyma of the mesencephalic aqueduct or leptomeninges blocking flow of CSF
  D. Intraventricular hemorrhage blocking CSF outflow: leptomeningeal, intraventricular

Clinical Signs

I. No or variable signs may be seen, even in the presence of considerable ventricular dilatation.
II. Prosencephalic signs include disturbed consciousness (lethargy to severe depression), increased tendency to sleep, hypoactivity, propulsive circling, head pressing, seizures, behavioral changes, dementia, and visual deficits (with normal pupillary responses).
III. Motor deficits include spastic paresis, particularly if the brainstem is involved.
IV. Occasionally cerebellar ataxia may occur if there is involvement of the cerebellum.
V. Sensory deficits include proprioceptive ataxia.

Diagnosis

I. Presumptive diagnosis is based on physical examination findings.
   A. Animals with congenital hydrocephalus often have palpable open fontanelles and develop a dome-shaped calvaria.
   B. Ventral-lateral strabismus may be noted.
II. Imaging findings
   A. Skull radiographs may reveal a homogenous "ground glass" appearance within the calvaria and open cranial suture lines.
   B. Ventriculomegaly may be demonstrated by computed tomography (CT), magnetic resonance imaging (MRI), and occasionally ultrasonography.

Differential Diagnosis

I. Metabolic or toxic encephalopathies
II. Meningoencephalitis
III. Other congenital brain anomalies
IV. Degenerative encephalopathies

Treatment and Monitoring

I. Corticosteroids may decrease CSF production.
   A. Prednisone 0.25 to 0.5 mg/kg PO BID, then tapered to QOD
   B. Dexamethasone 0.05 mg/kg PO SID, then tapered to QOD
   C. May be discontinued in some dogs
II. Diuretics may decrease the volume of CSF.
   A. Furosemide 1 to 2 mg/kg PO BID
   B. Acetazolamide 0.1 mg/kg PO TID
III. Anticonvulsants may help control seizures.
   A. Phenobarbital 1 to 2 mg/kg PO BID
   B. Potassium bromide (KBr) 20 to 30 mg/kg PO SID
IV. Ventriculoperitoneal shunting of CSF to the abdominal cavity may be effective in some cases that are refractory to medical management, but complications include infections and shunt failure.
V. Prognosis is guarded to poor in severely affected animals.
VI. Animals with minimal clinical signs can often be managed long term.

Hydranencephaly and Porencephaly

Definition

I. Hydranencephaly is the congenital absence of a large portion of cerebrum in which cerebral cortex is absent and a fluid-filled, membranous sac takes its place (Summers et al., 1995).
II. Porencephaly is a disorder in which single or multiple cavities within the cerebrum usually communicate with the lateral ventricles or the subarachnoid space (Summers et al., 1995).

Causes

I. Hydranencephaly in cats is associated with in utero vaccine-induced feline panleukopenia infection.
II. Porencephaly may occur when in utero infection with feline panleukopenia virus occurs later in the period of fetal central nervous system (CNS) vulnerability, or from less virulent viruses.

Pathophysiology

I. The pathophysiology is not well understood.
II. Parvoviral destruction of cerebral tissues is one potential mechanism.
III. Hydranencephaly may arise from a fetal cerebrovascular accident that results in severe necrosis and resorption of cerebral tissue (Barone et al., 2000).

Clinical Signs

I. Signs typically occur within several weeks of birth and are proportional to the extent of cerebral loss.
II. Prosencephalic signs include blindness and behavioral abnormalities, such as compulsive behavior, indifference to surroundings, episodes of rage, and central blindness.

Diagnosis

I. Presumptive diagnosis is based on clinical signs.
II. Antemortem diagnosis can be made with MRI or CT.

Differential Diagnosis

I. Metabolic or toxic encephalopathies
II. Meningoencephalitis
III. Other congenital brain anomalies
IV. Degenerative encephalopathies

Treatment and Monitoring

I. Treatment is similar to that for hydrocephalus.
II. The prognosis is guarded to poor.

Lissencephaly and Pachygyria

Definition and Cause

I. Lissencephaly is a congenital abnormality in which the cerebral hemispheres have a smooth surface and absence of normal development of gyri and sulci (Summers et al., 1995).
II. Pachygyria is a condition in which the neocortex is much thicker than normal.
III. In most cases the cause is unknown, but lissencephaly may be genetic in the Lhasa apso.

Pathophysiology

I. The normal laminar pattern of the neuronal cell body organization is disrupted.
II. Bundles of white matter are randomly scattered throughout a thick cortex.
III. There is no development of corona radiata.

Clinical Signs

I. Lissencephaly is most commonly observed in the Lhasa apso.
II. Many dogs are difficult to house break but have relatively normal behavior.
III. Prosencephalic signs include seizures starting around 1 year of age, behavioral changes, and visual deficits.

Diagnosis

I. MRI reveals an absence of cerebral sulci and gyri, pachygyria, and decreased organization of white mater.
II. Definitive diagnosis is made by postmortem examination.

Differential Diagnosis

I. Metabolic or toxic encephalopathies
II. Meningoencephalitis
III. Other congenital brain anomalies, such as hydrocephalus
IV. Degenerative encephalopathies

Treatment and Monitoring

I. No definitive treatment exists.
II. Treat seizures symptomatically with anticonvulsants (see Chapter 22).
III. Prognosis is guarded.

CONGENITAL CEREBELLAR DISORDERS

Definition and Causes

I. These include developmental defects or malformations of the cerebellum.
II. The cause of most malformations is unknown; however, some may be genetic in origin.
III. Hypoplasia can result from in utero infections with feline and canine parvoviruses (Schatzberg et al., 2003).

Pathophysiology

I. Malformations
   A. Various forms of cerebellar agenesis and hypoplasia have been reported in dogs (Summers et al., 1995).
   B. A unique cerebellar malformation (Dandy-Walker syndrome) is characterized by a hypoplastic or aplastic cerebellum, cystic lesions of the caudal fossa or fourth ventricle, and hydrocephalus (Summers et al., 1995).
II. Hypoplasia
   A. The external germinal layer of the cerebellum is destroyed in utero by a parvovirus, with hypoplasia of the granule layer and disorganization of the Purkinje cells.
   B. Viruses or their resulting inflammation may destroy previously differentiated Purkinje neurons and cerebellar parenchyma, causing atrophy of the cerebellum (de Lahunta 1983).

Clinical Signs

I. Signs are present from the time the animal is able to walk and are usually nonprogressive.
II. Signs include a wide stance, spastic-hypermetric gait (cerebellar ataxia), loss of balance, and intention tremors.

Diagnosis

I. Presumptive diagnosis is based on clinical signs present at or soon after birth.
II. Multiple animals in the litter may be affected.
III. MRI may reveal a small cerebellum and increased amounts of CSF between the folia.
IV. Definitive diagnosis is made by postmortem examination.

Differential Diagnosis

I. Degenerative encephalopathies
II. Congenital cerebellar and abiotrophies
III. Meningoencephalitis

Treatment and Monitoring

I. No definitive treatment exists.
II. Clinical signs are typically nonprogressive.
III. Although signs persist, some animals make good pets.

Caudal Occipital Malformation and Syringohydromyelia

Definition

I. Occipital bone malformation and/or hypoplasia causes overcrowding of the caudal fossa and foramen magnum, obstruction of CSF, and syringohydromyelia.
II. Syringohydromyelia is a fluid-filled cavity within the spinal cord (syrinx) and central canal (hydromyelia).

Causes and Pathophysiology

I. Malformation of the occipital bone causes elongation and caudal displacement of the cerebellar vermis through the foramen magnum.
II. The spinal cord is pushed caudally by the medulla and may have a kinked appearance.
III. Occasionally, mild to moderate obstructive hydrocephalus is present.
IV. Syringohydromyelia may develop secondarily, but the pathogenesis is uncertain.

Clinical Signs

I. The Cavalier King Charles spaniel is overrepresented, but any breed may be affected.
II. Affected animals range in age from 6 months to 10 years.
III. Signs may manifest acutely or have an insidious course over months to years.
IV. An unusual manifestation is the observation of paroxysmal involuntary flank or neck scratching in Cavalier King Charles spaniels.
V. Spinal cord signs include cervical pain, cervical dystonia (torticollis), hyperesthesia, proprioceptive ataxia, abnormal postural reactions, varying degrees of paresis and hypermetria, and exercise intolerance.
VI. Intracranial signs include seizures and deficits of cranial nerves VII and VIII.
VII. Denervation of epaxial muscles and lesions in the dorsal tracks of the spinal cord can lead to muscle atrophy and scoliosis.

Diagnosis

I. MRI reveals varying degrees of ventriculomegaly, syringohydromyelia, compression of the cerebellum by the occipital bone, caudal displacement and herniation of the cerebellar vermis, and obstruction of the subarachnoid space at the foramen magnum.
II. CSF analysis occasionally reveals a mild elevation in nucleated cells and total protein.

Differential Diagnosis

I. Intervertebral disc disease
II. Meningoencephalitis
III. Neoplasia
IV. Atlantoaxial subluxation

Treatment and Monitoring

I. Prednisone 0.5 mg/kg PO QOD may control signs (Rusbridge et al., 2000).
II. Surgical management (subtotal occipital craniectomy, dorsal laminectomy of first cervical vertebra and durotomy to relieve obstruction) may be indicated for dogs with progressive signs (Dewey et al., 2005).
III. Prognosis is fair to good depending on the severity of clinical signs.

DEGENERATIVE DISORDERS

Neuronal Abiotrophies and Dystrophies

Definition and Causes

I. Many of these disorders (Table 23-1) are familial, hereditary, and cause degeneration of the CNS within the first few months of life (Summers et al., 1995).
II. Abiotrophies are characterized by early or premature neuronal degeneration and cell death.
    A. They are typically associated with an inherent lack of vital trophic or nutritive factors.
    B. They are categorized by the location of the affected neurons.
        1. Cerebellar abiotrophies are the most common and affect cerebellar Purkinje cells.
        2. Multisystem neuronal abiotrophies affect neurons throughout the CNS.
        3. Motor neuron abiotrophies affect motor neurons and cause lower motor neuron signs, with marked denervation atrophy and debilitating muscle contractures (arthrogryposis).
III. Neuraxonal dystrophies are a group of inherited (often autosomal recessive) disorders characterized by axonal swellings (spheroids) in preterminal portions of axons and synaptic terminals.
IV. Leukodystrophies (demyelinating disorders) are primary disorders of myelin synthesis.
    A. Leukodystrophies can involve CNS and peripheral nervous system (PNS) myelin.
    B. White matter involvement is usually regional, bilateral, and symmetrical.
V. Hypomyelinogenesis is absent, delayed, or abnormal production of myelin.
    A. Histologically, oligodendrocytes are diminished in number or may be dysfunctional.
    B. An X-linked inheritance pattern is known or suspected.
    C. Other possible causes include in utero infections or intoxications.
VI. Spongy degenerations are characterized by diffuse CNS vacuolation in the white and grey matter.
VII. Axonopathies are characterized by diffuse CNS degeneration that result predominantly in encephalomyelopathies and neuropathies.
    A. A subset of these disorders (spinocerebellar degenerations) induces bilaterally symmetrical degeneration of ascending and descending tracts of the spinal cord.
    B. Despite lesions predominantly affecting the spinal cord, progressive cerebellar signs are seen clinically.

Clinical Signs

I. With cerebellar abiotrophies, signs are noted in the first few weeks to months of life.
    A. Affected animals slowly develop progressive signs over months to years.
    B. Signs of cerebellar disease include a wide stance, spastic-hypermetric gait, loss of balance, intention tremors, and absent menace response.
II. With neuraxonal dystrophies signs of spinal cord and cerebellar dysfunction occur.
    A. Lesions occur diffusely throughout the CNS, but spinal cord lesions predominate.
    B. Affected breeds include the rottweiler, Chihuahua, German shepherd dog, and domestic short-haired cat.
III. Hypomyelinating disorders are characterized by generalized tremors, especially in the pelvic limbs.
    A. They often abate with rest.
    B. Signs may resolve spontaneously or persist indefinitely.

Diagnosis

I. Diagnosis is suspected based on the signalment and clinical signs (see Table 23-1).
II. MRI may be useful to demonstrate the distribution of lesions.
III. Definitive diagnosis often requires postmortem examination.

Differential Diagnosis

I. Disorders of intermediary metabolism
II. Metabolic disorders
III. Meningoencephalitis
IV. Neoplasia

Treatment and Monitoring

I. No definitive treatment exists for these degenerative disorders.
II. Prognosis is variable and often poor for long-term survival.

DISORDERS OF INTERMEDIARY METABOLISM

Definition and Causes

I. These disorders are caused by inherited errors in intermediary metabolism that arise from abnormal or deficient enzyme systems (Summers et al.,1995).
II. Some disorders are storage diseases.

TABLE 23-1

Breed-Associated Degenerative Disorders of the Brain

BREEDS	DISEASE	ONSET AND CLINICAL SIGNS	DIAGNOSIS
Cats			
Birman cat	Distal central-peripheral axonopathy	8-10 months; hypermetria, progressive paraparesis, plantigrade pelvic limb posture	Nerve biopsy
	Spongiform encephalopathy	7 weeks; hypermetria, paraparesis, depression	Histopathology
Domestic short-haired cat	Neuraxonal dystrophy	5-6 weeks; head tremors, ataxia, hypermetria	Histopathology
Egyptian mau	Spongiform encephalopathy	7 weeks; hypermetria, paraparesis, depression	Histopathology
Dogs			
Airedale terrier	Cerebellar degeneration	Cerebellar signs*	Histopathology
	Cerebellar hypoplasia	Cerebellar signs	Histopathology, MRI
Akita	Cerebellar abiotrophy	Cerebellar signs	Histopathology, MRI
American cocker spaniel	Neuronal degeneration	10-14 months; behavior and personality changes, absent menace response, variable hypermetria and falling	Histopathology
	Cerebellar signs	1-2 months; cerebellar signs that may stabilize by 12 months	Histopathology
	Neuraxonal dystrophy	2-4 months; hypermetria, ataxia, intention tremor	Histopathology
Australian kelpie	Cerebellar abiotrophy	6-12 weeks; cerebellar signs	Histopathology, MRI
Beagle	Cerebellar abiotrophy	3 weeks; cerebellar signs	Histopathology, MRI
Bernese mountain dog	Hypomyelination	2-8 weeks; fine tremor of the head and limbs, weakness, stiffness; may improve with age	Histopathology, MRI
Border collie	Cerebellar abiotrophy	6-8 weeks; cerebellar signs	Histopathology, MRI
Boxer	Progressive axonopathy	2 months; progressive ataxia and weakness; diminished proprioception, muscle tone, patellar reflexes; intact nociception	EMG and nerve conduction studies, nerve biopsy, histopathology
Brittany spaniel	Cerebellar abiotrophy	7-13 years; progressive cerebellar signs	Histopathology, MRI
Bullmastiff	Cerebellar abiotrophy	4-9 weeks; progressive cerebellar signs	Histopathology, MRI
	Spongiosis of gray matter	6-9 weeks; ataxia, hypermetria, intention tremor, decreased menace response, visual deficits, poor proprioception	Histopathology
Bull terrier	Cerebellar abiotrophy	Cerebellar signs	Histopathology, MRI
Cairn terrier	Cerebellar abiotrophy	Cerebellar signs	Histopathology, MRI
	Multifocal neuronal degeneration	4-7 months; progressive tetraparesis, cataplexy, cerebellar dysfunction	Histopathology
Chow chow	Hypomyelination	2-4 weeks; intention tremors, dysmetria, bunny hopping, improves after 1 year	Histopathology, MRI
Dalmatian	Leukodystrophy	3-6 months; visual deficits, progressive ataxia	Histopathology
English springer spaniel	Hypomyelination	1-2 weeks; severe tremors	Histopathology, MRI
Finnish harrier	Cerebellar abiotrophy	Cerebellar signs	Histopathology, MRI
Gordon setter	Cerebellar abiotrophy	6-30 months; slowly progressive cerebellar and vestibular signs	Histopathology, MRI
Jack Russell terrier	Spinocerebellar degeneration	2-4 months; cerebellar ataxia, progressive dysmetria and spasticity	Histopathology
Kerry blue terrier	Cerebellar abiotrophy	8-16 weeks; pelvic limb stiffness and head tremors, then dysmetria	Histopathology, MRI

Adapted with permission from Platt RS, Olby N: BSAVA Manual of Canine and Feline Neurology. 3rd Ed. British Small Animal Veterinary Association, Quedgeley, England 2004.

MRI, Magnetic resonance imaging; *EMG*, electromyography.

*Cerebellar ataxia (dysmetria, hypermetria), intention tremors of the head, wide based stance, and occasionally lack of menace with normal vision.

Continued

TABLE 23-1

Breed-Associated Degenerative Disorders of the Brain—*cont'd*

BREEDS	DISEASE	ONSET AND CLINICAL SIGNS	DIAGNOSIS
Labrador retriever	Cerebellar abiotrophy	12 weeks; cerebellar signs	Histopathology, MRI
	Axonopathy	Birth; crouched, short-strided gait in thoracic limbs, hypermetria, unable to stand by 5 months	Histopathology
Old English sheepdog	Cerebellar abiotrophy	Progressive cerebellar signs	Histopathology, MRI
Papillon	Neuroaxonal dystrophy	14 weeks; rapidly progressive ataxia and hypermetria, decreased postural reactions	Histopathology
Poodle	Cerebellar abiotrophy	Cerebellar signs	Histopathology, MRI
Rottweiler	Spongiform degeneration with encephalomyelopathy and polyneuropathy	6-16 weeks; progressive ataxia and dysmetria, laryngeal paralysis, congenital cataracts, microphthalmia	Histopathology
	Leukoencephalopathy	1-4 years; ataxia, tetraparesis, hypermetria, increased muscle tone/spinal reflexes, often more severe in thoracic limbs	Histopathology
	Neuraxonal dystrophy	Within 12 months; slowly progressive ataxia, hypermetria, wide-based stance, eventually intention tremors and nystagmus	Histopathology
Rough-coated collie	Cerebellar abiotrophy	4-8 weeks; progressive cerebellar signs	Histopathology, MRI
Saluki	Spongiosis of gray matter	Behavior changes, seizures, aimless wondering electroencephalography	Histopathology
Samoyed	Hypomyelination	3 weeks; generalized tremors, nystagmus, absent menace response	Histopathology, possibly MRI
	Cerebellar abiotrophy	Cerebellar signs	Histopathology, MRI
Shetland sheepdog	Hypomyelination	2-4 weeks; severe generalized tremors, difficulty standing, seizures, progressive debilitation	Histopathology, MRI
Weimaraner	Hypomyelination	3 weeks; generalized tremors, dysmetria; several dogs normal by 12 months	Histopathology, MRI

Pathophysiology

I. Storage disorders are characterized by defective lysosomal enzymes that are catabolic or obligatory to cellular processes (Skelly and Franklin, 2002).
   A. Loss or dysfunction of a degradative enzyme results in the accumulation of specific substrates in the lysosomes that distend cells with stored products.
   B. Lesions may be multisystemic or limited to the CNS and/or PNS.
   C. Most storage diseases are autosomal recessive traits (Table 23-2).

II. Disorders of intermediary metabolism affect enzyme systems that are not catabolic and do not result in stored substrate.
   A. They typically result in a unique, degenerative encephalopathy.
   B. Most are breed specific, with an autosomal recessive mode of inheritance (see Table 23-2).

Clinical Signs

I. Signs often reflect diffuse CNS involvement; however, cerebellar signs often predominate in storage diseases.
II. See Table 23-2 for specific signs.

Diagnosis

I. Diagnosis is often suspected based on signalment and clinical signs.
II. DNA testing is available for some disorders (see Table 23-2).
III. Diagnosis can be made through metabolite analysis of tissues or body fluids (urine or blood).

Differential Diagnosis

I. Congenital cerebellar disorders or cerebellar abiotrophy (storage disorders)
II. Meningoencephalitis
III. Neoplasia
IV. Other degenerative encephalopathies

TABLE 23-2

Disorders of Intermediary Metabolism (Storage Diseases)

BREEDS	DISEASE	ONSET AND CLINICAL SIGNS	DIAGNOSIS
Cats			
Balinese cat	Niemann-Pick type A	Cerebellar/vestibular signs, depression, peripheral neuropathy	Enzyme assay in leukocytes, cultured fibroblasts
Domestic short-haired cat	Mannosidosis	Onset <6 months; connective tissue and skeletal malformation, possible peripheral neuropathy	DNA testing*
	GM_1 gangliosidosis	Cerebellar signs, dwarfism, facial dysmorphism	Oligosaccharide analysis in urine* Enzyme assay in skin fibroblasts, liver, leukocytes
	GM_2 gangliosidosis	Cerebellar/vestibular signs	Oligosaccharide analysis in urine* Enzyme assay in skin fibroblasts, liver, leukocytes
	Globoid cell leukodystrophy (Krabbe's disease)	Early cerebellar signs and ascending paralysis, cerebellar signs later or peripheral neuropathy	DNA testing† Peripheral nerve biopsy suggestive Enzyme assay in leukocytes, cultured fibroblasts
	Niemann-Pick type C	Ataxia, cerebellar/vestibular signs, peripheral neuropathy, possible hepatomegaly	Enzyme assay in leukocytes or cultured fibroblasts
	MPS VII	Progressive paraparesis	Urine metabolite screening*
	Mucolipidosis II (I-cell disease)	Dysmorphism, failure to thrive, delayed skeletal mineralization and abnormalities, retinal degeneration at 2.5 months of age	Inclusions in cultured fibroblasts, serum lysosomal enzyme assay
Korat cat	GM_2 gangliosidosis	Cerebellar/vestibular signs	Oligosaccharide analysis in urine* Enzyme assay in skin fibroblasts, liver, leukocytes
Norwegian forest cat	Glycogenosis	Incoordination, exercise intolerance	DNA testing*
Persian	Mannosidosis	Onset at 8 weeks; connective tissue and skeletal malformation, possible peripheral neuropathy	DNA testing* Oligosaccharide analysis in urine
Siamese	GM_1 gangliosidosis	Cerebellar signs, dwarfism, facial dysmorphism	Oligosaccharide analysis in urine* Enzyme assay in skin fibroblasts, liver, leukocytes
	Niemann-Pick type A	Cerebellar/vestibular signs, depression, peripheral neuropathy	Enzyme assay in leukocytes and cultured fibroblasts
	MPS VI	Dysmorphism, paraparesis from spinal abnormalities	DNA testing* Urine metabolite screening*
Dogs			
Akita	Glycogenosis (type III)	Muscular weakness, hepatomegaly	Liver, muscle, nervous system pathology
Bassett hound	Lafora's Disease	Myoclonic epilepsy	Intracytoplasmic PAS-positive inclusions in muscle biopsy
Beagle	GM_1 gangliosidosis	Cerebellar signs, dwarfism, facial dysmorphism	Oligosaccharide analysis in urine* Enzyme assay in skin biopsy fibroblasts, liver leukocytes
	Lafora's Disease	Myoclonic epilepsy	Intracytoplasmic PAS-positive inclusions in muscle biopsy

Adapted with permission from Platt RS, Olby N: BSAVA Manual of Canine and Feline Neurology. 3rd Ed. British Small Animal Veterinary Association, Quedgeley, England, 2004.

DNA, Deoxyribonucleic acid; *MPS,* mucopolysaccharidosis; *PAS*, periodic acid Schiff.

*DNA testing, oligosaccharide analysis, organic acid and metabolite screening in the urine, and serum lysosomal enzyme assays are performed by PennGenn/Section of Medical Genetics, Veterinary Hospital 4006, University of Pennsylvania, 3900 Delancey Street, Philadelphia, PA 19104.

†Lysosomal Diseases Testing Laboratory, Jefferson Medical College, Department of Neurology, 1020 Locust Street, Room 394, Philadelphia, PA 19107.

Continued

TABLE 23-2

Disorders of Intermediary Metabolism (Storage Diseases)—*cont'd*

BREEDS	DISEASE	ONSET AND CLINICAL SIGNS	DIAGNOSIS
Dogs—*cont'd*			
Beagle—*cont'd*	Globoid cell leukodystrophy (Krabbe's disease)	Early cerebellar signs and ascending paralysis, cerebellar signs later or periheral neuropathy	DNA testing† Peripheral nerve biopsy suggestive Enzyme assay in leukocytes, cultured fibroblasts
Border collie	Ceroid lipofuscinosis	Adult and juvenile forms Ataxia, seizures, progressive blindness (central ± retinal)	Lipopigment in skin biopsy
Boxer	Niemann-Pick type C	Ataxia, cerebellar/vestibular signs, peripheral neuropathy, possible hepatomegaly	Enzyme assay in leukocytes, cultured fibroblasts
Cairn terrier	Globoid cell leukodystrophy (Krabbe's disease)	Early cerebellar signs and ascending paralysis, cerebellar signs later or peripheral neuropathy	DNA testing† Peripheral nerve biopsy suggestive Enzyme assay in leukocytes, cultured fibroblasts
Dachshund	Lafora's Disease	Myoclonic epilepsy	Intracytoplasmic PAS-positive inclusions in muscle biopsy
	Ceroid lipofuscinosis	Ataxia, seizures, progressive blindness (central ± retinal) Adult and juvenile forms	Lipopigment in skin biopsy
Dashshund, wire-hired	MPS III-A	Ataxia, intention tremor, dysuria	Urine metabolite screening*
English setter	Ceroid lipofuscinosis	Ataxia, seizures, progressive blindness (cental ± retinal) Adult and juvenile forms	Lipopigment in skin biopsy
English springer spaniel	Fucosidosis	Onset at 1-4 years; cerebral signs	DNA testing to detect carrier or affected dogs*
	GM_1 gangliosidosis	Cerebellar signs, dwarfism, facial dysmorphism	Oligosaccharide analysis in urine* Enzyme assay in skin fibroblasts, liver, leukocytes
	Glycogenosis	Incoordination, exercise intolerance	Liver, muscle, nervous system pathology
German shepherd dog	Glycogenosis (type III)	Muscular weakness, hepatomegaly	Liver, muscle, nervous system pathology
German short-haired pointer	GM_2 gangliosidosis	Cerebellar/vestibular signs	Oligosaccharide analysis in urine* Enzyme assay in skin fibroblasts, leukocytes
Irish setter	Globoid cell leukodystrophy (Krabbe's disease)	Early cerebellar signs and ascending paralysis, cerebellar signs later or peripheral neuropathy	DNA testing† Peripheral nerve biopsy suggestive Enzyme assay in leukocytes, cultured, fibroblasts
Japanese spaniel	GM_2 gangliosidosis	Cerebellar/vestibular signs	Oligosaccharide analysis in urine* Enzyme assay in skin fibroblasts, liver, leukocytes
Labrador retriever	MPS II	Incoordination, exercise intolerance, visual deficits	Urine metabolite screening*
Lapland dog	Glycogenosis (type II)	Muscle weakness, vomiting, megaesophagus, cardiac and respiratory abnormalities	Liver, muscle, nervous system pathology, EMG abnormalities
Maltese	Malonic aciduria	Seizures, stupor	Organic acid screening*
Miniature pinscher	MPS VI	Dysmorphism, paraparesis from spinal abnormalities	DNA testing* Urine metabolite screening*
Mix-breed dogs	MPS VII	Pelvic limb weakness, joint laxity, atrioventricular valve incompetence	DNA testing* Urine metabolite screening*

EMG, Electromyography.

TABLE 23-2

Disorders of Intermediary Metabolism (Storage Diseases)—*cont'd*

BREEDS	DISEASE	ONSET AND CLINICAL SIGNS	DIAGNOSIS
Dogs—*cont'd*			
Plott hound	MPS I	Dysmorphism, paraparesis from spinal abnomalities	Urine metabolite screening*
Poodle	Globoid cell leukodystrophy (Krabbe's disease)	Early cerebellar signs and ascending paralysis, cerebellar signs later or peripheral neuropathy	DNA testing† Peripheral nerve biopsy suggestive Enzyme assay in leukocytes, cultured fibroblasts
Portuguese water dog	GM_1 gangliosidosis	Cerebellar signs, dwarfism, facial dysmorphism	Oligosaccharide analysis in urine* Enzyme assay in skin fibroblasts, liver, leukocytes
Siberian husky	GM_1 gangliosidosis	Cerebellar signs, dwarfism, facial dysmorphism	Oligosaccharide analysis in urine* Enzyme assay in skin fibroblasts, liver, leukocytes
Silky terrier	Glucocerebrosidosis (Gaucher disease)	Onset at 4-10 months; cerebellar signs, ataxia, seizures, dementia	Enzyme assay (β-glucosidase) in leukocytes
Staffordshire bull terrier	L-2-hydroxyglutaric aciduria	Onset at 6-8 months; ataxia, hypermetria	Urine organic acid screening*
Sydney silky dog	Glucocerebrosidosis (Gaucher disease)	Ataxia, seizures, progressive blindness (central ± retinal) Adult and juvenile forms	Enzyme assay in leukocytes, cultured fibroblasts
Tibetan terrier	Ceroid lipofuscinosis	Early cerebellar signs and ascending paralysis; late cerebellar signs or peripheral neuropathy	Lipopigment in skin biopsy
West highland white terrier	Globoid cell leukodystrophy (Krabbe's disease)	Ataxia, intention tremor	DNA testing† Peripheral nerve biopsy suggestive Enzyme assay in leukocytes, cultured fibroblasts

Treatment and Monitoring

I. Definitive treatment does not exist.
II. Prognosis is variable and often poor for long-term survival.

INFECTIOUS DISORDERS

Rickettsial Meningoencephalitis

Definition and Causes

I. Rickettsial disorders that can infect the brain include Rocky Mountain spotted fever *(Rickettsia rickettsii),* ehrlichiosis, and salmon poisoning (Greene, 2006).
II. Rocky Mountain spotted fever is transmitted by *Dermacentor andersoni*, *Dermacentor variabilis,* and *Amblyomma americanum* ticks.
III. Canine ehrlichiosis *(Ehrlichia canis)* is transmitted by the brown dog tick, *Rhipicephalus sanguineus.*
IV. Salmon poisoning *(Neorickettsia helminthoeca)* is acquired by consumption of salmonid and other fish that carry the metacercaria of the fluke, *Nanophyetus salmincola,* which is the intermediate host.

Clinical Signs

I. Signs arise from a nonsuppurative meningoencephalitis composed mostly of plasma cells.
II. See Chapter 115 for systemic signs.
III. Neurological signs reflect diffuse brain involvement.

Diagnosis

I. CSF analysis reveals a mononuclear pleocytosis, with mild to moderate elevations in protein content.
II. A complete blood count (CBC) may reveal thrombocytopenia, anemia, and leukopenia early in the course, followed by leukocytosis.
III. Intracytoplasmic ehrlichia morulae are occasionally identified in blood and CSF mononuclear cells.
IV. Definitive diagnosis is based on elevated serum titers, a four-fold rise in antibody titer, or positive polymerase chain reaction (PCR) assays (see Chapters 2 and 115).

Differential Diagnosis

I. Immune-mediated, noninfectious meningoencephalitis
II. Other CNS infections
III. CNS neoplasia: lymphoma, metastatic neoplasia

Treatment and Monitoring

I. Doxycycline is given 5 to 10 mg/kg PO BID for 2 to 3 weeks.
   A. Antibiotics may be effective if initiated early in disease course.
   B. Dogs may respond dramatically within 1 to 2 days, but prognosis is guarded to poor when severe neurological deficits are present.
II. Recovery may be prolonged, and residual neurological deficits are possible.

Mycotic and Algal Infections

Definition and Causes

I. Most mycotic infections are regional diseases that produce pyogranulomatous inflammation of the CNS and are treated similarly (Lavely and Lipsitz, 2005).
   A. Mycoses that may affect the CNS include *Cryptococcus ghatti*, *Blastomyces dermatitidis*, *Histoplasma capsulatum, Coccidioides immitis, Aspergillus* spp., phaeohyphomycosis, and hyalohyphomycosis.
   B. *Cryptococcus neoformans* may be the most common CNS mycotic infection.
II. Protothecosis is a rare CNS infection of dogs caused by the achlorophyllous algae, *Prototheca wickerhamii* and *Prototheca zopfii*.

Pathophysiology

I. Cryptococcosis is typically acquired from the environment (e.g., pigeon droppings, dead trees) rather than directly from infected animals.
II. The natural route of these infections is thought to be via the respiratory tract, with subsequent hematogenous and lymphogenous dissemination.

Clinical Signs

I. Clinical signs may reflect a focal mass lesion or a diffuse, multifocal process.
II. Signs also reflect the location of the lesions within the CNS and are variable.
III. A profound elevation in intracranial pressure may cause severe changes in mentation (depression, stupor, coma).
IV. Ocular and nasal discharge may be noted.
V. See Chapter 111 for systemic signs.

Diagnosis

I. Diagnosis of cryptococcosis utilizes the latex agglutination test (LAT), which detects capsular antigen in serum, urine, or CSF.
II. Serological testing for other agents is described in Chapters 2 and 111.
III. CSF analysis sometimes reveals cryptococcal organisms by staining with India ink.
   A. Mononuclear, neutrophilic, or eosinophilic pleocytosis, and elevated protein levels are often present.
   B. Fungal culture of CSF is usually unrewarding.
IV. MRI may show multiple inflammatory lesions that are hypointense on T1-weighted images and hyperintense on T2-weighted images, with multifocal parenchymal and leptomeningeal enhancement.

Differential Diagnosis

I. Immune-mediated, noninfectious meningoencephalitis
II. Other CNS infections
III. CNS neoplasia: lymphoma, metastatic neoplasia

Treatment and Monitoring

I. Amphotericin B may be given at 0.1 to 0.5 mg/kg IV, SC three times weekly.
   A. Animals treated with amphotericin B require weekly assessment of renal function, and it is contraindicated in animals with renal dysfunction.
   B. Liposome encapsulated preparations may be safer.
II. Imidazole drugs may be tried alone or in conjunction with amphotericin.
   A. Fluconazole 5 to 15 mg/kg PO BID (preferred)
   B. Itraconazole 5 to 10 mg/kg PO BID
III. For cryptococcosis, the LAT is monitored monthly during treatment.
   A. Treatment is discontinued after two negative LAT tests are documented 1 month apart or 1 month after resolution of clinical signs.
   B. Treatment is often prolonged (3 to 12 months).
   C. Prognosis is guarded, especially for disseminated disease.

Canine Distemper Encephalomyelitis

Definition and Cause

I. Canine distemper virus is a multisystemic disease affecting the respiratory, alimentary, urogenital, ocular, and nervous systems in dogs.
II. It is an RNA Morbillivirus of the family Paramyxoviridae.

Pathophysiology

I. Several forms and stages of CNS disease exist (Summers et al., 1995).
II. Lymphocytic meningoencephalomyelitis occurs during the first week of exposure.
   A. No neurological signs are seen during this phase.
   B. Infection may be self-limiting or may progress to affect either grey or white matter (more commonly).
III. Grey matter disease occurs approximately 1 week after initial infection.
   A. Typical sites of infection include the cerebral cortex, brainstem, and spinal cord.
   B. Grey matter disease typically occurs in puppies at 6 to 12 weeks of age; certain viral strains may cause disease in adult dogs.
   C. Postvaccinal disease (inadequately attenuated virus) can occur 7 to 10 days after vaccination and may result in severe brainstem lesions and death.
   D. Old-dog encephalitis is a rare, chronic form of the disease.
   E. Pathologic lesions include neuronal degeneration, gliosis, and eosinophilic inclusions in neurons and glial cells.

IV. White matter disease is the most common form of infection and occurs approximately 1 month after initial infection.
  A. Demyelination is the hallmark finding.
  B. Lesions occur in sites that are adjacent to CSF pathways (optic tracts, hippocampus, cerebellar peduncles, spinal cord).
  C. White matter lesions may be noninflammatory for 1 month, then progress to nonsuppurative meningitis and perivascular encephalitis.
  D. Inflammatory lesions ultimately become necrotizing.
  E. Eosinophilic inclusions can be observed in glial cells.

Clinical Signs

I. With grey matter disease, signs reflect nonsuppurative meningitis.
  A. Seizures, stupor, hysteria, and ataxia can be observed.
  B. Dogs may die within 2 to 3 weeks, recover, or develop white matter disease.
II. With white matter disease, signs are multifocal and variable.
  A. Commonly observed signs include cerebellovestibular ataxia and spinal cord paresis.
  B. Occasionally myoclonus develops of a single limb or the temporalis and/or masseter muscles.
  C. Some dogs die 4 to 5 weeks after initial infection, and some may recover with minimal CNS injury.
  D. Other dogs may have persistent CNS demyelination and nonsuppurative inflammation, with or without clinical signs.

Diagnosis

I. Presumptive diagnosis is based on history, signalment, vaccination status, and clinical signs, especially in nonvaccinated dogs.
II. Immunofluorescent or immunocytochemical techniques can detect canine distemper viral antigen in brain sections and other tissues (mononuclear cells in blood, conjunctival or tracheal washes, foot pad biopsies).
III. CSF analysis reveals moderate pleocytosis of mononuclear cells (lymphocytes, macrophages).
  A. Neutralizing antibody in CSF develops 2 to 3 weeks after onset of disease.
  B. The immunoglobulin G (IgG) index (calculated quotient of IgG and albumin levels in CSF compared to serum that detects intrathecal IgG synthesis) is elevated in most dogs except those with acute, noninflammatory distemper.
IV. Reverse transcriptase PCR of urine, CSF, and conjunctival swabs may identify the virus.

Differential Diagnosis

I. Affected puppies: congenital and developmental diseases
II. Immune-mediated or noninfectious meningoencephalitis
III. Other causes of infectious meningoencephalitis: bacteria, parasites, protozoa, rickettsia
IV. Other viral CNS infections
  A. Borna disease (staggering disease), LaCrosse virus
  B. Canine herpesvirus
  C. Rabies
  D. Tickborne encephalitis virus
  E. Eastern equine encephalitis virus
  F. West Nile virus
V. CNS neoplasia: lymphoma, metastatic disease

Treatment and Monitoring

I. No definitive treatment exists for the virus.
II. Treatment is largely supportive (fluid therapy, nutritional support).
III. Euthanasia is considered for dogs with progressive neurological signs that lead to incapacitation.

Feline Infectious Peritonitis Meningoencephalitis

Definition and Cause

I. Feline infectious peritonitis (FIP) is a fatal, systemic immunopathologic disease caused by a feline coronavirus.
II. Although meningitis may accompany the more acute form of peritoneal exudation, a second form affects the CNS and eye with little or no peritoneal involvement (Foley et al., 1998).

Pathophysiology

I. The underlying pathogenesis involves a type III immune reaction and immune complex-induced vasculitis.
II. This CNS infection is characterized by meningitis, ependymitis, and encephalomyelitis (Summers et al., 1995).
III. The mesencephalic aqueduct may be obstructed, causing hydrocephalus and hydromyelia.
IV. Focal brain or spinal cord lesions may also occur.

Clinical Signs

I. Signs are usually nonspecific, but often include profound cerebellovestibular involvement.
II. Signs from focal lesions reflect the site of the lesion.
III. See Chapter 112 for systemic signs.

Diagnosis

I. Antemortem diagnosis is very challenging.
II. CSF analysis reveals profound neutrophilic or mononuclear pleocytosis, with high elevations of protein.
III. Identification of antibody titers in CSF is supportive.
IV. Serum titers are difficult to interpret (see Chapter 112).
V. Serum hypergammaglobulinemia and increased fibrinogen levels may occur.
VI. MRI may show marked dilation of the ventricular system and enhancement of ependymal (periventricular) surfaces and the choroid plexus.
VII. Definitive diagnosis requires histopathology.

Differential Diagnosis

I. Congenital or developmental diseases
II. CNS neoplasia: lymphosarcoma
III. Other viral diseases: feline immunodeficiency virus, Borna disease

IV. Bacterial meningoencephalitis
V. Toxoplasmosis

Treatment and Monitoring

I. Because no definitive treatment exists, supportive care (fluid therapy, nutritional support) may be tried.
II. Prednisone 2 to 4 mg/kg PO SID to BID may provide palliative relief.
III. The prognosis is grave for long-term survival.

Bacterial Meningoencephalitis

Definition and Causes

I. It is inflammation of the brain and/or meninges from aerobic or anaerobic bacterial infections.
II. Organisms that can infect the CNS include *Pasteurella, Staphylococcus, Actinomyces, Nocardia, Streptococcus,* and *Klebsiella* spp., and *Eschericia coli*.

Pathophysiology

I. A variety of mechanisms allow bacterial entry into the CNS.
   A. Hematogenous spread from distant foci: lung abscess, vegetative endocarditis, urinary tract infection
   B. Direct extension from nasal and paranasal sinuses, ears, and eyes
   C. Secondary to trauma and wound contamination (bite wound)
   D. Meningeal spread along nerve roots
   E. Contaminated surgical instruments: spinal needles
II. Organisms usually disseminate through CSF pathways and produce meningitis and microabscesses of the brain and spinal cord.
III. Formation of inflammatory cytokines and tumor necrosis factor by monocytes and neural cells leads to altered blood-brain barrier permeability, recruitment of neutrophils, and purulent exudates in the subarachnoid space.
IV. Vasculitis leads to vasogenic brain edema.
V. Toxic oxygen metabolites released from degranulating leukocytes also cause cytotoxic brain edema.

Clinical Signs

I. Clinical signs begin acutely.
II. Systemic signs include fever, vomiting, bradycardia, anorexia, shock, and hypotension.
III. Neurological signs consist of hyperesthesia, cervical pain and rigidity (common), seizures (occasionally), and cranial nerve deficits (Radaelli and Platt, 2002).

Diagnosis

I. CSF analysis typically shows a profound neutrophilic pleocytosis and protein elevation.
   A. Organisms sometimes may be seen on CSF cytology.
   B. Bacterial culture of CSF (aerobic and anaerobic) provides a definitive diagnosis, but negative cultures do not rule out the disease.
II. Blood and urine cultures may yield a pathogenic organism.
III. A CBC may reveal a neutrophilic leukocytosis and left shift.
IV. MRI and CT can show meningeal, brain and/or ventricular enhancement, as well as abscessation.

Differential Diagnosis

I. Immune-mediated meningoencephalitis, especially steroid-responsive meningitis/arteritis
II. Intervertebral disc disease
III. Other CNS infections
IV. CNS neoplasia: lymphoma, metastatic neoplasia
V. Systemic bacterial infections

Treatment and Monitoring

I. Preferred antibiotic therapy is based on culture results and is continued for several weeks after clinical signs have resolved.
II. Empirical treatment choices in dogs are as follows:
   A. Chloramphenicol 50 mg/kg IV, IM, SC, PO BID
   B. Metronidazole 10 to 15 mg/kg PO TID
   C. Enrofloxacin 10 mg/kg IV, PO SID
   D. Azithromycin 5 to 10 mg/kg PO SID
   E. Trimethoprim-sulfonamide 15 to 30 mg/kg PO BID
III. Corticosteroids are generally contraindicated, but anti-inflammatory doses may be beneficial upon initiation of treatment.
IV. Prognosis is guarded.
   A. Death is common even if appropriate therapy is administered.
   B. Relapses are frequently encountered.

Toxoplasmosis

Definition and Cause

I. Toxoplasmosis may be the most common protozoa to affect the CNS in dogs and cats.
II. The causative agent is *Toxoplasma gondii.*

Pathophysiology

I. Organisms may form cysts in the CNS and in the skeletal and heart muscles.
II. Parasites are mainly intracellular, and subclinical infection may persist for life.
III. Activation may occur with severe immunosuppression, especially from viral infections.
IV. Nonsuppurative (focal or multifocal) necrotizing meningoencephalomyelitis occurs in the CNS, whereas radiculitis and myositis develop in the PNS.
V. Chorioretinitis commonly accompanies CNS lesions.
VI. Lesions may also occur in lungs, liver, spleen, and lymph nodes.

Clinical Signs

I. The disease most commonly affects animals <1 year of age or animals that are immunocompromised.
II. Clinical signs relate to either focal (granulomas) or multifocal CNS disease.

III. Possible signs include hyperexcitability, depression, intention tremors, paresis, paralysis, head tilt, and seizures.
IV. Spinal cord signs are more common in cats.
V. See Chapter 116 for systemic signs.

Diagnosis

I. Definitive diagnosis is often difficult to establish (see Chapter 116).
II. CSF analysis may demonstrate a mononuclear, neutrophilic, or eosinophilic pleocytosis, with elevated protein levels.
III. PCR may reveal the presence of the organism in CSF, muscle, or liver biopsies.
IV. Electromyography (EMG) may show abnormal spontaneous activity in animals with muscle and nerve involvement, and nerve conduction velocities may be decreased in animals with nerve involvement.
V. MRI or CT may reveal focal or multifocal CNS lesions.

Differential Diagnosis

I. Dogs
  A. *Neospora caninum*
    1. Most often affects dogs <2 years of age
    2. Predilection for lumbosacral nerve roots (radiculitis, neuritis, see Chapter 24)
    3. May cause encephalitis (especially cerebellitis) in adult dogs
  B. Sarcocystosis, encephalitozoonosis, trypanosomiasis
  C. Acanthamebiasis, babesiosis
  D. Leishmaniasis
  E. Autoimmune, bacterial, viral meningoencephalitis
  F. Neoplasia: lymphosarcoma, histiocytic tumors
II. Cats
  A. FIP
  B. Neoplasia: lymphosarcoma
  C. Borna disease
  D. Bacterial meningoencephalitis

Treatment and Monitoring

I. Clindamycin is the drug of choice and is given at 10 to 20 mg/kg PO, IM BID for 3 to 6 weeks.
II. Alternatively, trimethoprim-sulfonamide (15 to 20 mg/kg PO BID) is combined with pyrimethamine at 1 mg/kg PO SID for 4 to 8 weeks.
III. Prognosis is guarded with CNS involvement, but some animals survive with minimal residual neurological deficits.

NONINFECTIOUS INFLAMMATORY DISORDERS

Granulomatous Meningoencephalomyelitis

Definition and Cause

I. Granulomatous meningoencephalomyelitis (GME) is an idiopathic (mononuclear) meningoencephalomyelitis that most commonly occurs in young to middle-age dogs.
II. GME is thought to be an immune-mediated (delayed-type hypersensitivity) disease based on the presence of major histocompatibility complex class II and cluster differentiation (CD3) antigen-positive lymphocytes (Kipar et al., 1998).

Pathophysiology

I. Three morphological forms exist, namely disseminated, focal, and ocular disease (Summers et al., 1995).
II. Lesions consist of perivascular, concentric proliferations of inflammatory cells predominantly in the white matter.
III. Perivascular cellular accumulations consist of lymphocytes, plasma cells, and mononuclear cells.

Clinical Signs

I. Onset ranges from 9 months to 10 years of age.
II. Signs may be acute, rapidly progressive and fatal, or chronic and insidious.
III. The focal form of GME results in focal deficits, whereas the disseminated form causes multifocal signs.
IV. Neurological signs reflect lesion location and distribution.
  A. Brainstem (varying degrees of depression and spastic tetraparesis, vestibular ataxia, head tilt, abnormal nystagmus) and cerebellar signs are most common.
  B. Prosencephalic signs include seizures, depression, circling, and visual deficits.
  C. The ocular form causes visual deficits, anisocoria, and abnormalities in pupillary light reflexes.
V. A fever is often present.

Diagnosis

I. The CSF usually reveals a mild to severe pleocytosis of monocytes and lymphocytes, with mild protein elevation.
II. MRI and CT may reveal multifocal lesions, predominantly in the white matter of the CNS.
III. Definitive diagnosis requires histopathology.

Differential Diagnosis

I. Necrotizing meningoencephalitis
II. Necrotizing leukoencephalitis
III. Infectious meningoencephalitis
IV. CNS neoplasia: lymphoma, metastatic neoplasia

Treatment and Monitoring

I. Immunosuppression is the primary therapy.
II. Prednisone is given at 1.0 to 3.0 mg/kg PO BID for 1 month, then gradually tapered over several months to 0.5 mg/kg PO SID to QOD.
III. Additional drugs may allow a reduction in prednisone and ameliorate its side effects.
  A. Cytosine arabinoside 50 mg/m^2 SC BID for 2 days, repeated every 3 weeks (Zarfoss et al., 2006)
  B. Cyclosporine 5 to 10 mg/kg PO BID (Adamo and O'Brien, 2004)
  C. Others: leflunomide, procarbazine, CCNU (lomustine)
IV. Radiation therapy may be beneficial for the focal form.
V. GME is rarely cured and often requires lifelong therapy to control the inflammation.

Necrotizing Meningoencephalitis

Definition and Cause

I. It is an idiopathic meningoencephalitis of young pugs, Maltese, Shih tzus, and occasionally other small-breed dogs (Cordy and Holliday, 1989; Stalis et al., 1995).
II. It is presumed to be an immune-mediated disease.

Pathophysiology

I. Lesions consist of nonsuppurative meningoencephalitis and mild cerebral necrosis.
II. It typically affects the cerebral hemispheres, with inflammation extending from the leptomeninges through the cortex and into the corona radiata.
III. This pattern leads to a loss of demarcation between cortical grey and white matter in the brain.

Clinical Signs

I. Onset ranges from 9 months to 4 years of age.
II. Signs may be rapidly progressive and fatal.
III. Signs consist of prosencephalic signs, such as seizures, depression, circling, and visual deficits.
IV. Motor and sensory problems (ataxia, paresis), brainstem and cerebellar signs are also possible.

Diagnosis

I. CSF analysis shows a moderate to severe pleocytosis composed of monocytes and lymphocytes, with mild protein elevation.
II. MRI findings mirror the topography of the histopathologic lesions.
III. MRI typically demonstrates multifocal lesions in the superficial cortical grey matter at the junction of the cerebrum and leptomeninges.

Differential Diagnosis

I. Granulomatous meningoencephalomyelitis
II. Necrotizing leukoencephalitis
III. Infectious meningoencephalitis
IV. CNS neoplasia: lymphoma, metastatic neoplasia
V. Metabolic, toxic encephalopathies
VI. Other causes of seizures: see Chapter 22

Treatment and Monitoring

I. Immunosuppression is the primary therapy and is similar to that for GME.
II. The prognosis is grave.
III. If a response is seen to immunosuppression, lifelong therapy is necessary to control the inflammation.

Necrotizing Leukoencephalitis

Definition and Cause

I. It is an idiopathic (mononuclear) meningoencephalitis of young Yorkshire terriers, Chihuahuas, and occasionally other small-breed dogs (Tipold et al., 1993).
II. It is presumed to be an immune-mediated disease.

Pathophysiology

I. Lesions consist of nonsuppurative meningoencephalitis and moderate to severe cerebral necrosis.
II. Gross cavitations occur in periventricular cerebral and diencephalic (thalamocortical) white matter.

Clinical Signs

I. Onset is from 1 to 5 years of age.
II. The clinical course is slowly progressive, usually over many weeks to months.
III. Clinical signs reflect caudal brainstem or prosencephalic lesions.
IV. Brainstem signs often predominate and include varying degrees of depression, spastic tetraparesis, vestibular ataxia, head tilt, and abnormal nystagmus.
V. Prosencephalic signs consist of seizures, propulsive activity, and visual deficits.

Diagnosis

I. The CSF analysis usually reveals a moderate to severe pleocytosis of monocytes and lymphocytes and a mild protein elevation.
II. MRI and CT may show multifocal cavitating lesions predominantly in deep white matter.

Differential Diagnosis

I. Granulomatous meningoencephalomyelitis
II. Necrotizing meningoencephalitis
III. Infectious meningoencephalitis
IV. CNS neoplasia: lymphoma, metastatic neoplasia
V. Metabolic or toxic encephalopathies
VI. Other causes of seizures: see Chapter 22

Treatment and Monitoring

I. Immunosuppression is the mainstay of therapy (see under GME).
II. The prognosis is grave and therapy may be life-long.

Canine Meningeal Polyarteritis

Definition and Cause

I. The disease is a neutrophilic meningitis of young dogs that is characterized by episodes of severe pain, depression, and fever (Cizinauskas et al., 2000).
II. It is presumed to be immune-mediated.
III. It is also known as *steroid-responsive* (or *sterile*) *meningitis-arteritis, immune-mediated meningitis, Beagle pain syndrome, systemic necrotizing vasculitis,* and *juvenile polyarteritis syndrome.*

Pathophysiology

I. Inflammation occurs in the leptomeningeal arteries.
II. Leptomeningeal vascular lesions may be accompanied by lymphocytic thyroiditis, amyloidosis (splenic, hepatic, renal), or polyarthritis (Webb et al., 2002).

Clinical Signs

I. Affected dogs range in age from 6 months to a few years.
II. It affects the beagle, Bernese mountain dog, boxer, German short-haired pointer, and is sporadically reported in other breeds.
III. The predominant clinical signs are profound neck pain, depression, anorexia, and fever.
IV. Occasionally, ataxia and varying degrees of paresis are also present (see Chapter 24).
V. The clinical course is typically acute in onset.

Diagnosis

I. Signalment and clinical signs are suggestive.
II. CSF analysis reveals the following:
   A. CSF has a severe neutrophilic pleocytosis, with excessive protein and phagocytosed red blood cells (RBCs).
   B. Neutrophils in CSF do *not* show toxic changes, and intracellular bacteria are not observed.
   C. CSF aerobic and anaerobic bacterial cultures are negative.
   D. Consistent elevation of CSF and serum immunoglobulin (Ig) A concentrations occur.
III. Occasionally peripheral neutrophilia with a left shift and an elevated serum α2-globulin fraction are found.
IV. CT or MRI may demonstrate contrast enhancement of the meninges, spinal cord, or brain.

Differential Diagnosis

I. Intervertebral disc disease
II. Bacterial meningoencephalitis
III. Other immune-mediated meningoencephalitides
IV. CNS neoplasia

Treatment and Monitoring

I. Long-term immunosuppression is achieved with prednisone at 1 to 2 mg/kg PO BID, then tapered monthly over 6 months.
II. In refractory cases, azathioprine (1.5 mg/kg PO SID to QOD) may be added and eventually alternated with prednisone QOD.
III. Prognosis is guarded to favorable; recurrences are common.
IV. Monitor for recurrences, and consider repeating the CSF analysis if clinical signs persist.

Eosinophilic Meningoencephalitis

Definition and Cause

I. Eosinophilic meningoencephalitis is an uncommon disease, primarily of rottweilers and golden retrievers, that is characterized by severe, multifocal neurological signs (Smith-Maxie et al., 1989; Schultze et al., 1986).
II. It is presumed to be an immune-mediated disease.

Clinical Signs

I. Prosencephalic signs consist of behavioral and mentation changes, circling, pacing, head pressing, blindness, and generalized or partial seizures.
II. Brainstem signs include episodic collapse, facial paralysis, absent gag reflex, reduced pupillary light reflexes, torticollis, and varying degrees of ataxia and incoordination.

Diagnosis

I. CSF analysis shows variable pleocytosis, with 21% to 98% eosinophils, and elevated protein content.
II. Mild to moderate systemic eosinophilia may be observed.
III. Serology for infectious diseases is negative.

Differential Diagnosis

I. Other CNS infections: primary protozoal, fungal, parasitic
II. Other noninfectious meningoencephalitides
III. CNS neoplasia

Treatment and Monitoring

I. Prednisone therapy (and possibly additional immunosuppressive agents) is instituted similar to that for GME.
II. Prognosis is favorable to guarded.

IDIOPATHIC DISORDERS

Idiopathic Tremor Syndrome

Definition and Cause

I. Idiopathic tremor syndrome (shaker dog disease) is a meningoencephalitis of young, small, white dogs (de Lahunta, 1983).
II. Occasionally, dogs with pigmented coats are affected.
III. The exact pathogenesis remains uncertain, although it may be immune-mediated.
IV. Mild lymphoplasmacytic meningoencephalitis is the predominant lesion.

Clinical Signs

I. It most commonly affects Maltese and West Highland white terriers.
II. Other affected breeds include the bichon frisé, Spitz, samoyed, beagle, dachshund, and Yorkshire terrier.
III. The predominant clinical sign is continuous, whole-body tremors that worsen with exercise, stress, and excitement, but disappear with sleep.
IV. Neurological examination often is normal, with the exception of generalized tremors.
V. When present, neurological signs may include absent menace response, spontaneous nystagmus, poor to absent oculocephalic reflexes (physiological nystagmus), vestibular or cerebellar ataxia, head tilt, varying degrees of paresis, and seizures.

Diagnosis

I. CSF analysis reveals mild lymphocytic pleocytosis, with normal or mildly elevated protein levels.
II. MRI typically is normal, but may disclose symmetrical ventricular enlargement in some dogs.

Differential Diagnosis

I. Metabolic or toxic encephalopathies
II. Meningoencephalitis
III. Dysmyelinogenic disorders

Treatment and Monitoring

I. Prednisone is administered at 1 to 2 mg/kg PO SID for 4 weeks, then tapered to 0.5 to 1 mg/kg PO SID for 2 weeks, then to QOD for 2 weeks, then to every 72 hours for 4 weeks.
II. Diazepam 0.25 mg/kg PO BID to TID or propanolol 1 mg/kg PO TID may be beneficial in refractory cases.
III. Prognosis is favorable, with tremors usually decreasing by the end of the first week of therapy.
IV. Relapses can occur and may require additional immunosuppressive therapy (e.g., azathioprine).

Trigeminal Neuropathy

Definition and Cause

I. It is an idiopathic disorder characterized by acute onset of trigeminal nerve paresis or paralysis (de Lahunta, 1983).
II. It may be an immune-mediated condition.

Clinical Signs

I. Clinical signs include an acute onset of jaw paresis or paralysis with an inability to close the mouth, drooling, and difficult prehension of food and water.
II. Trigeminal sensory deficits are common.
III. Horner's syndrome (from effects on postganglionic sympathetic fibers incorporated in segments of the ophthalmic branch of the trigeminal nerve) is occasionally seen.
IV. Occasionally, the facial nerve is also involved.

Diagnosis

I. EMG of the muscles of mastication is abnormal.
II. CSF analysis may reveal a mild mononuclear pleocytosis, often with normal or mildly elevated protein content.
III. Definitive diagnosis of trigeminal neuropathy requires biopsy of the trigeminal nerve, but it is rarely done.

Differential Diagnosis

I. Lymphoma infiltrating the trigeminal nerves
II. Polyradiculoneuritis
III. Rabies
IV. Masticatory muscle myositis

Treatment and Monitoring

I. The condition is often self-limiting, with recovery occurring over 3 to 4 weeks to several months.
II. Corticosteroids do not seem to affect the clinical course.
III. Fluid and nutritional support may be necessary for animals unable to eat and drink on their own.
IV. The severity of muscle atrophy, clinical course, and recovery depends upon the extent of axonal degeneration.
V. Prognosis is favorable in most cases, but can be guarded in severely affected animals.

Idiopathic Facial Nerve Paralysis

Definition and Cause

I. It is a disorder of mature dogs and cats that is characterized by facial palsy or paralysis (Kern and Erb, 1987).
II. The cause is unknown.

Clinical Signs

I. Predisposition exists in the American cocker spaniel, Pembroke Welsh corgi, boxer, English setter, and domestic long-haired cat.
II. Clinical signs include ear drooping, commissural paralysis of the lip, sialosis, deviation of the nose away from the affected side, and collection of food on the paralyzed side of the mouth.
III. Menace response and palpebral reflexes are absent ipsilaterally.
IV. Facial paralysis is usually unilateral, but may be bilateral in some animals.
V. Horner's syndrome is not seen.

Diagnosis

I. Diagnosis is often presumptive, based on clinical signs and exclusion of other disorders.
II. EMG may reveal spontaneous denervation potentials in superficial facial muscles.

Differential Diagnosis

I. Polyradiculoneuritis (coonhound paralysis)
II. Endocrine disorders: hypothyroidism, insulinoma
III. Laryngeal paralysis syndrome
IV. Myasthenia gravis, botulism
V. Trauma near the stylomastoid foramen or in conjunction with petrosal bone fracture
VI. Middle ear infection, neoplasia
VII. Surgery of the external or middle ear, or side of the face
VIII. Extracranial tumors

Treatment and Monitoring

I. Application of ophthalmic lubricants helps prevent corneal drying.
II. Prognosis for a complete return to function is guarded.
III. Chronic lip paralysis may result in permanent contracture, and the inability to close the eyelids often leads to keratitis.

Peripheral Vestibular Syndrome

Definition and Cause

I. It is an acute disorder that occurs in cats of all ages and in older dogs (de Lahunta, 1983).
II. Mechanism and cause are unknown.
III. Most feline cases (80%) occur in the summer (Burke et al., 1985).

Clinical Signs

I. Clinical signs occur acutely.
II. Only signs of peripheral vestibular dysfunction (no evidence of facial nerve paralysis or Horner's syndrome) are present.

III. Signs include head tilt, asymmetrical ataxia, and horizontal or rotatory nystagmus with the fast phase directed away from the head tilt.
IV. More severe signs of falling, rolling, and vomiting (especially in dogs) are seen occasionally.

Diagnosis

I. Presumptive diagnosis is based on signalment, history, clinical signs, and exclusion of other etiologies.
II. Absence of otoscopic and radiographic abnormalities of the middle ear is supportive.
III. MRI or CT scan is normal.
IV. CSF analysis is normal.

Differential Diagnosis

I. Otitis media/interna
II. Neoplasia
III. Cerebrovascular accident of brainstem

Treatment and Monitoring

I. Supportive care is administered, as needed.
II. Affected animal tends to stabilize in a few days and improve gradually over several weeks.
III. Prognosis for spontaneous remission is good; however, residual deficits (e.g., mild head tilt) may occur.

PARASITIC DISORDERS

Parasitic Encephalomyelitis

Definition

I. Aberrant migration of parasite larvae through the CNS results in parenchymal damage and neurological signs (Braund, 2005).
II. It is also known as *cerebral larval migrans.*

Causes

I. *Toxocara canis*
II. *Ancylostoma caninum*
III. *Angiostrongylus cantonensis*
IV. *Dirofilaria immitis*
V. *Angiostrongylus vasorum*
VI. *Cysticercus cellulosae*
VII. *Baylisascaris procyonis*
VIII. *Coenurus serialis*

Pathophysiology

I. Migrating larvae damage neural tissue by two mechanisms.
II. Necrosis can occur in tissue along the migratory pathway.
III. Migrating larvae evoke an inflammatory response, which causes ischemia, edema, and toxic injury to myelin, axons, and neurons.

Clinical Signs

I. Clinical signs are acute in onset and rapidly progressive.
II. Signs reflect the location of the migratory pathway.
   A. Prosencephalon signs include blindness, circling, behavioral changes, seizures, and postural reaction deficits.
   B. Brainstem signs include varying degrees of ataxia and paresis, changes in mentation, cranial nerve deficits, head tilt, and spontaneous nystagmus.
   C. Cerebellar signs include a wide stance; a spastic, hypermetric gait; loss of balance; intention tremors; and absent menace response.
III. Neurological signs may reflect focal or multifocal disease.

Diagnosis

I. CSF is characterized by an eosinophilic or neutrophilic pleocytosis, and protein elevation.
II. A positive test for *D. immitis* is suggestive.
III. Definitive diagnosis requires histological demonstration of the parasite within the CNS.

Differential Diagnosis

I. Infectious meningoencephalitis
II. Eosinophilic meningoencephalomyelitis
III. GME
IV. Neoplasia

Treatment and Monitoring

I. No successful therapy to date
II. Guarded prognosis

Intracranial Myiasis

Definition and Cause

Aberrant migration of *Cuterebra* spp. larvae can occur within the CNS of cats and dogs (rarely) (Glass et al., 1998).

Pathophysiology

I. Larvae may migrate through the nose, ethmoids, and cribriform plate and enter the brain through the olfactory lobe.
II. Alternatively, larvae can migrate through foramina of the skull, travel through the external and middle ear, penetrate the mastoid region, invade venous sinuses and meninges, or enter hematogenously after penetrating a large vessel.
III. Microscopic necrosis of the brain occurs secondary to ischemia.
IV. Lesions are usually unilateral in regions supplied by the middle cerebral artery (see Cerebral Vascular Disease).
V. It is hypothesized that the larvae produce a toxin that causes vasospasm and cerebral infarction and may cause superficial laminar cerebrocortical necrosis (Williams et al., 1998).

Clinical Signs

I. Animals are often affected in summer months, when adult flies deposit their ova.
II. Typically outdoor cats (rarely dogs) are affected.
III. Many cats have signs consistent with upper respiratory disease (especially sneezing) before the appearance of neurological signs.
IV. Neurological signs are peracute in onset.
V. Prosencephalic signs, including unilateral postural reaction deficits, unilateral facial (and occasionally whole-body)

hypalgesia, and a menace deficit with a dilated, nonresponsive pupil from involvement of the optic tracts are noted.
VI. Seizures and profound behavioral and mentation changes are often present.

Diagnosis

I. CSF analysis may be normal or show a mild to moderate pleocytosis (neutrophilic, mononuclear, or occasionally eosinophilic), with mild protein elevation.
II. MRI may reveal the migratory path of the larvae, cerebrocortical lesions, and evidence of a focal or regional infarction.
III. Definitive diagnosis requires histopathology.

Differential Diagnosis

I. Other infectious or parasitic meningoencephalitis
II. Eosinophilic meningoencephalitis
III. Neoplasia

Treatment and Monitoring

I. The following may be beneficial, but controlled studies have not been done.
   A. Pretreat with diphenhydramine 4 mg/kg IM.
   B. Give ivermectin 400 µg/kg SC and dexamethasone 0.1 mg/kg IV.
   C. Repeat the treatment 24 to 48 hours later.
II. A third-generation cephalosporin, trimethoprim-sulfa drug, or metronidazole may be given to prevent bacterial infection associated with larval migration.
III. Although prognosis is guarded; some cats may recover over weeks to months with residual neurological deficits.

METABOLIC/TOXIC DISORDERS

General Information

Definition and Causes

I. These include disturbances in cerebral function from metabolic derangements or toxicoses that usually manifest as diffuse prosencephalic signs.
II. See Table 23-3 for a list of causes.

Pathophysiology

I. Energy deprivation leads to alterations in neuronal resting membrane potentials, and may disrupt neurotransmitter function and metabolism.
II. Certain toxins and metabolic abnormalities may interfere with energy metabolism in the brain, potentially causing neuronal death.
III. Electrolyte imbalances may alter neuronal excitability and neurotransmission.
IV. Changes in serum osmolality and water content lead to altered osmotic balance in neural cells, which may cause either brain cell swelling (edema) or dehydration.

Clinical Signs

I. Metabolic encephalopathies typically cause diffuse, symmetrical prosencephalic signs, such as seizures, altered mentation (confusion, disorientation, dementia, pacing, head pressing), circling, and altered consciousness (obtundation, stupor, coma).
II. Onset may be acute or chronic, and signs may wax and wane.
III. Motor signs include tremors, myoclonus, and varying degrees of paresis/paralysis.

TABLE 23-3

Causes of Metabolic or Toxic Encephalopathies

DISORDER	CAUSES
Hypoxia	Cardiopulmonary failure, disturbances in hemoglobin function, carbon monoxide poisoning, methemoglobinemia, cellular hypoxia (cyanide poisoning)
Hypoglycemia	Pancreatic beta-cell tumor (insulinoma), iatrogenic insulin overdose, hepatic dysfunction, septicemia, hypoadrenocorticism, paraneoplastic syndromes (e.g., leiomyosarcoma, hepatoma, lymphoma), neonatal animals, hunting dogs, storage diseases
Acidosis, alkalosis, hyperosmotic states	Hyperglycemia (diabetes mellitus), hypernatremia, dehydration, diabetes insipidus, nonketotic, hyperosmolar diabetes mellitus, hyperaldosteronism
Hypoosmotic states, hyponatremia	Hypoadrenocorticism, water intoxication, inappropriate secretion of antidiuretic hormone
Alterations in calcium homeostasis	
Hypercalcemia	Paraneoplastic syndromes, rodenticide toxicity (cholecalciferol-containing products), hyperparathyroidism, Vitamin D toxicity, renal disease, hypoadrenocorticism, certain granulomatous diseases
Hypocalcemia	Eclampsia, hypoparathyroidism
Endogenous neurotoxins	Hepatic insufficiency/failure, renal failure, pancreatitis
Endocrine disorders	Hyperthyroidism, hypothyroidism

Diagnosis

I. Other evidence of metabolic disturbances may be identified from the history or the physical examination.
II. A minimum laboratory database includes a complete blood count, biochemistry profile, and urinalysis.
III. Other diagnostic tests are considered based on initial findings.
  A. Serum bile acids
  B. Blood gas analysis
  C. Measurement of serum osmolality
  D. Endocrine function tests
  E. Cardiopulmonary function tests: electrocardiography, blood pressure measurement, radiography, echocardiography
  F. Abdominal radiography and ultrasonography

Differential Diagnosis

I. Degenerative encephalopathies
II. Meningoencephalitis
III. Neoplasia
IV. Brain malformations

Treatment and Monitoring

I. Ensure an adequate airway; support breathing and circulation if the animal is comatose.
II. Correct the underlying metabolic disturbance.
III. Consider anticonvulsants for seizures.
IV. Take care when treating seizures in animals with hepatic insufficiency, because they are unable to metabolize many anticonvulsants.
  A. Give diazepam (0.5 mg/kg IV), but reduce the dosage if hepatic encephalopathy is a primary concern.
  B. Give phenobarbital initially at 2.0 mg/kg PO, IV, IM BID, with caution.
    1. Metabolism may be compromised with hepatic dysfunction.
    2. Acidosis causes increased penetration of barbiturates into the brain.
  C. Seizures may be difficult to control until the underlying metabolic imbalance is corrected.
V. Administer dextrose if hypoglycemia is identified (see Chapter 46).
VI. In most cases, neurological signs resolve once the metabolic disturbance is corrected.

Hepatic Encephalopathy

See Chapter 37.

Cerebrovascular Disease

Definition

I. Cerebrovascular disease refers to conditions that result in brain ischemia, infarction, or hemorrhage.
II. These conditions include the following:
  A. Cerebrovascular accidents: thromboembolism and infarction, hemorrhage (Garosi et al., 2005)
  B. Vascular anomalies: aneurysm, hamartoma
  C. Cerebral arteriosclerosis secondary to severe hypothyroidism
  D. Meningoencephalitis
  E. Intravascular neoplasms: lymphoma

Causes and Pathophysiology

I. Cerebral ischemia occurs as a result of insufficient blood supply to the brain.
  A. Dogs may have transient ischemic attacks, possibly from vasospasm.
    1. Attacks are often of unknown etiology.
    2. Occasionally they are associated with hypertension.
  B. Feline ischemic encephalopathy (FIE) occurs in the late summer, most commonly in eastern North America.
    1. Aberrant migration of *Cuterebra* spp. larva is thought to be the primary cause (Glass et al., 1998).
    2. It is hypothesized that a toxin from the larva causes vasospasm (of the middle cerebral artery), resulting in a unilateral ischemic brain lesion (Williams et al., 1998).
II. Hypoperfusion of the brain is associated with atherothrombosis or embolism.
  A. With atherothrombosis, a localized thrombus forms and disrupts blood flow, with subsequent ischemia and/or infarction.
  B. With embolization, an artery is suddenly occluded, usually by a thrombus that arises from a distant site, such as in the heart (blood clot) or a neoplasm (e.g., neoplastic cells from hemangiosarcoma).
III. Systemic hypoperfusion causes a decrease in cerebral blood flow and can lead to infarction in the border zones between major cerebral arteries (watershed infarction).
IV. Impaired blood supply to the brain results in a decline in tissue oxygen levels (stagnant hypoxia), which cause brain ischemia.

Clinical Signs

I. Clinical signs are peracute and may be followed by progressive recovery over days to weeks.
II. Clinical signs reflect the location of brain infarction.
III. Although gait deficits are not typically seen with prosencephalic lesions, a transient gait deficit (hemiparesis) may be seen with prosencephalic infarcts.
IV. Vestibular signs may be seen with thalamic infarcts.

Diagnosis

I. Serial blood pressure measurements may indicate hypertension.
II. Results of a CBC, biochemistry profile, and urinalysis vary, depending on the presence of an underlying systemic disease.
III. Additional tests may include urine protein: creatinine ratio, serum antithrombin III activity, coagulation profile, and endocrine testing for hyperadrenocorticism, thyroid diseases, and pheochromocytoma.
IV. Thoracic radiography and abdominal ultrasonography may reveal evidence of an underlying disease.

V. MRI (and occasionally CT) may reveal ischemic brain lesions.
VI. CSF analysis usually shows normal to mild increases in nucleated cells, with elevated protein content.

Differential Diagnosis

I. Meningoencephalitis
II. Metabolic encephalopathy
III. Neoplasia

Treatment and Monitoring

I. No definitive treatment for the neurologic signs has been defined in animals.
II. Osmotic therapy (as described for cranial trauma) may be beneficial in severely affected animals.
III. Treatment is usually directed at the underlying disease.
IV. Prognosis and recovery are highly variable.

NUTRITIONAL DISORDERS

Thiamine Deficiency

Definition and Causes

I. Metabolic encephalopathy can arise from thiamine deficiency (de Lahunta, 1983).
II. Commercial rations or homemade diets may be low in thiamine.
III. Overcooking food before feeding or during food processing can affect thiamine levels.
IV. Thiamine can be destroyed by sulfites or sulfur dioxide used as a preservative in canned food.
V. All-fish diets may result in thiamine deficiency, as many fish contain thiaminase.
VI. Severe hepatic or renal disease can be associated with thiamine deficiency.

Pathophysiology

I. Thiamine is essential for complete oxidation of glucose through the Krebs cycle.
II. Tissues that derive energy from glucose or lactate-pyruvate are compromised.
III. Several proposed mechanisms for neuronal cell death include impaired vascular function, increased blood-brain barrier permeability, N-methyl-D-aspartic acid receptor-mediated excitotoxicity, and increased free radical formation (Leong and Butterworth, 1996).
IV. CNS lesions include bilateral, symmetrical degeneration of brainstem nuclei (caudal colliculi, vestibular, lateral geniculate, oculomotor and red nuclei), and cortical lesions (less common).

Clinical Signs

I. Signs are related to dysfunction of brainstem nuclei and include vestibular ataxia, seizures, dilated pupils, opisthotonus, coma, and death.
II. Severe head and neck ventriflexion is often present from neuromuscular weakness.
III. Dogs may have signs of central (bilateral) vestibular disease or cervical myelopathy (Garosi et al., 2003).

Diagnosis

I. History, signalment, clinical signs, and response to treatment allow a presumptive diagnosis.
II. MRI may disclose symmetrical lesions in affected brainstem nuclei (Garosi et al., 2003).
III. Serum levels of pyruvate and lactate may be increased.
IV. Red blood cell transketolase activity is usually decreased.

Differential Diagnosis

I. Meningoencephalitis
II. Metabolic or toxic encephalopathies
III. Neoplasia
IV. Other causes of central vestibular disease

Treatment and Monitoring

I. Even in severely affected animals, prognosis is fair to good if signs are recognized early.
II. Thiamine HCl (vitamin B_1) is administered at 25 to 50 mg/day IM to dogs for 3 to 7 days, and at 10 to 20 mg/day IM to cats until signs abate, or for 21 days.
III. Higher doses may be required in some animals.
IV. Dietary abnormalities should also be corrected.

NEOPLASIA

Definition

I. Primary brain tumors arise from neuroectodermal or mesodermal cells that are normally present within or associated with the brain (Summers et al., 1995).
II. Secondary tumors originate from surrounding tissues and extend into the brain or arise from hematogenous metastasis.
III. Classification of brain tumors (primary or secondary) is based on characteristics of the constituent cell types (Bagley et al., 1993).

Causes and Classification

I. Primary tumors
  A. Tumors of neuroepithelium
    1. Astrocytic tumors: astrocytoma, glioblastoma multiforme
    2. Oligodendroglial tumors: oligodendroglioma
    3. Mixed glial tumors: oligoastrocytoma, gliomatosis cerebri
    4. Embryonal tumors: primitive neuroectodermal tumors (PNETs), medulloblastoma
    5. Ependymoma
    6. Choroid plexus tumors
  B. Tumors of meninges: meningioma, meningeal sarcoma
  C. Tumors of hematopoietic tissue: lymphoma, histiocytic tumors
  D. Nerve sheath tumors
  E. Tumors of the sellar region
    1. Pituitary tumors: adenoma, adenocarcinoma
    2. Suprasellar germ cell tumors

II. Metastatic tumors
  A. Hemangiosarcoma
  B. Urogenital tumors: prostatic carcinoma, mammary gland adenocarcinoma
  C. Malignant melanoma
III. Secondary tumors of adjacent tissues
  A. Tumors arising from the calvaria: osteosarcoma, multilobulated tumor of bone
  B. Local extension of regional tumors
    1. Nasal tumor: adenocarcinoma, fibrosarcoma
    2. Tumors arising from the ear or osseous bullae: adenocarcinoma, squamous cell carcinoma

Pathophysiology

I. Direct effects of tumor growth include compression and invasion of normal brain parenchyma.
II. Indirect effects are often more significant than direct effects.
  A. Damage to the blood-brain barrier can result in cerebral edema.
  B. Obstruction to CSF flow causes secondary hydrocephalus.
  C. Brain herniation can occur as a result of increased intracranial pressure from an enlarging space-occupying mass within the rigid calvaria.
  D. Hemorrhage is also a possibility.

Clinical Signs

I. Breed predisposition has been reported for several tumors.
  A. Brachycephalic breeds (especially the boxer, English bulldog, and Boston terrier) are predisposed to gliomas (astrocytomas, oligodendrogliomas, mixed tumors) and pituitary tumors.
  B. Dolichocephalic dogs and Siamese cats may be predisposed to meningiomas.
II. Onset of disease may be acute or insidious, depending on the location, rate of growth, and indirect effects of the tumor.
III. Neurological signs reflect the location of the tumor.
  A. Cerebral or thalamic tumors (prosencephalic tumors) may cause seizures, circling, behavioral changes, contralateral postural reaction deficits, contralateral visual deficits, and contralateral nasal hypalgesia.
  B. Brainstem tumors can induce vestibular signs, ipsilateral postural reaction deficits, cranial nerve deficits, ataxia (both proprioceptive and vestibular), and changes in mentation.
  C. Cerebellar tumors can result in a wide stance; spastic, hypermetric gait (cerebellar ataxia); loss of balance; intention tremors; ipsilateral postural reaction deficits; and ipsilateral, absent menace response without visual deficits.
  D. Tumors of the floor of the calvaria may cause deficits of the oculomotor, trochlear, abducens nerves, and the ophthalmic branch of the trigeminal nerve.
    1. Disruption of the sympathetic innervation to the head may also occur.
    2. Clinical signs may include ophthalmoplegia, Horner's syndrome, mydriasis, and trigeminal sensory deficits involving the eye and the medial canthus.
IV. Metastatic tumors may involve single or multiple areas within the CNS and be associated with focal or multifocal signs.
V. Tumors involving the frontal and olfactory lobes of the cerebrum may cause seizures or changes in mentation without other deficits.

Diagnosis

I. A minimum database includes a CBC, biochemistry profile, urinalysis, and three radiographic views of the thorax.
II. MRI and CT may allow a presumptive diagnosis.
  A. Meningiomas often are extraaxial (on the periphery of the brain), have a broad-based attachment, and exhibit strong, homogeneous contrast enhancement.
  B. Glial tumors often are intraaxial (within brain parenchyma), display variable contrast enhancement, and occasionally have a ring-enhancement pattern.
  C. Choroid plexus tumors are located intraventricularly or at the cerebellomedullary angle and typically exhibit strong, uniform contrast enhancement.
  D. Tumors can occur in the ventricles, such as choroid plexus and ependymal tumors.
  E. Secondary consequences include compression of normal brain structures with shifting of midline structures, obstructive hydrocephalus, and cerebral (vasogenic) edema.
III. CSF analysis often reveals nonspecific abnormalities.
  A. An increased protein concentration and a normal cell count are typical.
  B. Neoplastic lymphocytes may be seen with lymphoma.
  C. Meningiomas may result in a neutrophilic pleocytosis from tumor necrosis.
  D. An increased risk of brain herniation is associated with elevated intracranial pressure and is a contraindication to CSF tap.
IV. Definitive diagnosis requires histopathologic evaluation.

Differential Diagnosis

I. Metabolic or toxic encephalopathies
II. Meningoencephalitis: infectious, noninfectious
III. Vascular disorders
IV. Other causes of seizures, altered mentation

Treatment and Monitoring

I. Certain treatments are directed at the secondary consequences.
  A. Osmotic diuretics are used to draw edema out of the brain.
    1. Give mannitol at 0.25 to 1.0 g/kg IV over 10 to 15 minutes.
    2. Administer furosemide (0.7 mg/kg IV) 15 minutes after mannitol to prolong the effects of mannitol.
    3. Administer hypertonic saline at 1.0 to 2.0 mL/kg IV over 10 to 15 minutes.

4. Repeat osmotic therapy up to every 6 hours unless the animal becomes dehydrated or hypovolemic.
5. Evaluate packed cell volume (PCV) and total solids (TS) before administration of osmotic therapy to evaluate hydration status.
6. Do not use osmotic therapy in dehydrated, hypovolemic animals, or in animals with decreased cardiac function.

B. Prednisone (0.5 to 1.0 mg/kg PO, IV) can be administered to reduce peritumoral (vasogenic) edema and inflammation.
C. Anticonvulsants are administered for seizures.
1. Phenobarbital (2.0 to 4.0 mg/kg PO, IM, IV BID) is usually the first option.
2. KBr (30 mg/kg PO SID) may also be added.
3. Animals with intracranial neoplasia may become extremely sedate with anticonvulsants.
4. Dosages less than the recommended amount may be used initially to avoid extreme sedation.

II. Definitive treatment includes surgery and/or radiation therapy.
A. Surgery allows for tumor resection or cytoreduction and provides a histological diagnosis.
B. Surgery often is reserved for tumors that are extraaxial (superficial), and more easily approached and removable.
C. Radiation therapy (alone or in combination with surgery) has been shown to increase survival time (Axlund et al., 2002; Bley et al., 2005).
D. Overall prognosis is fair to guarded and depends on the location and type of tumor.

CRANIAL TRAUMA

Definition and Causes

I. Neurological dysfunction secondary to head trauma is caused by brain contusion, laceration, edema, or hemorrhage.
II. Trauma may occur from a fall, automobile accident, or blunt or penetrating injuries.

Pathophysiology

I. Depressed skull fractures may cause compression and injury to underlying brain parenchyma.
II. Angular acceleration of the brain can cause diffuse, axonal injury.
III. The impact of the brain against the skull results in coup (occurring in tissue under the area of impact) and contrecoup injuries (occurring in tissue on the side opposite the impact).
IV. Hemorrhage and hematoma formation can compress brain parenchyma.
V. The end result is vasogenic edema of the brain.

Clinical Signs

I. Signs may be indicative of focal or diffuse brain disease.
II. Prosencephalic injury may result in loss of consciousness in severe cases, but more frequently leads to circling, altered mentation, and contralateral postural reaction deficits, blindness, and facial hypalgesia.
III. Brainstem injury typically causes altered mentation (depression, obtundation, or sometimes a comatose state), pupillary changes, and loss of conjugate eye movements
IV. Cerebellovestibular injury can result in dysmetria, cerebellar or vestibular ataxia, dysequilibrium, head tilt, and spontaneous or positional nystagmus.
V. Evidence of progressive clinical signs suggests cerebral edema, herniation, or hematoma formation.

Diagnosis

I. Signs of brain dysfunction in an animal known to have suffered an injury are suggestive.
II. Abrasions, penetrating wounds, or other evidence of head trauma are supportive.
III. Although difficult to interpret, radiographs may reveal skull fractures.
IV. MRI or CT can identify skull fractures, areas of hemorrhage, hematoma formation, and edema within the brain.

Differential Diagnosis

I. Other disorders are considered if trauma was not witnessed or if external evidence of trauma is absent.
II. Consider metabolic and toxic encephalopathies, as well as inflammatory, vascular, and neoplastic disorders.

Treatment and Monitoring

I. Nonspecific therapy is often initiated before or in conjunction with specific therapies.
A. Ensure airway patency, adequate ventilation, and stabilize cardiovascular function.
B. Institute fluid therapy to correct any hypovolemia and associated hypotension.
C. Provide oxygen to prevent further tissue hypoxia.
D. Turn recumbent animals every 6 hours, and keep them clean and well padded.
E. Provide nutritional support after they are stabilized.

II. Specific therapy is directed at reducing cerebral edema and intracranial pressure.
A. Recumbent animals are positioned with their heads slightly elevated (15 to 30 degrees).
B. Osmotic therapy is started for cerebral edema.
1. Mannitol 0.25 to 1.0 g/kg IV over 10 to 15 minutes
2. Hypertonic saline 7% 1 to 5 mL/kg IV over 3 to 5 minutes
3. Furosemide (0.7 mg/kg IV) can be given 15 minutes after mannitol to prolong its effect.
4. Osmotic therapy can be repeated every 6 to 8 hours unless dehydration or hypernatremia develops.
5. Electrolytes, PCV, and TS are monitored closely with osmotic therapy.

C. Osmotic therapy is contraindicated in hypovolemic animals and those with clinical signs suggestive of active intracranial hemorrhage.
D. Surgery is indicated for depressed skull fractures or if the animal's condition deteriorates despite medical management.

III. Prognosis depends on the severity and location of the injury.
IV. Although most improvements are seen within the first month of the injury, recovery may take weeks to months.
V. Long-term sequelae may include seizures and persistent neurological deficits.

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CHAPTER 24

Disorders of the Spinal Cord

Simon R. Platt

CONGENITAL AND DEVELOPMENTAL DISORDERS

Atlantoaxial Subluxation

Definition

I. Instability or malformation of the atlantoaxial joint allows excessive flexion of the cervical (C) 1-2 vertebral joint.
II. Subsequent ventral cord compression occurs from the cranial aspect of the body of the axis.

Causes and Pathophysiology

I. It most commonly occurs in young, toy, and small-breed dogs (<2 years).
II. Subluxation is often associated with failure of normal structural development of the atlas, axis, and their supporting ligaments.
III. It can occur following minor trauma in the presence of joint instability.
IV. Clinical signs arise from concussion and compression of the spinal cord by the axis.

Clinical Signs

I. Onset is usually acute; however, signs can be slowly progressive and may wax or wane.
II. Neck pain occurs in at least 60% of cases (Beaver et al., 2000).
III. Ataxia, tetraparesis, postural reaction deficits, with normal to exaggerated spinal reflexes occur in 85% of cases (Beaver et al., 2000).
IV. Animals with tetraplegia are at risk of death from respiratory failure.
V. Occasionally, signs of brainstem dysfunction are seen.

Diagnosis

I. Confirm the diagnosis with lateral survey radiographs of the cervical spine.
II. Note an increased space between the dorsal lamina of C1 and the spinous process of the C2.
III. Use ventrodorsal views to assess most accurately the presence and size of the dens.
IV. Flex the neck carefully to confirm instability, if subluxation is not readily apparent.
V. Computed tomography (CT) can provide accurate information about the dens.
VI. Magnetic resonance imaging (MRI) can provide important information about spinal cord compression, parenchymal pathology, and ligamentous involvement.

Differential Diagnosis

I. Trauma
II. Intervertebral disc disease
III. Meningomyelitis: various forms

Treatment

I. Treat cases with acute onset of severe neurological signs with external head and neck splinting.
II. Conservative therapy may be appropriate for some dogs with mild signs.
III. Apply external splinting and restrict exercise strictly for 6 to 8 weeks.
   A. Long-term efficacy of this approach is uncertain.
   B. Dogs are always at risk of repeated injury following splint removal.
IV. Surgical management is recommended for dogs with neurological deficits.
   A. Dorsal and ventral approaches to the atlanto-axial junction have been described (McCarthy et al., 1995; Platt et al., 2004).
   B. Surgery is aimed at realignment of the vertebrae, decompression of the spinal cord, and osseous fusion of the atlantoaxial joint.
   C. Surgical complications include injury to soft tissues, laryngeal paralysis, implant failure, and death in up to 20% of cases (Beaver et al., 2000).

Monitoring of Animal

I. Nonsurgical approach is most successful in dogs that are affected for ≤30 days (Havig et al., 2005).
II. Surgical success ranges from 50% to 90% (McCarthy et al., 1995; Beaver et al., 2000).
III. Prognosis is better in young dogs (<24 months) and in those with clinical abnormalities for ≤10 months (Beaver et al., 2000).
IV. Prognosis is fair to good for those with mild to moderate neurological deficits, and guarded for those with an acute onset of tetraplegia.
V. Radiographs repeated 6 to 8 weeks after surgery may help determine the presence of osseous healing.

Congenital Vertebral Anomalies

Definition

I. Several distinct types of malformation are recognized.
II. Hemivertebrae are wedge-shaped, with the apex directed dorsally, ventrally, or medially across the midline, which often results in angulation of the vertebral column.
III. Block vertebrae appear as fusion of adjacent vertebrae, which may involve the vertebral bodies, vertebral arches, dorsal spinous processes, or entire vertebrae at any level of the vertebral column.
IV. Butterfly vertebrae have a sagittal cleft in the vertebral body.
V. Transitional vertebrae have the characteristics of, and occur at, two major divisions of the vertebral column.

Causes and Pathophysiology

I. Vertebral malformations are the result of a disturbance in embryonic development.
II. Hemivertebrae are inherited in the German shorthaired pointer, English bulldog, and Yorkshire terrier.
III. High prevalence of hemivertebrae and butterfly vertebrae occurs in the French bulldog, pug, and Boston terrier.

Clinical Signs

I. Most congenital malformations of the vertebrae cause no clinical signs.
II. Spinal cord compression can occur from canal stenosis, vertebral malalignment, or instability.
III. Hemivertebrae are most commonly associated with clinical signs.
IV. Signs are often slowly progressive, owing to the chronic compression.
V. Neurological deficits are consistent with a transverse myelopathy and include the following:
   A. Conscious proprioception deficits
   B. Ataxia
   C. Paresis or paralysis

Diagnosis

I. Confirmation of a vertebral anomaly is done by survey radiography.
II. Myelography is useful for determining the extent of associated cord compression or stenosis.
III. MRI is valuable in determining associated spinal cord compression or concurrent spinal cord anomalies.

Differential Diagnosis

I. Compression caused by traumatic or pathologic vertebral fractures
II. Vertebral neoplasia
III. Healed osteomyelitis (diskospondylitis)

Treatment

I. If clinical signs are nonprogressive, conservative management is recommended.
II. Surgical decompression combined with stabilization is recommended for progressive clinical signs from spinal cord compression.

Monitoring of Animal

I. Prognosis is good if the defect is an incidental finding; vertebral anomalies can become clinical later in life.
II. Prognosis is guarded with chronic, progressive cord compression.

Spina Bifida

Definition

I. Spina bifida is characterized by a midline cleft in the vertebral arch.
II. Spina bifida occulta indicates that the spinal cord and meninges are normal.
III. Clinical spina bifida is accompanied by a meningocele or a meningomyelocele.
IV. Meningocele is a protrusion of the meninges through the vertebral cleft.
V. Meningomyelocele is a protrusion of the meninges and spinal cord through the vertebral cleft.

Causes and Pathophysiology

I. Spina bifida is likely the result of abnormal development of the neural tube.
II. Teratogenic compounds, nutritional deficiencies, and environmental factors may be associated with spina bifida.
III. A high incidence in the bulldog and Manx cats suggests a heritable cause.
IV. In Manx cats and bulldogs, there is an association with sacrocaudal dysgenesis.
V. In the Manx, an autosomal-dominant condition leads to absence of the tail and to several sacral-related abnormalities.

Clinical Signs

I. Spina bifida is rarely associated with clinical signs.
II. When present, signs vary with the degree of spinal cord and meningeal involvement.
III. Most lesions occur in the caudal lumbar region, but can occur in any vertebra.
IV. Physical examination may reveal abnormal directions of hair growth, a skin dimple, or an open tract draining cerebrospinal fluid (CSF) at the site of the lesion.
V. Fistulous meningocele can cause hypochloremia and hyponatremia subsequent to CSF loss.

Diagnosis

I. Caution must be used when attributing clinical signs to a vertebral anomaly.
II. Dorsoventral radiographs of the vertebral column may reveal an absence of the spinous process(es).
III. CT is useful for confirmation of subtle lesions.
IV. Myelography may detect a meningocele.
V. MRI may detect specific spinal cord changes and is advised before surgical intervention.

Differential Diagnosis

I. Other congenital spinal cord anomalies
II. Meningomyelitis

Treatment and Monitoring

I. Treatment is not necessary for spina bifida occulta.
II. Meningoceles can be surgically resected in cases without concurrent spinal cord lesions.
III. Tethered spinal cord syndrome can be treated surgically by severing the filum terminale.
IV. Surgical closure of spina bifida aperta, removal of the fistulous tract, and broad-spectrum antibiotics may be necessary to reduce the incidence of bacterial meningomyelitis.
V. Prognosis is poor in cases with fecal and urinary incontinence, or severe neurological deficits.
VI. Frequent bladder and bowel expression may be necessary in some cases.

Myelodysplasia

Definition

I. Myelodysplasia refers to a variety of embryologic abnormalities of the spinal cord.
II. A specific form of myelodysplasia, spinal dysraphism, maybe hereditary in Weimaraners.

Causes and Pathophysiology

I. Myelodysplasia results from incomplete closure or development of the neural tube.
II. Anomalies of the central canal include hydromyelia, duplication, or absence of the canal.
III. Anomalies of the grey matter involve the ventral median fissure or dorsal median septum.
IV. Grey matter ectopias, chromatolysis, and loss of nerve cell bodies may also be present.
V. Syringomyelia is a fluid dilatation, usually in the dorsal funiculus of the spinal cord.
VI. With the exception of the Weimaraner, the pathogenesis of this condition is unknown.

Clinical Signs

I. The most common sign is a symmetrical, "bunny hopping" pelvic limb gait.
II. A variable transverse thoracolumbar myelopathy usually occurs in young animals (4 to 6 weeks), which is typically nonprogressive.
   A. Proprioception deficits
   B. Ataxia
   C. Paresis or paralysis
III. A classic finding is a bilateral flexor reflex in the pelvic limbs (both limbs respond to stimulation of one limb).
IV. In Weimaraners, myelodysplasia may be associated with abnormal hair "streams" on the dorsum and koilosternia.

Diagnosis

I. A tentative diagnosis is made on the basis of history, signalment, and clinical signs.
II. Radiographs, CSF analysis, CT, and MRI are usually normal.
III. MRI can detect the presence of hydromyelia and syringomyelia.

Differential Diagnosis

I. Vertebral malformation
II. Spina bifida
III. Myelitis

Treatment and Monitoring

I. No effective treatment exists.
II. Prognosis varies with severity of the clinical signs.

Syringomyelia and Hydromyelia

Definition

I. Hydromyelia is a fluid dilatation of the central canal.
II. Syringomyelia is a fluid dilatation in the spinal cord that may communicate with the central canal.
III. It is often difficult to distinguish between these two conditions.

Causes and Pathophysiology

I. Both conditions can be a secondary, long-term complication of any spinal cord disease.
II. Any condition that causes obstruction of normal CSF flow along the spinal cord can cause these abnormalities.
III. They are most commonly seen in the cervical region, but lesions can occur in any portion of the spinal cord.
IV. Cervical syringohydromyelia occurs as a component of congenital anomalies associated with caudal occipital malformation syndrome, which is most commonly reported in the Cavalier King Charles spaniel, but can be seen in other small breed dogs.
V. Occipital bone malformation causes "overcrowding" of the caudal fossa that interferes with the normal flow of CSF between the intracranial and spinal compartments.

Clinical Signs

I. Clinical signs vary with lesion location.
II. Signs are often progressive, but can be acute and can occur at any age.
III. Clinical signs do not correlate with the severity of the syringohydromyelia or with the concurrent severity of cerebellar herniation and hydrocephalus (Lu et al., 2003).
IV. Typical signs consistent with a transverse myelopathy include the following:
   A. Proprioception deficits
   B. Ataxia
   C. Paresis or paralysis
V. Additional signs include pain, paresthesia, spinal deformity (torticollis, scoliosis), and persistent flank scratching (Rusbridge et al., 2000).

Diagnosis

I. MRI is essential to document parenchymal changes and associated lesions, such as occipital malformation.
II. Survey radiographs are usually normal unless concurrent scoliosis is present.
III. Myelography may show obstruction of the flow of CSF at the foramen, but is often normal.

IV. Cisterna magna puncture is contraindicated given the likelihood of inadvertent puncture of the spinal cord.
V. Lumbar CSF analysis may show chronic inflammation, but is frequently normal.

Differential Diagnosis

I. Other developmental disorders
II. Intervertebral disc disease
III. Meningomyelitis
IV. Neoplasia

Treatment

I. Medical therapy involves antiinflammatories (prednisone 0.5 to 1.0 mg/kg PO SID and carprofen 2.0 mg/kg PO BID).
II. A diuretic, such as acetazolamide (10 mg/kg PO TID to QID), may be used concurrently on a short-term basis to reduce CSF production.
III. Gabapentin (10 mg/kg PO BID) can be used for neuropathic pain and paraesthesia.
IV. Physical therapy (e.g., massage, passive range-of-motion exercises) may be helpful.
V. Surgical therapy can be performed in cases of caudal occipital malformation syndrome.
   A. Foramen magnum decompression with dura and arachnoid excision is preferred for syringohydromyelia associated with occipital malformation syndrome (Vermeersch et al., 2004).
   B. Myelotomy with syrinx decompression and marsupialization of the dura can be used for treatment when the condition is related to other causes.

Monitoring of Animal

I. Medical therapy may be effective in mildly affected animals.
II. Surgical therapy aims to stabilize the condition rather than improve it.
III. Surgical therapy often alleviates neck pain.
IV. Recurrence of signs from reformation of the syrinx requires repeated surgery.
V. Overall prognosis depends on the severity of signs.

Spinal Intraarachnoid Cysts

Definition

I. These lesions are CSF-filled diverticuli of the arachnoid membrane rather than true cysts.
II. Synonyms include *subarachnoid cyst, meningeal cyst,* and *leptomeningeal cyst.*

Causes and Pathophysiology

I. Most commonly a congenital malformation, these lesions may be secondary to trauma, inflammation, subarachnoid hemorrhage, and neoplasia.
II. The intraarachnoid accumulation of CSF in the diverticulum results in compression of the spinal cord.
III. Typically solitary lesions occur commonly at the C2 to C3 and C5 to C6 intervertebral sites or in the caudal thoracic region; however, they can occur at any site (Jurina et al., 2004).
IV. The diverticuli are usually located dorsally over the spinal cord.

Clinical Signs

I. They can occur as an incidental finding.
II. They are most commonly seen in the cranial cervical cord of young adult, large-breed dogs, particularly rottweilers, or in the thoracolumbar spinal cord of older, smaller breeds (e.g., pug) (Rylander et al., 2002; Skeen et al., 2003).
III. Signs usually consist of a chronic and progressive transverse myelopathy.
   A. Proprioception deficits
   B. Ataxia
   C. Paresis or paralysis
IV. Neurological deficits may be asymmetrical and pain is a variable feature.
V. Dogs may have early onset of fecal or urinary incontinence (Skeen et al., 2003).

Diagnosis

I. Survey radiographs are unremarkable.
II. Myelography reveals a focal "tear-drop" accumulation of contrast medium in the subarachnoid space or an intradural filling defect.
III. Contrast-enhanced CT or MRI demonstrates the CSF-filled diverticulum within the arachnoid membrane and spinal cord compression.
IV. MRI can also identify associated parenchymal abnormalities, especially in rottweilers.
V. Surgical findings and histopathology of excised tissues confirm the diagnosis.

Differential Diagnosis

I. Cystic neoplasms
II. Meningomyelitis
III. Other developmental disorders
IV. Intervertebral disc disease

Treatment

I. Medical therapy may improve a small proportion of dogs and is only recommended in cases with mild neurological deficits.
II. Medical therapy involves antiinflammatory drugs and exercise restriction.
   A. Prednisone 0.5 to 1.0 mg/kg PO SID
   B. Carprofen 2.0 mg/kg PO BID
III. Surgical exploration is used to confirm the diagnosis and decompress the spinal cord.
IV. Complete surgical excision is usually not possible.
V. Partial excision (fenestration) and marsupialization of the dura is recommended.

Monitoring of Animal

I. Depending of the degree of signs, the overall prognosis is good following surgery.

II. Factors associated with a good outcome include an age <3 years and duration of clinical signs <4 months (Skeen et al., 2003).
III. Recurrence of signs from reformation of the diverticulum is possible.
IV. Lifelong antiinflammatory therapy has been advised in some cases.

Dermoid Sinus

Definition

I. A dermoid or pilonidal sinus is an invagination of the skin, dorsal to the spine, that extends below the skin to variable depths.
II. It can extend to the dura mater and may communicate with the subarachnoid space.

Causes and Pathophysiology

I. Sinus formation results from a failure of separation of the neural tube from the ectoderm.
II. An autosomal dominant mutation causing the presence of a dorsal ridge predisposes for dermoid sinus formation in the Rhodesian ridgeback.
III. Communication with the subarachnoid space predisposes to meningomyelitis.

Clinical Signs

I. Signs depend on location, with most occurring in the cervical region.
II. Clinical signs of meningitis and myelitis may be seen as a result of extension of infection.
III. Localized or generalized spinal pain and rigidity may occur with meningitis.
IV. Neurological deficits indicative of a transverse myelopathy may occur from myelitis.
    A. Proprioception deficits
    B. Ataxia
    C. Paresis or paralysis

Diagnosis

I. A dermoid sinus may be palpable or visualized as an opening of the skin on the dorsum.
II. Fistulography can be used to determine communication with the spinal canal.
III. CSF analysis can identify meningitis.
IV. Myelography identifies communication with CSF or compression of the spinal cord.
V. MRI defines the extent of the sinus and secondary compression of the spinal cord.

Differential Diagnosis

I. Meningomyelitis
II. Neoplasia
III. Intervertebral disc disease
IV. Other congenital or developmental anomalies of the vertebrae or spinal cord

Treatment and Monitoring

I. Antimicrobial therapy is indicated for meningomyelitis based on culture and sensitivity results.
II. Surgical excision, possibly combined with laminectomy, is warranted in symptomatic cases.
III. Prognosis is excellent in cases with no communication between the sinus and spinal cord.

Storage Disorders

Globoid Cell Leukodystrophy

See Chapter 23, Table 23-2.

Mucopolysaccharidosis

See Chapter 23, Table 23-2.

Degenerative Disorders

Intervertebral Disc Disease

Definition

I. Intervertebral disc disease (IVDD) implies degeneration of the intervertebral disc structures and subsequent herniation of disc material into the vertebral canal.
II. Extrusion of the nucleus pulposus through the annulus fibrosis is a Hansen type I lesion.
III. Protrusion of the annulus caused by shifting of nucleus pulposus is a Hansen type II lesion.
IV. Explosive disc disease that occurs peracutely, without compression, is a type III or high-velocity low-volume disc herniation.

Causes and Pathophysiology

I. Type I disc disease commonly affects chondrodysplastic breeds (e.g., dachshund, beagle, Pekingese, Lhasa apso, shih tzu) and chondrodystrophic-like breeds (e.g., American and English cocker spaniel, miniature poodle) (Cherrone et al., 2004).
    A. Type I disc disease is most commonly associated with chondroid disc degeneration.
    B. Disc degeneration occurs in 75% to 100% of all discs by 1 year of age in chondrodystrophoid breeds (Morgan and Miyabayashi, 1988).
    C. Type I disc disease is associated with an acute onset of signs.
    D. Often there is mineralization of the nucleus pulposus.
II. Type II disc disease commonly affects older, large-breed, achondrodystrophic dogs.
    A. Type II disc disease is associated with degeneration characterized by fibrous metaplasia of the nucleus pulposus.
    B. Type II disc disease causes slow, progressive spinal cord compression.
III. Although uncommon in cats, type I disc disease occurs most frequently (Munana et al., 2001).

Clinical Signs

I. Type I disc disease typically occurs in dogs between 3 and 5 years of age.

II. Type II disc disease typically occurs in dogs between 6 and 9 years of age.
III. On average, affected cats are 10 years of age (Munana et al., 2001).
IV. Signs reflect the region of the affected spinal cord.
V. Cervical disc disease accounts for 15% of cases (Coates, 2000).
VI. Thoracolumbar (T-L) disc disease accounts for 85% of cases (Coates, 2000).
VII. Thoracolumbar disc disease typically occurs between T11 to L3 vertebrae.
VIII. Severity of signs ranges from pain, paresis and ataxia, loss of motor abilities, or loss of nociception (deep pain perception).
IX. IVDD most commonly causes a transverse myelopathy.
  A. Proprioception deficits
  B. Ataxia
  C. Paresis and paralysis
X. Asymmetrical clinical signs are often seen.
XI. Cervical disease usually results in less-severe clinical signs than thoracolumbar disease.
  A. Apparent neck pain is the most common clinical sign with cervical disc disease.
  B. Nonambulatory tetraparesis is more common in large-breed dogs with cervical disease than small-breed dogs (Cherrone et al., 2004).
  C. Lower motor neuron (LMN) deficits or monoparesis can be seen with caudal cervical disc disease.
XII. LMN deficits may be seen in the pelvic limbs with herniations caudal to L3 that cause compression of the lumbosacral spinal cord or cauda equina.
XIII. Progressive hemorrhagic myelomalacia occurs in up to 11% of dogs that have lost nociception (Olby et al., 2003).
  A. The lesion may ascend, resulting in cranial progression of analgesia, and ultimately cause tetraplegia and respiratory failure.
  B. The lesion may descend, resulting in LMN signs in the pelvic limbs, as well as urinary and fecal incontinence.

Diagnosis

I. Spinal radiographs may be suggestive of disc herniation or be normal.
  A. Characteristic findings include a narrowed or wedged intervertebral disc space, small intervertebral foramen with narrowed articular processes, or mineralized disc material in the vertebral canal.
  B. Type I disease is not associated with spondylosis, although spondylosis may be associated with type II disease (Levine et al., 2006).
II. Myelography is important for determining the site (or sites) of disc herniation before surgery.
  A. Characteristic findings include extradural spinal cord compression or diffuse spinal cord swelling.
  B. Myelography may be normal when there is lateral or intraforaminal extrusion.
III. CSF analysis is needed before myelography.
IV. CT can accurately identify the site and lateralization of type I disc herniation, without the need for concurrent myelography (Olby et al., 2000).
V. MRI is extremely sensitive in localizing disc disease, extradural compressions, and associated parenchymal disease (Ito et al., 2005; Besalti et al., 2006; Chang et al., 2006)

Differential Diagnosis

I. Type I disc disease
  A. Trauma
  B. Diskospondylitis
  C. Atlantoaxial subluxation
  D. Fibrocartilaginous embolic myelopathy
  E. Meningomyelitis
II. Type II disc disease
  A. Neoplasia affecting the spinal cord
  B. Degenerative myelopathy
  C. Myelitis
  D. Orthopedic disease

Treatment

I. Medical therapy
  A. Medical therapy is reserved for cases with only pain or cases with mild, nonprogressive neurological deficits.
  B. Medical therapy consists of corticosteroid or nonsteroidal antiinflammatory therapy.
    1. Prednisone 0.5 to 1.0 mg/kg PO, IV SID, tapered over 1 to 2 weeks
    2. Carprofen 2.0 mg/kg PO BID
  C. Consider concurrent use of centrally acting muscle relaxants for 1 to 2 weeks (diazepam 0.25 mg/kg PO TID).
  D. Strict exercise restriction is of equal importance and is done concurrently for 4 to 6 weeks.
II. Surgical therapy
  A. Surgery is considered for cases with severe motor dysfunction or recurrent, refractory spinal pain.
  B. Rapid decompression is undertaken to avoid further damage to the spinal cord from continued compression.
  C. Cervical lesions are decompressed via a ventral slotting technique for ventral midline lesions.
  D. Lateralized cervical disc herniation can be treated via a dorsal or modified lateral laminectomy (Rossmeisl et al., 2005).
  E. Thoracolumbar lesions cranial to L4 are decompressed via a dorsolateral hemilaminectomy.
  F. Lesions caudal to L4 are decompressed via a dorsal laminectomy.
  G. Postoperatively, exercise restriction is continued for 4 to 6 weeks.
  H. Bladder care, such as manual expression, catheterization, and pharmacological manipulation is crucial to reduce the potential for detrusor muscle atony and secondary urinary tract infections.
III. Methylprednisolone sodium succinate therapy
  A. High doses of methylprednisolone sodium succinate *(Solu-Medrol)* have been used in acute disc disease as a component of medical or surgical therapy.

B. Contradictory data exist on its efficacy when administered within 8 hours of the onset of the disc extrusion (Olby et al., 1999).
C. The recommended dose is 30 mg/kg IV followed 2 and 6 hours later by 15 mg/kg IV and continued QID for a maximum of 48 hours.
D. Potential side effects include pancreatitis, gastrointestinal hemorrhage, diarrhea, and colonic perforation.

Monitoring of Animal

I. Recovery of nonambulatory dogs varies according to the time interval from onset of signs to surgery, initial severity of neurological dysfunction, and speed of onset of signs.
II. The prognosis is good for dogs with mild to moderate sensory and/or motor deficits.
III. Success rates following cervical disc surgery range from 87% to 100%, whereas success following thoracolumbar disc surgery range from 58% to 95% (Coates, 2000).
IV. Recovery rates with medical therapy in nonambulatory dogs with thoracolumbar disc disease range from 43% to 51% (Coates, 2000).
V. Paraplegic dogs with loss of nociception have a 69% chance of recovering the ability to walk and a 58% chance of recovering nociception, if treated within 48 hours of onset of signs (Olby et al., 2003).
VI. The return of nociception within 2 weeks of surgery is a good prognostic indicator for recovery (Olby et al., 2003; Laitinen and Puerto, 2005)
VII. Recurrence rates after surgery range from 2.7% to 41.7% with thoracolumbar IVDD (Coates, 2000).
VIII. Recurrence rates after surgery range from 10% to 33% with cervical IVDD (Cherrone et al., 2004).
IX. Recurrences usually (96%) develop within 3 years of the initial event (Mayhew et al., 2004).
X. Recurrence rates of 34% to 40% have been reported following conservative therapy, with an average interval to recurrence of 1.7 years (Coates, 2000).

Cervical Spondylomyelopathy

Definition

I. Cervical vertebral malformation or malarticulation results in compression of the cervical spinal cord segments.
II. Synonyms include wobbler syndrome, caudal cervical malformation-malarticulation, cervical spondylopathy, cervical vertebral instability, and cervical vertebral stenosis.

Causes and Pathophysiology

I. The etiology remains undetermined.
II. It commonly affects male, large to giant breeds of dogs.
III. Genetic factors are suspected for the Doberman pinscher and Great Dane.
IV. Clinical disease occurs most frequently in young Great Danes (<2 years) and middle-aged Doberman pinschers (3 to 9 years).
V. The C5-C6 and C6-C7 vertebrae and discs are affected most commonly.
VI. Compression of the spinal cord can be static or dynamic.
A. Great Danes most commonly have a static compression from dorsal or dorsolateral osseous malformation (Abramson et al., 2003).
B. Dobermans most commonly have a ventral dynamic compression, and possibly dorsal soft-tissue hypertrophy.
1. Dorsal compression occurs from hypertrophy of the ligamentum flavum and joint capsules.
2. Ventral compression occurs from annulus hypertrophy and dorsal longitudinal ligament pathology.

Clinical Signs

I. Clinical signs reflect chronic compression of the cervical spinal cord.
II. Onset of clinical signs is gradually progressive over several months or years; however, acute onset is occasionally seen.
III. Initial signs usually begin in the pelvic limbs and progress to tetraparesis.
IV. Signs usually reflect a C1-C5 or C6-T2 myelopathy.
V. Neck pain is uncommon, although the dogs may resist movement of the neck.

Diagnosis

I. Survey radiography may be normal or show a variety of pathologic changes.
II. Radiographic changes include malalignment remodeling and sclerosis of the vertebrae, narrowing of the intervertebral disc (IVD) space, degenerative changes of the articular facets, and spondylosis.
III. Myelography is essential to determine neural involvement, and to identify static and dynamic lesions.
IV. CT or MRI can identify spinal cord compression and atrophy, as well as parenchymal pathology secondary to chronic compression.

Differential Diagnosis

I. Intervertebral disc disease
II. Neoplasia affecting the spinal cord
III. Myelitis
IV. Trauma
V. Diskospondylitis

Treatment

I. Therapy for dogs with mild clinical signs is conservative.
A. Prednisone 0.5 to 1.0 mg/kg PO SID
B. Carprofen 2.0 mg/kg PO BID
C. Exercise restriction
D. Dietary protein restriction in young Great Danes
II. Surgical therapy is often used for moderately to severely affected dogs.
III. The primary objectives of all surgical procedures are to decompress the spinal cord and/or stabilize of the affected vertebrae.
IV. Available surgical techniques include ventral slotting; ventral distraction and fusion, with or without ventral slotting; or continuous dorsal laminectomy (De Risio et al., 2002).

V. The high potential for morbidity and postoperative complications must be considered and discussed with the owner.

Monitoring of Animal

I. Most affected dogs require surgical therapy for long-term relief.
II. The prognosis with surgery depends on the number of sites affected, chronicity, and neurological status of the dog; it can vary from 20% to 80%.
III. Recurrence can occur from implant failure or adjacent disc disease (domino effect).

Spondylosis Deformans

Definition

I. Spondylosis deformans is a chronic, degenerative, noninflammatory disease characterized by the production of osteophytes on the spine that result in the formation of spurs or complete bony ridges across the intervertebral disc space.
II. Ankylosing spondylosis and ankylosing spondylitis are sometimes used synonymously; however, ankylosis is uncommon and the condition is not inflammatory.

Causes and Pathophysiology

I. Osteophyte production occurs in response to degenerative changes in the intervertebral discs.
II. The changes may be secondary to aging and trauma.
III. The disease has been reported in dogs >2 years of age, with 75% of dogs affected to some extent by 9 years of age (Levine et al., 2006).
IV. Because of the high prevalence in female boxers, it is possibly an inherited disease; however, all dog breeds can be affected.
V. The caudal thoracic, lumbar, and lumbosacral spinal segments are most frequently affected in dogs, and the highest incidence occurs at the level of T7-T8 in cats.
VI. An association may exist between radiographically apparent spondylosis and type II disc disease (Levine et al., 2006).

Clinical Signs

I. Compression of the cord or spinal nerves from osteophytic projections into the spinal canal is rare.
II. Rarely, compression of neural tissue may result in a transverse myelopathy or neuropathy.

Diagnosis

I. Diagnosis is based on radiographic identification of osteophyte formation on the ventral surface (in the region of the metaphysis) of the vertebral body or bodies.
II. Osteophytes may occur at either normal or narrowed disc spaces.
III. Myelography can detect associated spinal cord compression and its cause.
IV. CT or MRI helps identify spinal cord compression or foraminal stenosis.

Differential Diagnosis

I. Diskospondylitis
II. Trauma
III. Intervertebral disc disease

Treatment and Monitoring

I. Treatment is usually not necessary.
II. Analgesia and exercise restriction may help dogs that exhibit only discomfort.
III. Surgical decompression may be necessary in cases with clinical signs.
IV. If clinical, the prognosis is guarded owing to the high risk of recurrence.

Spinal Synovial Cyst

Definition

Spinal extradural synovial cysts arise from the articular facets and surrounding connective tissues of the cervical and thoracolumbar vertebrae of dogs.

Causes and Pathophysiology

I. The cysts commonly occur in the cervical spine of young, large-breed dogs and in the thoracolumbar spine of older, large-breed dogs (Dickinson et al., 2001b).
II. Occurrence has been associated with degenerative disc disease and trauma.
III. Increased mechanical stress and joint motion may predispose the thoracolumbar junction to osteoarthritis and synovial cyst formation.
IV. Histopathology of the cyst reveals fibrous connective tissue with a synovial cell lining.

Clinical Signs

I. Clinical signs are consistent with a transverse myelopathy at the site of the lesion.
II. Signs include proprioception deficits, ataxia, paresis or paralysis, often accompanied by paraspinal hyperesthesia.

Diagnosis

I. Degeneration and remodeling of the articular processes are seen at the site of the lesion.
II. Myelography demonstrates spinal cord compression.
III. CT and MRI better define the lesion.

Differential Diagnosis

I. Spinal stenosis
II. Intervertebral disc disease
III. Cervical spondylomyelopathy
IV. Neoplasia

Treatment and Monitoring

I. Surgical decompression of the spinal cord with cyst removal is indicated in dogs with neurological deficits or refractory pain.
II. Recurrence rates are unknown, but surgery usually provides long-term resolution of signs (Dickinson et al., 2001b).

Spinal Stenosis

Definition

I. Spinal stenosis indicates a narrowing of the vertebral canal that may be focal, segmental (affecting several adjacent vertebrae), or generalized (present throughout the vertebral column).
II. Bony impingement on neural elements may be congenital, developmental, acquired, or idiopathic.
III. Compression of neural tissue occurs by nonosseous components of the vertebral canal.
IV. Hypertrophy of the dorsal, longitudinal ligament and the ligamentum flavum may be involved.
V. Disc extrusion or protrusion may occur.

Causes and Pathophysiology

I. Congenital stenosis may occur as a primary lesion or may be seen in association with other congenital vertebral anomalies.
II. Segmental vertebral stenosis occurs in the cranial thoracic spine of several dog breeds (e.g., Doberman pinscher).
III. Developmental stenosis may result from inborn errors of skeletal growth in dogs.
IV. Hypertrophy of the nonosseous components of the vertebral canal has been reported in rottweilers secondary to ligamentous proliferation at C2-C3.

Clinical Signs

I. Clinical signs reflect the location of the lesion, regardless of the precise cause.
II. Onset of signs is usually insidious and progressive.

Diagnosis

I. Diagnosis can be made by survey radiography.
II. Myelography is essential for precise localization of the spinal stenosis.
III. CT or MRI may aid in identification of the location and the extent of soft tissue and parenchymal involvement (Abramson et al., 2003).

Differential Diagnosis

I. Other congenital anomalies of the vertebrae
II. Intervertebral disc disease
III. Cervical spondylomyelopathy
IV. Spinal synovial cysts

Treatment and Monitoring

I. Conservative therapy may be appropriate in mildly affected cases.
   A. Prednisone 0.5 to 1.0 mg/kg PO SID
   B. Carprofen 2.0 mg/kg PO BID
   C. Exercise restriction
II. Decompressive surgery is indicated in animals with persistent pain or progressive neurological deficits.

Osteochondromatosis

Definition

I. A skeletal osteochondroma is a cartilage-capped exostosis arising from the surface of a bone formed by endochondral ossification.
II. Synonyms include multiple or solitary cartilaginous exostoses, hereditary multiple exostoses, multiple osteochondromatosis, diaphyseal aclasis, dyschondroplasia, and hereditary deforming chondrodysplasia.

Causes and Pathophysiology

I. Outgrowths are related to the metaphysis of growing bones in the appendicular and axial skeleton, particularly affecting vertebrae.
II. Feline osteochondromatosis is seen in mature cats (2 to 4 years) in association with feline leukemia virus (FeLV) and feline sarcoma virus.
III. Canine osteochondromatosis is usually seen before 18 months of age and may have an hereditary basis.
IV. Malignant transformation has been reported.

Clinical Signs

I. Clinical signs reflect the location of any vertebral exostosis producing a transverse myelopathy (if there is associated cord compression).
   A. Proprioception deficits
   B. Ataxia
   C. Paresis or paralysis
II. Lesion may result in asymmetrical signs.
III. Pain may be the only clinical sign.

Diagnosis

I. Radiographically, vertebral lesions tend to be circular and smooth with sclerotic borders and are often radiopaque, with radiolucent areas.
II. Myelography is necessary to demonstrate associated spinal cord compression.
III. CT may better define the extent of the bony proliferation within the vertebral canal.
IV. Surgical biopsy is necessary to confirm the diagnosis.

Differential Diagnosis

I. Benign bone tumors: osteomas
II. Neoplasia
III. Osteomyelitis

Treatment

I. Asymptomatic lesions do not require treatment.
II. Surgical excision is indicated if spinal cord compression is causing neurological signs.

Monitoring of Animal

I. For dogs, prognosis varies with severity of signs.
II. The prognosis for dogs having reached skeletal maturity is better than for immature dogs.

III. The prognosis for cats concurrently infected with FeLV is guarded because of increased risk of recurrence.

Degenerative Myelopathy

Definition

I. It is a slowly progressive noninflammatory disease of the spinal cord consisting of axonal degeneration and demyelination.
II. It is synonymous with *chronic degenerative radicular myelopathy.*

Causes and Pathophysiology

I. The etiology remains unknown.
II. Immune-related degeneration has been proposed.
III. German shepherd dogs may have a genetic predisposition.
IV. Pathologic changes have been identified throughout the spinal cord, as well as in the red, lateral vestibular, and dentate nuclei (Johnston et al., 2000).
V. Lesions are most prominent in thoracic segments of the spinal cord.

Clinical Signs

I. Signs are usually nonpainful, insidious, progressive ataxia and paraparesis of the pelvic limbs that ultimately leads to bladder incontinence and paraplegia over 6 to 12 months.
II. It occasionally (10% to 20%) causes reduced patella reflexes from dorsal nerve root involvement (Averill, 1973).
III. Nociception (deep pain perception) is usually unaffected.
IV. It occurs most frequently in the German shepherd dog, and is also recognized in the Pembroke Welsh corgi, boxer, and other breeds.
V. It is rare in cats.
VI. Average age of affected dogs is 9 years old; dogs younger than 5 years are rarely affected (Longhofer et al., 1990).

Diagnosis

I. Tentative antemortem diagnosis is based on classic clinical signs and the exclusion of other diseases.
II. An increased protein level may be found in lumbar CSF.
III. CT and myelography reveal spinal cord atrophy (Jones et al., 2005).

Differential Diagnosis

I. Intervertebral disc disease
II. Neoplasia
III. Myelitis
IV. Orthopedic disease

Treatment and Monitoring

I. Effective treatment has not been reported.
II. Medical treatments that have been advised but not proven include the following:
   A. Aminocaproic acid 500 mg PO TID
   B. N-acetylcysteine 70 mg/kg PO TID for 2 weeks then TID every other day
III. Long-term prognosis is uniformly poor.

Leukoencephalomyelopathy of Rottweilers

Definition

I. It is a demyelinating disorder of the brain and spinal cord.
II. It is reported in rottweilers in United States and Europe.

Causes and Pathophysiology

I. Bilateral symmetrical demyelination occurs in the white matter of the spinal cord, brainstem, and cerebellum.
II. Lateral and dorsal funiculi are commonly affected in the cervical and thoracic spinal cord.
III. The precise etiology is unknown, but the condition may be heritable.

Clinical Signs

I. Onset is at 18 to 42 months of age.
II. Slow progressive clinical signs develop over a 6- to 12-month period.
III. Clinical signs are consistent with a C1-C5 myelopathy and include tetraparesis, hypermetria, and exaggerated segmental reflexes.

Diagnosis

I. Tentative diagnosis is based on signalment, clinical signs, and exclusion of other diseases.
II. Definitive diagnosis is made with histopathology.

Differential Diagnosis

I. Myelitis
II. Neoplasia
III. Cervical spondylomyelopathy
IV. Other degenerative diseases of the spinal cord

Treatment and Monitoring

I. No effective treatment exists.
II. Progression of the disease frequently leads to recumbency and euthanasia.

INFLAMMATORY AND INFECTIOUS DISORDERS

Diskospondylitis/Vertebral Osteomyelitis

Definition

I. Diskospondylitis is infection of the intervertebral disc and adjacent vertebrae.
II. Vertebral osteomyelitis is infection of only the vertebra.
III. Vertebral physitis is infection restricted to the physis.

Causes and Pathophysiology

I. Infection of the intervertebral disc is most commonly associated with *Staphylococcus intermedius*.
II. Other less commonly identified organisms include *Streptococcus* spp., *Escherichia coli*, *Actinomyces* spp., *Brucella canis*, and *Aspergillus* spp.
III. Young German shepherd dogs are predisposed to aspergillosis.

IV. Young basset hounds may be predisposed to diskospondylitis associated with systemic tuberculosis.
V. Infection may arise from hematogenous spread from distant foci of infection, extension of a paravertebral infection, penetrating wounds, surgery, or plant material (grass awn) migration.
VI. Infection causes extradural spinal cord or cauda equina compression.
VII. It is infrequently seen in cats.

Clinical Signs

I. It occurs most commonly in intact male, middle-aged, large- and giant-breed dogs.
II. Single or multiple sites can be infected.
III. The L7-S1 IVD space is most commonly affected.
IV. The thoracolumbar spine is more commonly affected than the cervical spine.
V. Clinical signs reflect the location of the lesion.
VI. Spinal pain is the most frequent initial clinical sign.
VII. Approximately 30% of dogs have signs of systemic illness (e.g., fever, weight loss) (Thomas, 2000).
VIII. Clinical signs may be present for several weeks or months before diagnosis.

Diagnosis

I. Diskospondylitis should be considered in animals with spinal pain or pyrexia.
II. Imaging of the entire spine is done to look for foci of infection.
III. Hematological changes are not usually present unless there is concurrent, systemic infection.
IV. Urinalysis may reveal bacterial or fungal agents.
V. Aerobic, anaerobic, and fungal cultures of blood and urine are positive in up to 75% and 50% of cases, respectively (Thomas, 2000).
VI. Serology for brucellosis is positive in 10% of cases and is performed in all dogs suspected of having diskospondylitis, because of its zoonotic potential (Thomas, 2000).
VII. Definitive diagnosis is usually made with spinal radiography.
   A. Radiographic changes include narrowing of the IVD space and lysis of the vertebral endplates, which are surrounded by sclerosis.
   B. The entire spine must be evaluated.
   C. Radiographs also are used to monitor response to therapy (Shamir et al., 2001).
   D. Radiographic changes often lag behind clinical improvement.
VIII. Myelography is indicated in animals with substantial neurological deficits.
IX. CSF analysis may be normal or may have an increased white blood cell (WBC) count and/or protein content.
X. CT can identify subtle endplate erosion and paravertebral soft-tissue swelling.
XI. MRI can identify inflammatory lesions within the disc space and adjacent soft tissues (Gonzalo-Orden et al., 2000; Cherubini et al., 2004).
XII. Percutaneous, fluoroscopic-guided needle aspiration and culture of the disc space may confirm the etiology in up to 75% of cases (Thomas, 2000).
XIII. Surgical biopsy of the lesion may be warranted in refractory cases.

Differential Diagnosis

I. Spondylosis deformans
II. Vertebral neoplasia
III. Intervertebral disc disease
IV. Meningomyelitis
V. Myositis
VI. Polyarthritis

Treatment and Monitoring

I. Treatment consists of long-term use of an antimicrobial that is effective against the causative organism, as determined by culture and sensitivity testing.
II. If an organism is not cultured, direct empirical therapy against *Staphylococcus* spp. is started.
   A. Cephalexin 20 to 30 mg/kg PO TID
   B. Cefazolin 20 mg/kg IV, IM, SC QID
   C. Amoxicillin 20 mg/kg PO BID
III. Intravenous antimicrobials are given to animals with severe neurological deficits.
IV. Antimicrobials are provided for a minimum of 6 to 8 weeks.
V. Resolution of signs usually occurs within 2 weeks of instituting therapy; however, neurological deficits can persist.
VI. Continued pain is indicative of active disease.
VII. Failure to respond to first-line antimicrobials requires the addition of a second antimicrobial.
   A. Enrofloxacin 5 to 11 mg/kg PO BID (dogs)
   B. Doxycycline 25 mg/kg PO SID (dogs); may cause vomiting
   C. Trimethoprim-sulfadiazine 15 mg/kg PO BID
VIII. Surgical exploration for internal decompression and possible stabilization may be necessary in refractory cases (Auger et al., 2000; Kinzel et al., 2005).
IX. Fluconazole 2.5 to 5 mg/kg PO BID is recommended for *Aspergillus* spp. infections.
X. Ideally, fungal infections are treated based on sensitivity testing.
XI. Nonsteroidal antiinflammatory drugs can be used to alleviate pain.
   A. Carprofen 2 mg/kg PO BID
   B. Ketoprofen 1 mg/kg PO SID for 5 days
XII. The prognosis is very good unless there is an associated endocarditis or a fungal etiology.

Steroid-Responsive Meningitis-Arteritis

Definition

I. It is a noninfectious, inflammatory disease affecting the meninges and associated vasculature.
II. Synonyms include necrotizing vasculitis, juvenile polyarteritis syndrome, corticosteroid-responsive meningitis/

meningomyelitis, aseptic suppurative meningitis, and pain syndrome.

Causes and Pathophysiology

I. The etiology and pathogenesis of this condition are not well understood.
II. The disease may be triggered by an environmental factor that leads to dysregulation of the immune system (Tipold et al., 1999).
III. Immunoglobulin (Ig) A may play a role in the pathogenesis (Tipold et al., 1995).

Clinical Signs

I. It is reported in the beagle, Bernese mountain dog, boxer, German short-haired pointers; it may occur in other breeds.
II. Affected dogs are often young, large-breed dogs between 7 and 18 months old.
III. Signs occur acutely or may follow a waxing and waning course over weeks to months.
IV. Dogs are usually febrile, anorexic, and hyperesthetic, with cervical rigidity.
V. Concurrent immune-mediated polyarthritis or glomerulonephritis may be present.
VI. Neurological deficits, weakness, and ataxia can be seen in the chronic cases.

Diagnosis

I. A marked neutrophilia with a left shift is often seen on a CBC.
II. CSF analysis reveals severe neutrophilic pleocytosis and protein elevation.
   A. Cell counts >100 cells/μL are common.
   B. Neutrophils are nondegenerate.
   C. Marked elevations of protein are common (40 to 350 mg/dL).
   D. Infectious agents are not identified.
III. Blood and CSF cultures, serology, and polymerase chain reaction (PCR) analysis are negative for infectious agents.
IV. Nonspecific elevations of IgA are detected in the CSF and serum (Tipold et al., 1995).

Differential Diagnosis

I. Infectious meningomyelitis
II. Granulomatous meningoencephalomyelitis
III. Diskospondylitis
IV. Polyarthritis, polymyositis
V. Intervertebral disc disease

Treatment and Monitoring

I. Treatment consists of long-term immunosuppressive doses of corticosteroids.
   A. Prednisone 4 mg/kg PO, IV SID for 2 days, *then*
   B. Prednisone 2 mg/kg PO, IV SID for 14 days, and if clinical signs have improved, *then*
   C. Prednisone 1 mg/kg PO SID for 28 days, and if clinical signs have resolved, *then*
   D. Prednisone 0.5 mg/kg PO SID for 2 months, then stopped if dog remains normal
II. Approximately 50% of dogs have a recurrence after discontinuation of the corticosteroids.
III. CSF analysis should be normal before stopping the prednisone.
IV. Additional immunosuppressive therapy may be necessary in some cases (see Chapter 23).

Granulomatous Meningoencephalomyelitis

See Chapter 23.

Distemper Myelitis

Definition and Cause

I. Distemper myelitis is infection of the canine spinal cord with canine distemper virus (CDV).
II. CDV is a Morbillivirus of the family of Paramyxoviridae.
III. Infection of the CNS can cause focal or diffuse lesions in both the grey and white matter.

Pathophysiology

I. Focal or diffuse demyelination can occur in the white matter of the spinal cord.
II. Resultant lesions depend upon host immunity, age, and duration of infection.
   A. Acute polioencephalomyelopathy with glial and neuronal necrosis occurs in immature or immunodeficient dogs.
   B. Chronic leukoencephalomyelopathy with demyelination occurs in older or immunosuppressed dogs.
   C. Demyelination is more frequent in the chronic stages of the disease.
   D. The mechanism by which demyelination occurs may be a primary effect of the virus on glial cells or may occur secondary to immunological mechanisms (Vandevelde and Zurbriggen, 2005).
   E. The white matter of cerebellum, cerebellar peduncles, optic nerves, optic tracts, and spinal cord are most frequently affected.

Clinical Signs

I. Distemper myelitis can occur in any age or breed of dog and vaccination does not always confer protection.
II. The CNS may be the only system affected.
III. Spinal cord signs depend on the location of the lesion, with T3-L3 segments frequently involved.
IV. Signs may be acute or chronic, progressive or relapsing, and occur bilaterally, with occasional asymmetry (Vandevelde and Zurbriggen, 2005).
V. In addition to a transverse myelopathy causing paraparesis and/or plegia, several other signs have been associated with this infection.
   A. Self-mutilation of the limbs and tail
   B. Paraphimosis and/or urinary incontinence
   C. Infrequent paraspinal hyperesthesia from pia arachnoid inflammation
   D. Myoclonus of the limbs that persists during sleep

Diagnosis

I. A tentative antemortem diagnosis is based on history and compatible clinical signs.
II. Diagnosis is often based on exclusion, as a definitive antemortem diagnosis is often difficult to obtain.
III. Hematological and CSF findings are nonspecific.
IV. Positive immunofluorescent assays for CDV antigen on conjunctival tissue, CSF, urine, skin, or blood can facilitate a diagnosis.
V. Analysis of CSF-specific IgG levels and determining the CSF:serum IgG ratio can be used to detect chronic CDV infections.
VI. PCR analysis of CSF and urine is a sensitive method for detecting infection (Amude et al., 2006; Saito et al., 2006).

Differential Diagnosis

I. Infectious meningomyelitis
II. Congenital, inherited neurodegenerative diseases
III. Degenerative myelopathy
IV. Type II disc disease
V. Neoplasia affecting the spinal cord

Treatment and Monitoring

I. Specific antiviral therapy is not available.
II. Administration of modified-live virus vaccines is only effective if given before clinical signs appear.
III. Short-duration prednisone therapy (0.5 to 1.0 mg/kg PO SID to BID for 1 to 3 days) may provide some relief.
IV. The prognosis for recovery is poor.

Infectious Meningomyelitis

Definition

I. Meningitis is inflammation of the meninges.
II. Myelitis is inflammation of the parenchyma of the spinal cord.

Causes

I. Viral causes include feline infectious peritonitis (FIP), FeLV, rabies, CDV, and canine adenovirus.
II. Bacterial causes include *Staphylococcus* spp., *Pasteurella* spp., *Actinomyces* spp., and *Nocardia* spp.
III. Protozoal causes include *Toxoplasma gondii* (dogs, cats), *Neospora caninum* (dogs), and *Sarcocystis* spp. (dogs, cats) (Dubey et al., 2006).
IV. Rickettsial causes include *Rickettsia rickettsii* (Rocky Mountain spotted fever [RMSF]) and *Ehrlichia canis*.
V. Fungal causes include *Cryptococcus neoformans*, *Blastomyces dermatitidis*, *Histoplasma capsulatum*, and *Coccidioides immitis*.

Pathophysiology

I. FIP causes granulomatous inflammation of the meninges, ependymal cells, and choroid plexus.
II. FeLV-associated myelopathy has been reported in chronically infected cats (Carmichael et al., 2002).
III. Bacteria and fungal diseases can infect the spinal cord through extension, penetration, and hematogenous routes.
IV. *T. gondii* and *N. caninum* can infect the spinal cord, peripheral nerves, and muscles.
V. Rickettsial disease affects the spinal cord through immune-mediated vasculitis.

Clinical Signs

I. The hallmark of infectious diseases is multifocal clinical signs.
II. Neurological signs reflect the region of the spinal cord affected.
III. Signs include paresis and ataxia.
IV. Often there are concurrent, systemic signs of inflammation.
V. Viral diseases may produce the following:
   A. FIP
      1. Cats can be affected at any age but are often between 6 months and 5 years of age.
      2. Signs are insidious and may reflect multiorgan involvement.
      3. The CNS signs may be focal, diffuse, or multifocal.
      4. Intracranial signs are more common than spinal signs.
      5. Clinical signs reflect the location of the pathology.
   B. FeLV causes hyperesthesia and progressive paraparesis to paralysis.
VI. Bacterial and fungal diseases
   A. Signs reflect the location and severity of the pathology.
   B. Neurological signs are often acute and rapidly progressive, but occasionally fungal infections can be slowly progressive.
   C. Fever occurs intermittently and is more likely with concurrent bacteremia or disseminated fungal infection.
VII. Protozoal diseases are characterized by the following:
   A. *T. gondii*
      1. Affected animals usually have signs of progressive multifocal disease.
      2. A focal transverse or diffuse myelopathy may be seen.
      3. Neurological signs reflect the location of the infection.
      4. In dogs <1 year of age, a syndrome of progressive paralysis and rigid extension of one or both pelvic limbs may be seen, as well as muscle contracture of the affected limbs.
      5. Concurrent signs of systemic infection include fever, lymphadenopathy, pneumonia, gastrointestinal disease, and chorioretinitis.
   B. *N. caninum*
      1. Puppies are more severely affected than adult dogs.
      2. Young dogs develop an ascending paralysis.
      3. Concurrent signs include dysphagia and jaw paresis.
VIII. Rickettsial disease may affect dogs of all ages.
   A. Mental depression is the most common clinical finding.
   B. Concurrent, systemic signs include fever, anorexia, lymphadenopathy, dyspnea, diarrhea, vomiting, hemorrhagic diatheses, and joint pain.

C. Clinical signs of spinal disease may be accompanied by those of intracranial disease and reflect the location of the lesion.
D. Cervical rigidity and pain may occur with RMSF.

Diagnosis

I. Viral diseases
  A. FIP
    1. Confirmation antemortem is difficult.
    2. Biopsy of affected tissue is necessary for definitive diagnosis.
    3. CSF analysis reveals a neutrophilic pleocytosis and markedly elevated protein levels.
    4. Indicators of disease are a positive coronavirus titer or PCR analysis in CSF, a high serum total protein concentration, and findings on imaging that include CNS periventricular enhancement, ventricular dilation, and hydrocephalus.
  B. FeLV-associated disease can only be definitively confirmed postmortem.
II. Bacterial and fungal diseases
  A. A diagnosis of bacterial or fungal meningomyelitis is made by isolating a causative organism in CSF.
  B. CSF cytology may demonstrate the presence of organisms.
    1. Classically bacterial diseases produce marked neutrophilic pleocytosis, and fungal diseases are associated with a mixed mononuclear and polymorphonuclear pleocytosis frequently with eosinophils.
    2. Aerobic, anaerobic, and fungal cultures are performed in suspected cases.
  C. Serology may be useful for diagnosis of fungal infections.
III. Protozoal diseases
  A. Tentative antemortem diagnosis is based upon serological evidence, compatible clinical signs, and positive response to treatment.
  B. CSF analysis shows a mixed-cell or mononuclear pleocytosis, and elevated protein levels.
  C. PCR of the CSF may confirm the diagnosis (Schatzberg et al., 2003).
IV. Rickettsial diseases
  A. CSF analysis may be normal or show mild increases in protein and pleocytosis (predominantly lymphocytes).
  B. Serology can confirm the diagnosis.

Differential Diagnosis

I. Steroid-responsive meningitis-arteritis
II. Diskospondylitis
III. Polyarthritis, polymyositis
IV. Cervical disc disease
V. Neoplasia

Treatment and Monitoring

I. Viral diseases
  A. Treatments include immunosuppression and prevention of secondary bacterial infections.
    1. Give prednisolone 2 to 4 mg/kg PO, IV SID.
    2. Cyclophosphamide 2 mg/kg PO SID for 4 consecutive days of each week has also been used.
    3. Give broad-spectrum antibiotics for 2 to 3 weeks.
  B. Despite aggressive therapy, the prognosis for FIP infection is poor.
II. Bacterial and fungal diseases
  A. Use high-dose, IV bactericidal drugs for at least 4 to 6 weeks in bacterial infections.
    1. Penicillin and penicillin derivatives in high doses (10 to 30 mg/kg IV, IM, PO BID to QID) are recommended for gram-positive infections for the first week.
    2. Most cephalosporins penetrate the CNS poorly.
      a. Several third-generation cephalosporins may reach therapeutic levels in the CNS and are advisable for gram-negative infections.
      b. Drugs to consider include cefotaxime 30 to 40 mg/kg IV, IM, SC TID to QID and ceftazidime 20 to 50 mg/kg IV BID to TID.
    3. Use metronidazole 10 mg/kg IV, PO TID for the treatment of anaerobic infections.
    4. Trimethoprim-sulfadiazine 15 mg/kg SC, PO BID penetrates the CNS effectively.
  B. Surgical drainage of an abscess may be necessary.
  C. Prognosis for bacterial infections is guarded.
  D. Several antifungals may be tried.
    1. Amphotericin B
      a. Dose is 0.15 to 0.5 mg/kg IV three times a week.
      b. When the total dose reaches 4 to 6 mg/kg, a maintenance dose of amphotericin is used (0.15 to 0.25 mg/kg IV once monthly), and rifampin 10 to 20 mg/kg PO TID is started.
    2. Ketoconazole (poor CNS penetration)
      a. Initial dose is 15 to 20 mg/kg PO BID for at least 2 to 3 months or until remission
      b. Maintenance dose is 10 mg/kg PO SID.
    3. Fluconazole
      a. Option 1: 2.5 to 5.0 mg/kg PO, IV BID
      b. Option 2: 5 to 10 mg/kg PO, IV SID for 56 to 84 days
  E. Fungal infections are difficult to eliminate from the CNS, and the prognosis is poor.
III. Protozoal diseases
  A. Early treatment for 2 to 4 weeks is essential.
  B. Trimethoprim-sulfadiazine 15 mg/kg SC, PO BID or ormetoprim-sulfadimethoxine 15 mg/kg PO BID, and clindamycin 15 mg/kg IV, PO for 28 days may improve clinical signs.
  C. Pyrimethamine 0.25 to 0.5 mg/kg PO SID for 28 days can be used adjunctively, but bone marrow suppression can occur in young animals.
  D. Prognosis is poor with rapidly progressive disease, pelvic limb hyperextension, and disease chronicity.
IV. Rickettsial diseases
  A. Give tetracycline 22 to 30 mg/kg PO TID for at least 14 days.
  B. Doxycycline 10 to 20 mg/kg PO BID is often used because of its excellent CNS penetration.
  C. Chloramphenicol 15 to 30 mg/kg PO TID for 7 days has good CNS penetration and is indicated in young (<6 months) dogs to avoid dental staining.

VASCULAR DISORDERS

Ischemic Myelopathy

Definition

I. Ischemic myelopathy involves vascular compromise of the spinal cord that often progresses to local infarction.
II. The term is often used synonymously with fibrocartilaginous embolic myelopathy (FCEM), which denotes a specific cause of the ischemia.

Causes and Pathophysiology

I. Acute spinal cord infarction can be secondary to FCEM, neoplastic emboli, and intravascular coagulation.
II. FCEM is characterized by acute spinal cord infarction from embolization of fibrocartilage identical to that of the nucleus pulposus.
   A. Many theories exist as to the pathophysiology of the embolization, but none are proven.
   B. Fibrocartilaginous emboli occlude arteries and/or veins of the leptomeninges and spinal cord parenchyma.
   C. Achondrodystrophic, medium- to large-breed dogs are predisposed.
   D. There is an increased incidence in miniature schnauzers.
   E. It is infrequently reported in cats (Mikszewski et al., 2006).

Clinical Signs

I. Classically, clinical signs are peracute in onset, nonprogressive, nonpainful, and often asymmetrical.
II. Transverse myelopathy occurs, with signs compatible with the location of the infarction.
   A. Proprioception deficits
   B. Ataxia
   C. Paresis or paralysis
III. Thoracolumbar signs are more common than cervicothoracic, but signs can occur in any region and often involve the intumescence.
IV. Clinical onset is frequently associated with trauma or exercise.
V. Maximal neurological deficits develop within 12 hours and are then nonprogressive.
VI. Severe signs are accompanied by loss of nociception (deep-pain perception).

Diagnosis

I. Tentative diagnosis is based upon history, signalment, and compatible clinical signs.
II. Myelography may demonstrate intramedullary spinal cord swelling in the early stages (Gandini et al., 2003).
III. MRI documents parenchymal pathology (Abramson et al., 2005; Mikszewski et al., 2006).
IV. CSF may reveal mild pleocytosis or a normal cell count with an elevated protein level (albumino-cytological dissociation).

Differential Diagnosis

I. Trauma of the spinal cord
II. Intervertebral disc disease
III. Myelitis
IV. Neoplasia affecting the spinal cord
V. Hemorrhage of vessels in or around the spinal cord

Treatment and Monitoring

I. There is no specific medical therapy for FCEM; however, the use of high-dose corticosteroid therapy has been considered.
   A. The dose of methylprednisolone recommended is 30 mg/kg IV followed 2 and 6 hours later by 15 mg/kg IV and continued QID for a maximum of 48 hours.
   B. Potential side-effects include pancreatitis, gastrointestinal hemorrhage, diarrhea, and colonic perforation.
II. Clinical improvement depends on the severity of sensorimotor dysfunction.
III. A poor prognosis has been correlated with lack of improvement within 14 days, involvement of the intumescences, and a lack of deep pain perception.
IV. Supportive care, physiotherapy, and hydrotherapy may aid in recovery.

NEOPLASIA

Vertebral and Spinal Tumors

Definition and Causes

I. Primary and secondary tumors can affect the vertebrae, meninges, and spinal cord.
II. Feline lymphoma may be associated with FeLV infection.
III. Neoplasia can be classified as extradural, intradural-extramedullary, or intramedullary.
   A. Extradural tumors can be primary or secondary.
      1. Primary vertebral tumors: fibrosarcoma, osteosarcoma, chondrosarcoma, hemangiosarcoma, myeloma
      2. Secondary vertebral tumors: mammary, prostatic, thyroid carcinomas, malignant melanoma, metastatic osteosarcoma
      3. Epidural tumors: lymphoma, metastatic tumors
   B. Intradural extramedullary tumors include meningioma, peripheral nerve sheath tumor, lymphoma, and nephroblastoma.
   C. Intramedullary tumors include astrocytoma, oligodendroglioma, ependymoma, and metastases.
IV. Primary and secondary extradural tumors are more common than intradural extramedullary tumors; intramedullary tumors are rare.
V. Spinal neoplasia accounts for 27% of all spinal disease in cats (Marioni-Henry et al., 2004).
   A. Epidural lymphoma is the most common spinal tumor of cats.
   B. Meningioma is the most common benign, nonlymphoid tumor of cats (Rossmeisl et al., 2006).
   C. Osteosarcoma is the most common malignant, nonlymphoid tumor of cats.

Pathophysiology

I. Spinal tumors occur most commonly in animals >5 years old (Dernell et al., 2000).

A. Dogs with spinal nephroblastoma are usually 4 to 38 months old (Summers et al., 1988).
B. Median age for cats with spinal lymphoma is 4.5 years (Marioni-Henry et al., 2004).

II. Any breed can be affected.
A. All classes of spinal neoplasia occur more frequently in large-breed dogs.
B. German shepherd dogs and golden retrievers may be predisposed to spinal nephroblastoma.

III. Spinal neoplasia occurs throughout the spinal cord and vertebral column.
A. Meningiomas most commonly occur in the cervical spine.
B. Nephroblastoma occurs most commonly between T10 and L2 vertebrae.
C. Feline lymphoma has a predilection for the thoracic and lumbar spinal cord.

Clinical Signs

I. Clinical findings depend on the location of the tumor.
II. Pain is the most common initial clinical signs.
III. The most common sign is a transverse myelopathy that is often bilateral, but can be asymmetrical.
A. Proprioception deficits
B. Ataxia
C. Paresis and paralysis
IV. Signs may progress over 1 week to 1 year.
V. An acute onset may occur from pathologic fractures, hemorrhage, or ischemia.

Diagnosis

I. Tentative diagnosis is based on clinical, radiographic, and CSF analysis, and on advanced imaging findings.
II. Thoracic radiography (three views) and abdominal ultrasonography are performed to identify primary or secondary neoplastic lesions.
III. Radiography can identify bony lesions of the vertebrae.
A. Bone lysis is most common finding associated with a vertebral tumor.
B. Punched-out lytic lesions in multiple vertebrae commonly occur with multiple myeloma.
C. Usually only one vertebra is involved (unless secondary).
IV. CSF analysis often reveals nonspecific changes.
A. The CSF may be normal or may have elevated protein levels.
B. Mild to moderate neutrophilic pleocytosis may occur with tumors affecting the leptomeninges.
C. Tumor cells are rarely identified, except with lymphoma.
V. Advanced imaging may be useful.
A. Myelography helps to differentiate intramedullary, intradural-extramedullary, and extradural lesions.
B. CT is used to identify bony lesions.
C. MRI is the best imaging modality for spinal neoplasia.
1. MRI allows specific determination of extramedullary or intramedullary lesions (McConnell et al., 2003).
2. Intravenous contrast administration helps determine the soft-tissue and osseous extent of the tumor.
3. MRI determines extent of disease and assists with surgical planning (McDonnell et al., 2005).

VI. Definitive diagnosis requires histopathologic interpretation of biopsy specimens.

Differential Diagnosis

I. Intervertebral disc disease
II. Diskospondylitis, osteomyelitis
III. Meningomyelitis
IV. Degenerative myelopathy
V. Spinal trauma

Treatment and Monitoring

I. Long-term prognosis is poor, with survival time often inverse to the severity of neurological deficits (Dernell et al., 2000).
II. Medical therapy consists of the following:
A. Prednisone 0.5 to 1.0 mg/kg PO SID can be used palliatively.
B. Chemotherapy may be tried for certain tumors.
1. Tumors amenable to chemotherapy include lymphoma and multiple myeloma.
2. In cats with spinal lymphoma, remission rate is 50%, with complete remission duration of 14 weeks, and partial remission duration of 6 weeks (Spodnick et al., 1992).
3. Long-term control of solitary plasmacytomas can be achieved with chemotherapy and radiation (Rusbridge et al., 1999).
C. Radiation therapy may be tried as primary, adjunctive, or palliative therapy (Dickinson et al., 2001a).

III. Surgical therapy involves surgical decompression of the spinal cord and debulking of the tumor.
A. Most vertebral tumors are not surgically respectable.
B. The median survival time of dogs with vertebral tumors was 135 days following multimodality therapy that included surgical resection (Dernell et al., 2000).
C. Surgical resection of meningiomas in dogs may lead to remissions of >6 months, and adjunctive radiotherapy may increase remission time to approximately 15 months (Levy et al., 1997).
D. Cytoreductive surgery of malignant, nonlymphoid spinal tumors in cats provides a median survival time of 110.5 days (Rossmeisl et al., 2006).
E. Cytoreductive surgery of benign, nonlymphoid spinal tumors in cats provides a median survival time of 518 days (Rossmeisl et al., 2006).
F. Intramedullary tumors are often difficult to excise without damage to the surrounding parenchyma (Sanders et al., 2002).

TRAUMATIC DISORDERS

Spinal Cord Trauma

Definition

I. Injury to the spinal cord may be caused by endogenous (intervertebral disc disease) or exogenous (vehicular trauma) factors.

II. Direct trauma to the spinal cord results in primary and secondary injuries.
III. Direct trauma to the spinal cord (concussion) may be followed by sustained compression, distraction, or both.

Causes

I. Type I intervertebral disease
II. Vertebral fractures and luxations
III. Fibrocartilaginous embolism
IV. Spinal instability: atlantoaxial subluxation

Pathophysiology

I. Acute spinal cord injury is often caused by a combination of events that can include concussion, compression, ischemia, and laceration (primary injuries).
II. Each of these primary injuries can lead to secondary injury, which is a series of biochemical and metabolic events that expand the primary zone of tissue necrosis.
III. Most secondary injuries occur within 24 hours and contribute to clinical deterioration.

Clinical Signs

I. Neurological examination is performed (carefully) to localize the site of the trauma before any sedation or analgesia is done.
II. Concurrent trauma involving other organ systems is frequently present and must also be assessed.
III. Neurological signs reflect the site of injury.
IV. Progressive hemorrhagic myelomalacia is suspected with continued deterioration.

Diagnosis

I. The diagnosis is made based on history and supportive clinical signs.
II. Thorough evaluation of the entire animal is essential to identify concurrent abnormalities.
III. Survey spinal radiography commonly delineates traumatic luxation and/or subluxation and fractures of the vertebral column.
   A. Lateral survey radiographs are taken of the whole spine before manipulation of the animal.
   B. General anesthesia maybe necessary for accurate positioning, but is delayed until the animal is stabilized.
   C. Sedation or analgesia may assist with positioning, but increases the risk of neurological deterioration secondary to paravertebral muscle relaxation.
IV. Advanced imaging is required to assess nervous tissue.
V. Myelography assists in assessing the degree of associated spinal cord compression.
VI. CT is invaluable in identifying bony defects that may not be apparent on survey radiography.
VII. MRI provides information about spinal cord compression, extradural hemorrhage, and parenchymal structure, but may not provide much detail about fractures and luxations.

Differential Diagnosis

I. Type I intervertebral disc disease
II. Pathologic fracture secondary to neoplasia
III. Fibrocartilaginous embolic myelopathy
IV. Ischemic neuromyopathy

Treatment and Monitoring

I. Initiate stabilization of the cardiovascular and respiratory systems before assessing and treating the spinal injury.
II. Immobilize the spine to prevent further vertebral displacement.
III. Delay administration of analgesia or sedation until the initial assessments, neurological examination, and diagnostics have been performed.
IV. Medical treatment is indicated for animals with mild clinical signs and no evidence of vertebral instability.
   A. Methylprednisolone sodium succinate
      1. The dose recommended is 30 mg/kg IV followed 2 and 6 hours later by 15 mg/kg IV and continued QID for a maximum of 48 hours.
      2. Potential side effects include pancreatitis, gastrointestinal hemorrhage, diarrhea, and colonic perforation.
   B. Cage rest for 6 weeks.
V. If spinal instability is detected but the owner declines surgery, an external splint is required to immobilize the area for 6 to 8 weeks.
VI. Surgical treatment is indicated in cases with instability, vertebral malalignment, or spinal cord compression.
   A. Laminectomy ± durotomy are necessary for decompression.
   B. Realignment and fixation can be achieved using Steinmann pins, screws, and polymethylmethacrylate, or vertebral body plates.
   C. Postoperative care involves exercise restriction, analgesia, soft bedding, and management of bladder evacuation.
   D. Physiotherapy and hydrotherapy may also help recovery.
   E. Prognosis depends on the degree of sensorimotor loss and chronicity of lesion at time of surgery, in addition to severity of any systemic disorders.

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CHAPTER 25

Disorders of the Peripheral Nerves

Laurent Garosi

CONGENITAL/DEVELOPMENTAL DISORDERS

Inherited Motor Neuron Diseases

Definition

I. Motor neuron diseases are a group of neurodegenerative disorders characterized by premature degeneration and loss of motor neurons in the spinal cord and/or brainstem.
II. These processes can affect both upper and lower motor neurons.
III. The term *spinal muscular atrophy* can be used to describe cases in small animals in which lower motor neuron (LMN) signs predominate.

Causes and Pathophysiology

I. In most cases, a presumed genetic or inherited basis is suspected; however, in only a few disorders is the exact mode of inheritance known.
II. Affected breeds include the Swedish Lapland, English pointer, German shepherd dog, Doberman pinscher, Saluki, giant-breed crosses, and Griffon bassett vendeen.

Clinical Signs

I. Clinical signs are usually progressive and dominated by LMN signs
   A. Generalized weakness
   B. Generalized muscle atrophy
   C. Decreased to absent segmental spinal reflexes
   D. Decreased muscle tone
II. Arthrogryposis can be observed as a result of neurogenic atrophy of the appendicular musculature (Kent et al., 1999).

Diagnosis

I. Presumptive diagnosis is made based on signalment and neurological examination (Table 25-1).
II. Electrophysiology can also be used to support the diagnosis.
   A. Abnormalities that can be identified with electromyography (EMG) include positive sharp wave and fibrillation potentials.
   B. Abnormalities can also be identified with motor nerve studies and include motor nerve conduction velocities (NCV) in the low to normal reference range.
III. Diagnosis is supported by evidence of denervation atrophy on evaluation of muscle biopsies.
IV. Definitive diagnosis requires histopathologic evaluation of the spinal cord to demonstrate neuronal loss and gliosis in the ventral horn of the spinal cord.

Differential Diagnosis

I. Toxic neuropathies (Table 25-2)
II. Metabolic neuropathies (see Table 25-2)
III. Infectious diseases of the spinal cord, peripheral nerve, or muscles (see Chapters 24 and 82)

Treatment and Monitoring

I. No therapy exists for any of the congenital neuropathies.
II. Affected animals, as well as parents and siblings, should not be used for breeding.
III. The prognosis is guarded to poor, with most affected animals having a progressive course leading to euthanasia.

INFECTIOUS DISORDERS

Protozoal Polyradiculoneuritis

Definition and Causes

I. *Neospora caninum* and *Toxoplasma gondii* are the most common infectious causes of neuropathy and myopathy (Evans et al., 2004).
II. *T. gondii* infection has been associated with concurrent canine distemper infection.
III. *N. caninum* appears to be a primary pathogen (Ruehlmann et al., 1995).
IV. *N. caninum* is a more common pathogen than *T. gondii*.

Pathophysiology

I. *N. caninum* has a predilection for lumbosacral roots in puppies, resulting in pelvic limb atrophy and immobile joints (contractures) (Ruehlmann et al.,1995).
II. Inflammation consisting of macrophages, lymphocytes, and plasma cells are frequently identified in the nerve roots of the lumbosacral spinal cord.
III. Muscle biopsy is indicated and may reveal nonsuppurative inflammation and tachyzoites within myocytes (Dubey and Lindsay, 1996).

TABLE 25-1

Congenital/Developmental Disorders of Peripheral Nerves

DISORDER/BREEDS	CAUSE/PATHOLOGY	CLINICAL SIGNS/PROGRESSION	REFERENCES
I. Inherited Neuropathies Characterized by Loss of Motor Neuron (Ventral Horn Cell)			
Progressive neuronopathy in Cairn terriers	Both sexes are affected; genetics uncertain; chromatolysis of neurons in spinal ventral gray matter, numerous brain stem nuclei, and spinal, autonomic, and myenteric ganglia.	Pelvic limb weakness begins between 12 and 24 wk of age and progresses to tetraparesis over 2 mo. Head tremor is a consistent finding. Nystagmus, head tilt, and cataplexy were reported in a single case.	Cummings et al. (1988, 1991) Palmer and Blakemore (1989)
Focal spinal muscular atrophy in German shepherd dogs	Both sexes are affected; genetics uncertain; asymmetrical loss of motor neurons in cervical intumescence.	Forelimb weakness begins around 2 wk of age. One animal was euthanized; the other case reached a plateau around 8 wk.	Cummings et al. (1989)
Hereditary progressive spinal muscle atrophy in pointers	Both sexes are affected; probable autosomal recessive condition; lipid accumulation in spinal motor neurons and brainstem neurons.	Pelvic limb weakness begins between 18 and 23 wk of age and progresses to tetraparesis over 3-4 mo.	Inada et al. (1978)
Spinal muscular atrophy in rottweilers	Only affected females have been reported; genetics uncertain; chromatolysis and perikaryal swelling noted in spinal motor neurons and neurons in the brainstem.	Paraparesis at 4 wk of age progresses to tetraparesis within 1-2 wk with pelvic limb rigidity. Megaesophagus is present in some.	Shell et al. (1978)
Spinal muscular atrophy in Brittany spaniels	Both sexes are affected; autosomal dominant inheritance with variable penetrance. Motor neurons have chromatolysis secondary to internodal swellings in proximal axons. Swellings contain massive accumulations of neurofilaments. Neurofilaments are also present in cell body and proximal dendrites of some motor neurons. Nerves that innervate proximal muscle groups are preferentially affected.	Paraparesis progresses to tetraparesis. Late features include respiratory muscle paresis causing dyspnea and ineffective thermoregulation, and cranial nerve involvement causing difficulty grasping food and swallowing. There are three variants of the disease: 1. Accelerated form occurs in homozygotes. Onset occurs between 6 and 8 wk, with tetraparesis by 3-4 mo of age. 2. Intermediate form occurs in heterozygotes. Onset between 6 and 12 mo, with tetraparesis by 2-3 yr. 3. Chronic form occurs in heterozygotes, with onset during adulthood and mild clinical signs that are gradually progressive.	Cork et al. (1979, 1982) Sack et al. (1984)
Neuronal abiotrophy in Swedish Lapland dogs	Both sexes are affected; probable autosomal recessive. Chromatolysis occur in spinal motor neurons, neurons in dorsal root ganglia, cerebeller Purkinje cells, and other brainstem nuclei.	Thoracic or pelvic limb weakness begins at 5-7 wk of age and progresses to tetraparesis within 1-2 wk.	Sandefelt et al. (1973)

From Inzana KD: Disorders of peripheral nerves. p. 276. In Morgan RV, Bright RM, Swartout MS (eds): Handbook of Small Animal Practice. 4th Ed. WB Saunders, Philadelphia, 2003.

TABLE 25-1

Congenital/Developmental Disorders of Peripheral Nerves—*cont'd*

DISORDER/BREEDS	CAUSE/PATHOLOGY	CLINICAL SIGNS/PROGRESSION	REFERENCES
II. Inherited Neuropathies Characterized by Loss of Motor Axon			
Giant axonal neuropathy in Alsatians (German shepherd dogs)	Both sexes are affected; probable autosomal recessive. Giant axonal swelling containing masses of neurofilaments is found in distal segments of myelinated and unmyelinated axons. Both central and peripheral nervous systems are involved.	Paraparesis begins at 14-15 mo, with gradual progression to thoracic limbs. Megaesophagus and laryngeal paralysis are also features of the disease.	Griffiths et al. (1980b) Duncan and Griffiths (1981)
Hereditary polyneuropathy in Alaskan malamutes	Both sexes are affected; probable autosomal recessive. Axonal loss of both motor and sensory fibers occurs in peripheral nerves and in spinal nerve roots, and white matter degeneration is seen in spinal cord and brainstem.	Paraparesis begins in pelvic limbs between 7 and 18 mo of age, with gradual progression to thoracic limbs. Megaesophagus is a prominent feature.	Moe (1992)
Neuropathy in Birman cats	Only affected females have been reported; genetics uncertain. Diffuse loss of myelinated fibers occurs in peripheral nerves, spinal cord, and cerebellum, with a predominantly distal distribution.	Paraparesis begins between 8 and 10 wk of age; data insufficient to report progression.	Moreau et al. (1991)
Polyneuropathy in rottweilers	Both sexes are affected; possible autosomal recessive. Distal axonal degeneration occurs in both motor and sensory fibers, with secondary demyelination.	Paraparesis in adult dogs (1.5-4 yr) that gradually progresses over 1 yr to tetraparesis	Braund et al. (1994)
Progressive axonopathy in boxers	Both sexes are affected; autosomal recessive inheritance. Paranodal axonal swellings containing accumulations of disorganized neurofilaments and vesiculotubular structures are present in spinal nerve roots and in lateral and ventral funiculi of spinal cord. This is associated with reduced axonal diameter in distal segments of peripheral nerves.	Pelvic limb ataxia with paraparesis is seen at 1-3 wk, with gradual progression to involve the thoracic limbs by 1 yr of age and then reaches a plateau. Head bobbing and ocular tremor are seen in a few cases.	Griffiths et al. (1980a) Griffiths (1985)
III. Inherited Neuropathies Characterized by Schwann Cell Dysfunction			
Hypomyelinating neuropathy in golden retrievers	Both sexes are affected; genetics uncertain; reduced myelination in peripheral nerves.	Pelvic limb ataxia begins between 5 and 7 wk of age, with minimal progression.	Matz et al. (1990) Braund et al. (1989)
Hypertrophic neuropathy in Tibetan mastiffs	Both sexes are affected; probable autosomal recessive. Recurrent demyelination and remyelination create thickening of peripheral nerves. Schwann cells have accumulations of 6- to 7-nm filaments.	Paraparesis by 7.5-10 wk of age rapidly progresses over a few days to tetraplegia. Clinical signs improve over the following 4-6 wk, but animals remain weak.	Cummings et al. (1981a) Cooper et al. (1984a, 1984b)

Continued

TABLE 25-1

Congenital/Developmental Disorders of Peripheral Nerves—*cont'd*

DISORDER/BREEDS	CAUSE/PATHOLOGY	CLINICAL SIGNS/PROGRESSION	REFERENCES
IV. Inherited Neuropathies Characterized by Loss of Sensory Neuron or Axon			
Sensory neuronopathy in long-haired dachshunds	Both sexes are affected; probable autosomal recessive; Loss of axons in distal peripheral nerve segments (including vagus nerve) and terminal regions of primary sensory axons in fasciculus gracillis suggests a distal axonopathy of primary sensory neurons.	Generalized ataxia is noted around 8 wk of age. Diminished pain perception noted over whole body. Urinary and fecal incontinence and genital self-mutilation are prominent features. Disease appears nonprogressive.	Duncan and Griffiths (1982) Duncan et al. (1982)
Acral multilation in English pointers and German short-haired pointers	Both sexes are affected; probable autosomal recessive. Reduction in the size of neurons in dorsal root ganglia and degeneration of primary sensory neurons in peripheral nerves and spinal cord are accompanied by a loss of substance P immunoreactivity in the spinal cord.	Onset is between 2 and 12 mo of age. Loss of pain perception and multilation of feet are the most prominent signs.	Cummings et al. (1981b, 1983)
V. Inherited Neuropathies Associated with Inborn Errors of Metabolism			
Hyperchylomicronemia in cats (domestic short-haired, Himalayan, Persian, Siamese breeds)	Both sexes are affected; probable autosomal recessive condition. Deficiency in lipoprotein lipase activity causes hyperlipidemia, and xanthomas with infiltration and entrapment of peripheral nerves near intervertebral foramen and other bony prominences.	Clinical signs of dysfunction of one or more peripheral nerves usually begin around 8 mo of age. Loss of sympathetic supply to the eye (Horner's syndrome), and tibial and radial nerve paralysis are common.	Jones (1993)
Hyperoxaluria in domestic short-haired cats	Both sexes are affected; autosomal recessive condition. Deficiency in D-glycerate dehydrogenase occurs. Peripheral nerve changes are characterized by marked accumulations of neurofilaments in proximal axons of motor and sensory axons.	Animals develop acute signs of renal failure and generalized weakness between 5 and 9 mo of age.	McKerrell et al. (1989)
α-L-Fucosidosis in English springer spaniels	Both sexes affected; autosomal recessive deficiency in the lysosomal enzyme α-L-fucosidase. Proximal enlargements of multiple cranial and spinal nerves occur from infiltration by foamy macrophages and fibroedematous tissue containing fructose-containing substances. There is extensive cytoplasmic vacuolation in neurons and glia in central nervous system.	Behavioral changes may be noted as early as 4-6 mo of age and progress slowly over 2-3 yr. Aphonia, depressed gag reflex, and dysphagia reflect cranial neuropathies. Spinal nerves are affected during the terminal stages.	Taylor et al. (1987) Barker et al. (1988)

TABLE 25-1

Congenital/Developmental Disorders of Peripheral Nerves—*cont'd*

DISORDER/BREEDS	CAUSE/PATHOLOGY	CLINICAL SIGNS/PROGRESSION	REFERENCES
Globoid cell leukodystrophy in West Highland white terriers, Cairn terriers, Pomeranians, basset hounds, bluetick hounds, domestic short-haired cats	Both sexes are affected; probable autosomal recessive deficiency of lysosomal enzyme galactocerebroside β-galactosidase. Accumulations of lipid-laden macrophages (globoid cells) are found in both peripheral and central nervous systems, accompanied by a loss of myelination and a decrease in oligodendrocyte and Schwann cell numbers.	Pelvic limb ataxia and generalized tremor typically begin between 3 and 5 mo of age. They progress to paraplegia, then tetraplegia, hyporeflexia, and eventually blindness and dementia by 1 yr of age.	Blakemore et al. (1974) Vicini et al. (1988)
Niemann-Pick disease in Siamese cats	Both sexes are affected; probable autosomal recessive deficiency of sphingomyelinase. Sphingomyelin and other lipids acumulate in liver, renal tubular cells, bone marrow cells, neurons, and glia. Siamese cats also have demyelinating peripheral neuropathy.	Pelvic limb ataxia and generalized tremor typically begin between 2 and 5 mo of age.	Cuddon et al. (1989)
Glycogen storage disease type IV in Norwegian forest cats	Both sexes are affected; probable autosomal recessive deficiency in glycogen branching enzyme. Intracytoplasmic storage of glycogen occurs in nervous system and cardiac and skeletal muscles, with loss of spinal motor neurons.	Generalized tremors, weakness, and fever begin at 5 mo of age and progress to tetraplegia by 8 mo of age.	Fyfe et al. (1990) Coates et al. (1996)
VI. Inherited Neuropathies Associated with Laryngeal Paralysis			
Laryngeal paralysis in Bouviers des Flandres	Both sexes are affected; autosomal dominant. Degeneration of recurrent laryngeal nerves occurs, with loss of neurons in nucleus ambiguous and occasional axonal loss in tibial nerve.	Inspiratory dyspnea, laryngeal stridor, and exercise intolerance begins between 4 and 6 mo of age. Progression of the syndrome is not reported.	Venker-van Haagen et al. (1978, 1981)
Laryngeal paralysis in Siberian husky dogs and their crosses	Both sexes are affected; genetics not determined. Degeneration is reported only in recurrent laryngeal nerve. Spontaneous activity may occur in other muscles as well.	Inspiratory dyspnea, laryngeal stridor, and exercise intolerance are noted between 2 and 6 mo of age. Progression of this syndrome has not been reported.	O'Brien and Hendriks (1986)
Laryngeal paralysis in dalmatians	Both sexes are affected; inheritance uncertain. Distal axonal degeneration of medium- and large-diameter fibers occurs in all peripheral nerves, including the recurrent laryngeal nerves. Megaesophagus is also present in more than 50% of cases.	Inspiratory dyspnea, laryngeal stridor, exercise intolerance, and regurgitation are first noticed between 2 and 6 mo of age. Clinical signs of more generalized polyneuropathy may develop before, concurrently, or after laryngeal paralysis. Aspiration pneumonia results in death within a year of diagnosis in most cases.	Braund et al. (1994)

Continued

TABLE 25-1

Congenital/Developmental Disorders of Peripheral Nerves—*cont'd*

DISORDER/BREEDS	CAUSE/PATHOLOGY	CLINICAL SIGNS/PROGRESSION	REFERENCES
Laryngeal paralysis-polyneuropathy complex in young rottweilers	Both sexes are affected; inheritance uncertain. Axonal degeneration is noted in both proximal and distal levels of limb nerves, with degeneration more severe in distal recurrent laryngeal nerve. Brain and spinal cord are normal.	Inspiratory dyspnea, laryngeal stridor, exercise intolerance are noted between 2 and 3 mo of age. Clinical signs rapidly progress to generalized weakness. Three of 5 dogs were euthanized within a week of diagnosis because of rapid deterioration.	Mahony et al. (1998)

TABLE 25-2

Summary of Neuromuscular Disorders

CLASS OF DISORDER	NEUROPATHY	JUNCTIONOPATHY	MYOPATHY
Congenital/degenerative	Inherited motor neuron disease Inherited peripheral neuropathy	Congenital myasthenia gravis	Muscular dystrophies Labrador retriever myopathy Inherited myopathy of Great Danes Congenital myotonia
Infectious	Protozoal polyradiculoneuritis/myositis	Botulism Tick paralysis	Infectious myopathies
Inflammatory	Chronic inflammatory demyelinating polyneuropathy Acute polyradiculoneuritis Hypertrophic neuritis	None	Idiopathic polymyositis Familial dermatomyositis Extraocular muscle myositis Masticatory muscle myositis
Idiopathic	Distal denervating disease	Acquired myasthenia gravis	Exercise-induced collapse in Labrador retrievers Exertional rhabdomyolysis
Metabolic	Diabetes mellitus Hypothyroidism Hyperadrenocorticism Hypoglycemic neuropathy	None	Mitochondrial myopathies Lipid storage myopathies Glycogen storage myopathies Hypothyroid myopathies Hyperthyroid myopathies Myopathies related to glucocorticoid excess Adrenocortical insufficiency Hypokalemic myopathy
Toxic	Drug-induced toxic neuropathy	Iatrogenic muscular blockade Organophosphate/carbamate toxicosis	Drug-induced myositis Toxic myopathy
Vascular	Ischemic neuromyopathy	None	Ischemic neuromyopathy
Neoplastic	Peripheral nerve sheath tumor Other primary or secondary tumor Paraneoplastic neuropathy	Paraneoplastic myasthenia gravis	Paraneoplastic inflammatory myopathies
Traumatic	Traumatic neuropathy Brachial plexus avulsion	None	Fibrotic myopathy Myositis ossificans

Clinical Signs

I. Onset of signs is usually observed before 6 months of age.
II. Affected dogs have progressive, ascending paralysis and muscle atrophy, usually with the pelvic limbs more severely affected.
III. Bilateral rigidity of the pelvic limbs is a frequent finding in puppies from polyradiculitis and polymyositis.

Diagnosis

I. Clinicopathologic values are usually not altered.
II. Serum creatine kinase (CK) levels are often increased.
III. Elevated serum and cerebrospinal fluid (CSF) antibody concentrations for N. *caninum* or T. *gondii* support the presence of infection.
IV. Definitive diagnosis can be made by identification of organisms in muscle biopsies.

Treatment and Monitoring

I. Treatment consists of an 8-week course of the combination of trimethoprim-sulfadiazine 15 to 20 mg/kg PO BID, pyrimethamine 1 mg/kg PO SID, and clindamycin 20 to 30 mg/kg PO BID.
II. Although improvement in neurological function is commonly observed, complete resolution of pelvic limb hyperextension is unlikely.

INFLAMMATORY/IMMUNE-MEDIATED DISORDERS

Acute Polyradiculoneuritis

Definition

Polyradiculoneuritis is an inflammatory disorder involving spinal nerve roots.

Causes and Pathophysiology

I. Acute canine polyradiculoneuritis (inflammation of the nerve roots and peripheral nerves) is considered the most common peripheral neuropathy in dogs.
II. A similar condition has been reported in cats, but is less common than in dogs (Gerritsen et al., 1996; Lane and de Lahunta,1984).
III. Acute canine polyradiculoneuritis can be subclassified into three categories according to the presumptive cause.
    A. Coonhound paralysis appears in dogs 7 to 10 days after they have been bitten or scratched by a raccoon.
        1. A protein constituent of raccoon saliva may induce a delayed hypersensitivity against myelin.
        2. Dogs that have recovered from coonhound paralysis are not immune to future attacks.
    B. Vaccination (especially against rabies) has been incriminated as a possible cause of acute canine polyradiculoneuritis.
    C. Another condition exists that appears to be identical to coonhound paralysis with respect to onset, clinical signs, course, and pathologic findings.
        1. It occurs worldwide in dogs that have had no possible exposure to raccoons and is named *idiopathic polyradiculoneuritis*.
        2. The exact pathogenesis is unknown; however, it may be an immune-mediated process.

Clinical Signs

I. Signs are caused by an inflammatory reaction affecting axons and myelin sheaths, mainly in ventral nerve roots.
II. Signs consist of a stiff, stilted, short-strided gait in all four limbs.
III. Weakness initially develops in the pelvic limbs and then ascends rapidly, resulting in a flaccid symmetrical tetraparesis or tetraplegia that usually peaks within 10 days of onset.
IV. Cranial nerves (CN) are rarely affected, although there may be signs of facial weakness and aphonia.
V. Nociception remains intact, and some dogs seem to be hyperesthetic and experience considerable discomfort with light palpation of the extremities.
VI. Some dogs can develop significant respiratory compromise as a result of paralysis of the intercostal muscles and diaphragm that can progress to complete respiratory paralysis.

Diagnosis

I. Diagnosis is usually based on history and compatible clinical findings.
II. CSF analysis may be normal or may reveal an increased total protein concentration, with a normal nucleated cell count (albumino-cytological dissociation).
III. The most reliable electrophysiologic indicators are EMG changes, such as significantly decreased compound-muscle action potential amplitudes, increased minimum F-wave latencies, increased F ratios, and decreased F-wave amplitudes (Cuddon, 1998).
IV. An enzyme-linked immunosorbent assay (ELISA) test is available, and it is sensitive and specific for detecting circulating antibodies to raccoon saliva in dogs.

Differential Diagnosis

I. Tick paralysis
II. Botulism
III. Myasthenia gravis

Treatment and Monitoring

I. Treatment is mainly supportive.
    A. Physiotherapy and rehabilitation efforts are needed.
    B. Adequate nutrition and hydration are essential.
    C. Provide soft bedding to prevent pressure sores related to recumbency.
II. Affected dogs must be closely monitored for respiratory depression.
III. Most dogs recover fully within a few weeks, but recovery can take up to 6 months depending on the severity.

Myasthenia Gravis

Definition and Causes

I. Myasthenia gravis (MG) is a disorder characterized by a deficiency of functional acetylcholine receptor (AChR) that results in reduced sensitivity of the postsynaptic membrane

to the neurotransmitter acetylcholine (ACh) and failure of neuromuscular transmission.

II. Two forms of the disease occur: acquired and congenital.
   A. The acquired form of MG arises from antibody-mediated (predominantly immunoglobulin [Ig] G) destruction of nicotinic AChR on the postsynaptic membrane of the neuromuscular junction (Shelton et al., 1988).
      1. The acquired form can either be idiopathic or secondary.
      2. Acquired MG has been reported as a paraneoplastic syndrome associated with a variety of tumors, including thymomas.
      3. Other predisposing causes in dogs include hypothyroidism, hypoadrenocorticism, systemic lupus erythematosus, and polymyositis.
      4. Acquired MG also has been reported in hyperthyroid cats receiving methimazole therapy (Kuroda et al., 1991; Shelton et al., 2000).
      5. Dogs with acquired MG range in age from 7 weeks to 15 years, with all breeds and genders potentially affected.
      6. Breeds with the highest risk are the Akita, several terrier breeds, German short-haired pointer, and Chihuahua (Shelton et al., 1997).
      7. A familial predisposition has been suggested in Newfoundlands (Lipsitz et al., 1999).
      8. In cats, Abyssinians and related Somalis are predisposed.
   B. Congenital MG is a rare disease and is defined as an inherited disorder in which the safety margin of neuromuscular transmission is compromised by one or more specific mechanisms.
      1. It can arise from presynaptic, synaptic, or postsynaptic defects (Engel et al., 2003).
      2. Decreased muscle AChR content is a consistent finding in congenital MG secondary to postsynaptic defects.
      3. An inherited, autosomal recessive form of MG has been recognized in the Parson (Jack) Russell terrier, English springer spaniel, and smooth fox terrier (Shelton, 1998).
      4. Suspected cases of congenital MG have also been reported in two related mongrel dogs (Van Ham, 1992).

Pathophysiology

I. Antibodies bound to postsynaptic AChR of the muscle membrane (acquired MG) block neuromuscular transmission.

II. Deficiency in AChR (congenital MG) results in a failure of neuromuscular transmission.

Clinical Signs

I. The hallmark sign of MG is episodic weakness that is exacerbated by exercise and resolves with rest.

II. Acquired MG can occur in three distinct clinical forms.
   A. The focal form is characterized by weakness of an isolated muscle group.
      1. It has been associated with regurgitation (megaesophagus), dysphagia (pharyngeal dysfunction), and decreased palpebral reflex (facial muscles), without detectable limb muscle weakness.
      2. Alternatively, megaesophagus may be the sole abnormality.
      3. The reason for selective involvement of particular muscle groups is unknown (Shelton et al., 1990).
   B. The generalized form consists of generalized appendicular weakness.
      1. Concurrent megaesophagus causing regurgitation and aspiration pneumonia is also common in dogs because of the large amount of skeletal muscle in the esophagus of dogs.
      2. Occasionally, facial, laryngeal, or pharyngeal weakness accompanies the appendicular muscle weakness (Dewey et al., 1997).
   C. An acute, fulminating form of MG also has been described in dogs.
      1. It is characterized by frequent regurgitation of large volumes of fluid associated with megaesophagus, and rapid loss of muscle strength resulting in recumbency.
      2. Respiratory failure is a consistent complication and a common cause of death.

III. Congenital MG generally occurs in puppies 6 to 9 weeks of age, with multiple pups in a litter affected.

Diagnosis

I. A presumptive diagnosis can be made with dramatic improvement in strength in response to the administration of edrophonium hydrochloride *(Tensilon)*, which is referred to as the *Tensilon test.*
   A. Edrophonium chloride is an ultrashort-acting anticholinesterase drug that blocks the hydrolysis of ACh by ACh-esterase, thereby increasing the concentration of ACh within the synaptic cleft.
   B. Edrophonium chloride is administered at 0.22 mg/kg IV.
   C. Tensilon testing is not a sensitive or specific testing method for MG.
   D. A lack of response to *Tensilon* administration does not rule out the diagnosis of MG (especially in cases of acute fulminant MG), because some dogs with other myopathic and neuropathic disorders have mild improvements in their weakness (Shelton, 1998).
   E. Occasionally, Tensilon testing can cause a cholinergic crisis by overstimulation of AChR, thereby producing a depolarizing blockade.
      1. Cholinergic crisis consists of dyspnea, bradycardia, profuse salivation, miosis, cyanosis, and limb tremors.
      2. Cholinergic crisis can be reversed with atropine 0.05 mg/kg IV.

II. The definitive diagnosis of acquired MG is based on demonstration of serum antibodies to muscle AchRs by immunoprecipitation radioimmunoassay (Shelton, 1998).
   A. The prevalence of seronegative canine myasthenia is considered to be very low, and false-positive results have not been documented.

B. Seronegative, acquired MG may occur from very low titers of high-affinity AChR antibodies, where most antibodies are complexed to AChRs in muscles or are antibodies directed against other end-plate proteins.
C. Other methods of diagnosis include immunocytochemical staining of muscle endplates, repetitive nerve stimulation, and single-fiber electromyography (Shelton, 1989).

Differential Diagnosis

I. Tick paralysis
II. Acute polyradiculoneuritis
III. Botulism
IV. Acute metabolic or toxic neuropathies

Treatment and Monitoring

I. Anticholinesterase therapy is the primary treatment for acquired MG in dogs.
   A. Pyridostigmine, a long-acting AChE inhibitor, is the most commonly used anticholinesterase drug.
      1. Administer by mouth or a gastric tube at 0.5 to 3.0 mg/kg PO BID to TID.
      2. To avoid a cholinergic crisis, start with the low dose and increase as needed.
   B. If oral treatment is not possible because of severe regurgitation, give neostigmine at 0.04 mg/kg IM QID.
II. Overdosage of anticholinesterase drugs results in a cholinergic crisis that consists of tachypnea and/or dyspnea, bradycardia, hypersalivation, excessive lacrimation, miosis, and generalized weakness.
III. Differentiation between inadequate therapy and overdosage can be made by administration of edrophonium, which should alleviate clinical signs if therapy is inadequate and has little to no effect on clinical signs from overdosage.
IV. Adjunctive immunosuppressive treatment is indicated if limb muscle strength has not returned to normal following anticholinesterase therapy and if there is no evidence of aspiration pneumonia.
   A. Give prednisone initially at an antiinflammatory dosage (0.5 mg/kg PO SID to BID) and increase gradually to immunosuppressive levels (2 to 4 mg/kg PO SID to BID) over 7 to 10 days to avoid initial exacerbation of muscle weakness (Shelton, 1998).
   B. Other immunosuppressive drugs, such as azathioprine 1 to 2 mg/kg PO SID or mycophenolate mofetil 20 mg/kg PO BID can also be tried.
V. In animals with megaesophagus, provide nutritional support via a gastrostomy tube.
VI. In animals with acquired MG secondary to neoplasia, treat the underlying neoplastic condition.
VII. Spontaneous clinical and immunological remission has occurred in >85% of dogs with acquired MG, over an average of 6.4 months (Shelton and Lindstrom, 2001).
   A. Base decisions regarding treatment regimen and duration on clinical signs and periodic testing of AChR antibody titers.
      1. Test AChR antibody titers every 4 to 6 weeks.
      2. Continue treatment as long as AChR antibody titers are positive.
   B. For animals not receiving immunosuppressive agents that become seronegative, consider stopping anticholinesterase therapy .
VIII. Congenital MG requires life-long therapy.
IX. Long-term prognosis for congenital MG is usually considered poor; however, spontaneous remission has occurred in two dachshunds by 6 months of age without medical therapy (Dickinson et al., 2005).

Chronic Inflammatory Demyelinating Neuropathy

Definition and Cause

I. Chronic inflammatory demyelinating polyneuropathy (CIDP) is considered to be an immune-mediated disorder in which the peripheral nerve myelin sheath is the target of an inflammatory reaction.
II. CIDP occurs in dogs and cats of either sex and does not appear to be breed related (Braund et al., 1996; Cummings, 1974; Shores, 1987).
III. CIDP is one of the more common neuropathies in dogs and cats.
IV. An immune-mediated process is suggested by the presence of focal and multifocal endoneural mononuclear cells, such as lymphocytes, macrophages, and plasma cells, and by positive staining for IgG in peripheral nerves.

Pathophysiology

I. CIDP is characterized by multifocal, segmental demyelination, and remyelination.
II. Changes in teased single fibers are dominated by multifocal paranodal demyelination.
III. Axonal loss is not a feature of this disease.

Clinical Signs

I. Onset of signs is usually insidious, and the course is typically chronic, sometimes relapsing, and often slowly progressive.
II. Clinical signs consist of LMN tetraparesis that can progress to tetraplegia with hyporeflexia.

Diagnosis

I. The diagnosis is based in part on history, clinical signs, and exclusion of other disease processes.
II. Electrophysiological testing reveals abnormal NCV, increased latency, and temporal dispersion of the muscle action potential, with minimal EMG abnormalities.
III. Definitive diagnosis requires histopathologic evaluation of nerve biopsies.

Differential Diagnosis

I. Other immune-mediated neuropathies
II. Metabolic or toxic neuropathies
III. Paraneoplastic neuropathies

Treatment and Monitoring

I. Treatment in dogs and cats consists of immunosuppressive dosage of prednisone 1 mg/kg PO BID for 2 weeks, then slowly tapered over 3 to 6 months.
II. Response to treatment is generally good; however, relapses can occur.
III. Adjunctive immunosuppressive treatment (dogs: azathioprine 1 to 2 mg/kg SID PO) is indicated in cases that relapse.

IDIOPATHIC DISORDERS

Distal Denervating Disease

Definition and Cause

I. Distal denervating disease is a common peripheral neuropathy in the United Kingdom that affects the distal segments of peripheral nerves.
II. The etiology is unknown.

Pathophysiology

I. Pathologic changes are confined to the distal branches of motor nerves, with intramuscular nerve fascicles showing marked demyelination (Summers, 1995).
II. There are no pathologic changes in the proximal segments of peripheral nerves.

Clinical Signs

I. There is no apparent age, sex, or breed association.
II. Signs of weakness are usually first observed in the pelvic limbs.
III. Within days to weeks, initial clinical signs progress to LMN tetraplegia accompanied by severe, generalized muscle atrophy.
IV. Sensory function remains intact.

Diagnosis

I. Electrophysiology is consistent with a motor nerve disorder affecting the distal segments.
   A. Abnormal spontaneous EMG activities occur in affected musculature.
   B. Motor nerve studies show decreased amplitude, but normal NCV.
   C. Sensory nerve studies are normal.
II. Muscle and nerve biopsies provide histopathologic confirmation of denervation.

Differential Diagnosis

I. Depending on the rapidity of the onset, distal denervating disease must be differentiated from acute diseases (e.g., acute polyradiculoneuritis, tick paralysis, MG).
II. More chronic and progressive forms must be differentiated from metabolic, toxic, and paraneoplastic disorders.

Treatment and Monitoring

I. There is no treatment.
II. In most dogs, full recovery usually follows spontaneous improvement within 4 to 6 weeks after the onset of clinical signs (Griffiths and Duncan, 1979).

METABOLIC/TOXIC NEUROPATHIES

Diabetes Mellitus–Related Neuropathy

Definition and Cause

I. Poorly controlled diabetes mellitus can be associated with a peripheral neuropathy.
II. Cats are particularly susceptible, whereas dogs are often subclinical.

Pathophysiology

I. Several theories regarding the pathogenesis have been proposed.
II. Activation of the polyol pathway in which aldose reductase reduces free glucose to sorbitol may lead to a depletion of myoinositol, a constituent of the plasma cell membrane important in impulse conduction (Cuddon, 2002).
III. Decreased insulin-like growth factor with diabetes leads to decreased production and axonal transport of microtubules and neurofilaments that are important to axonal health.
IV. Hyperglycemia leads to reduced blood flow and increased oxidative stress through alterations in the microvascular tone, which results in lipid peroxidation.

Clinical Signs

I. In cats, clinical signs are consistent with a sciatic neuropathy that causes a plantigrade posture when standing or walking.
   A. Most commonly, cats display pelvic limb weakness, with reduced to absent patellar and withdrawal reflexes.
   B. Occasionally, tetraparesis is seen.
II. In dog, clinical signs are usually subclinical.

Diagnosis

I. The diagnosis of diabetes mellitus is described in Chapter 44.
II. Electrophysiological findings suggest a sensorimotor neuropathy with conduction deficits, increased F waves, and increased cord dorsum potential latencies, with little or no EMG abnormalities except in the most severely affected animals (Mizisin et al., 2002).
III. Nerve biopsy reveals Schwann cell injury with myelin defects (e.g., splitting, ballooning), and subsequent demyelination, with minimum axonal degeneration (Mizisin et al., 2002).

Differential Diagnosis

I. Other metabolic or toxic neuropathies
II. Inflammatory or immune-mediated neuropathies
III. Vascular neuropathies

Treatment and Monitoring

I. Abatement of neuropathic signs can follow insulin therapy and achievement of a euglycemic state.
II. Clinical signs generally take weeks to months to resolve.
III. Persistent neurological signs are not uncommon despite aggressive management.

Hypothyroid-Related Neuropathy

Definition

I. Hypothyroidism is a relatively common endocrinopathy in older dogs.
II. Primary hypothyroidism has been associated with various nervous system abnormalities in dogs, including neuromyopathy.

Pathophysiology

I. The exact mechanism of hypothyroid-related neuropathies is unknown.
II. Resolution of clinical signs after supplementation is evidence of a causal link between the neuropathy and hypothyroidism.
III. Compression of cranial nerves as they exit their respective foramina in the calvaria may occur from myxedema (Cuddon, 2002).
IV. Axonal flow may also be reduced.

Clinical Signs

I. Clinical signs include generalized LMN signs, as well as cranial nerve dysfunction.
II. Generalized weakness, particularly in the pelvic limbs, exercise intolerance, reduced segmental spinal reflexes, and muscle atrophy are most commonly seen (Cuddon, 2002).
III. Cranial nerve dysfunction include deficits in CNs V, VII, and VIII.
IV. Laryngeal paralysis has been observed, and an association with megaesophagus has been suggested (Jaggy et al., 1994).

Diagnosis

I. The diagnosis is made by identifying hypothyroidism concurrent with clinical signs of LMN disease or cranial nerve dysfunction, followed by resolution of clinical signs with thyroxine supplementation.
II. The diagnosis of hypothyroidism consists of demonstrating a low free T4 with an elevated thyroid-stimulating hormone (TSH) level (see Chapter 42).
III. Electrophysiological findings are nonspecific.
    A. EMG findings include increased insertional activity and abnormal spontaneous activity.
    B. Nerve conduction studies reveal decreased amplitudes and slowed conduction that are evidence of demyelination and axonal loss, respectively.
IV. Peripheral nerve biopsies show demyelination, axonal loss, and evidence of remyelination.

Differential Diagnosis

I. Other metabolic or toxic neuropathies
II. Inflammatory or immune-mediated neuropathies
III. Paraneoplastic neuropathies

Treatment and Monitoring

I. Supplementation with synthetic levothyroxine is started at 0.02 mg/kg PO BID.
II. Dose adjustments are made based on clinical signs and serum thyroxine monitoring (see Chapter 42).
III. Neurological signs may take 1 to 2 months to improve.

Tick Paralysis

Definition and Cause

I. Tick-induced paralysis results from transfer of salivary neurotoxins to the host during parasitic feeding, usually by an adult female tick.
II. The neurotoxin interferes with ACh release, leading to failure of neuromuscular transmission.
III. Various species of tick (mostly *Dermacentor* and *Ixodes* spp.) are incriminated in different parts of the world.

Clinical Signs and Diagnosis

I. Clinical signs of rapidly ascending LMN paralysis are apparent 5 to 9 days after tick attachment (Malik and Farrow, 1991).
II. Weakness begins in the pelvic limbs and rapidly ascends to affect the thoracic limbs.
III. Dogs become recumbent in 24 to 72 hours.
IV. Left untreated, death occurs from paralysis of the respiratory muscles.
V. Presumptive diagnosis is made based on clinical signs and rapid improvement after tick removal.

Differential Diagnosis

I. Acute polyradiculoneuritis
II. Myasthenia gravis
III. Botulism

Treatment and Monitoring

I. After tick removal, clinical improvement is typically seen within 24 hours, with return of normal function by 48 hours.
II. Topical insecticides, such as those containing imidacloprid and permethrin (Advantix) or fipronil (Frontline Plus), are advocated over topical organophosphates.

Botulism

Definition and Cause

I. Botulism occurs following the ingestion of preformed toxin produced by *Clostridium botulinum* in carrion or raw meat.
II. *C. botulinum* is a saprophytic organism found worldwide that requires an anaerobic environment.
III. Botulism is an uncommon disease in dogs.
IV. Domestic cats seem to be remarkably resistant to botulinum toxin.
V. There are several antigenically distinct botulinus toxins (type A, B, C1, C2, D, E, F, and G).
VI. Type C1 is the botulinum toxin most often reported to affect dogs (Inzana, 2000).

Pathophysiology

I. After ingestion, the preformed toxin is absorbed and distributed to cholinergic receptors.
II. The toxin binds to presynaptic receptors at the neuromuscular junction.

III. The toxin diffuses into the axonal terminal and interferes with ACh release, leading to failure of neuromuscular transmission.

Clinical Signs

I. Clinical signs usually develop within a few hours after ingestion but can occasionally take several days to develop.
II. Clinical signs are characterized by progressive, symmetrical weakness to severe tetraplegia, with absent segmental spinal reflexes.
III. Cranial nerve abnormalities, such as facial paralysis, dysphonia, dysphagia, decreased jaw tone, and megaesophagus, may be seen (Coleman, 1998).
IV. Autonomic nervous system imbalance can cause keratoconjunctivitis sicca, constipation, urinary retention, and poorly responsive mydriasis.

Diagnosis

I. Diagnosis is made by the exclusion of other causes of similar clinical signs.
II. Base definitive diagnosis on identification of the toxin in the material ingested, in serum, vomitus or feces.
III. Fecal culture for *C. botulinum* can provide supportive evidence of ingestion of the toxin.

Differential Diagnosis

I. Acute polyradiculoneuritis
II. Myasthenia gravis
III. Tick paralysis

Treatment and Monitoring

I. Treatment primarily consists of supportive care.
   A. Adequate nutrition and hydration are essential.
   B. Provide soft bedding to prevent pressure sores related to recumbency.
   C. Animals with megaesophagus are fed in an upright position to prevent aspiration pneumonia, or alimentation is provided through a gastrotomy tube.
   D. Animals with known or suspected aspiration pneumonia are treated with antibiotics based on culture and susceptibility testing.
II. Antitoxin therapy is available, but must be specific for the particular antigenic type.
   A. A polyvalent antitoxin containing type C is recommended for dogs.
   B. Recommended dosage is 10,000 to 15,000 units IV or IM with two doses administered 4 hours apart.
   C. A test dose of 0.1 mL is given intradermally before administration to identify animals at risk for anaphylaxis.
III. Recovery is usually slow, taking weeks to months to regain function.

Miscellaneous Toxins

Definition

I. Numerous toxins and drugs can cause clinical signs consistent with polyneuropathies.
II. Many also result in central nervous system signs.
III. Systemic signs and clinicopathologic abnormalities are common in toxin-induced neuropathies.

Causes and Pathophysiology

I. Vincristine
   A. Vincristine is a vinca alkaloid that is commonly used in the treatment of hematopoietic neoplasia.
   B. Vincristine causes cessation of microtubule assembly, which causes decreased axonal transport by interfering with neurofilaments.
II. Organophosphates
   A. Organophosphates (OPs) are used as insecticides (see Chapter 125).
   B. OP toxicity can be acute or chronic.
   C. Toxicity results from inhibition of ACh esterase, which leads to overstimulation of AChR by acetylcholine.
   D. With chronic toxicity, axonal degeneration can occur.
III. Heavy metals
   A. Lead is the most common cause of heavy metal intoxication (see Chapter 126).
   B. Lead intoxication is usually the result of ingestion of lead-based products (e.g., paints, fishing weights, lead-based batteries, various plumbing products).
   C. Generally, lead intoxication causes CNS signs; however, peripheral neuropathies can occur.
   D. Lead may cause segmental demyelination by affecting Schwann cells.

Clinical Signs

I. Clinical signs vary with the amount of exposure.
II. Generalized weakness can be acute or chronic.
III. With vincristine, signs range from mild weakness in the pelvic limbs to more severe weakness, intermittent collapse, and loss of pelvic limb reflexes and tone.
IV. Organophosphates may cause signs of muscarinic AChR overstimulation, such as excessive lacrimation, defecation, urination, hypersalivation, drooling, miosis, bradycardia, and dyspnea.
V. Chronic OP toxicity with agents like chlorpyrifos may only cause muscular weakness and fatigue, without signs of muscarinic AChR stimulation (Jaggy and Oliver, 1990).
VI. Neurological signs associated with lead toxicity consist most commonly of seizures; however, abnormal behavior, ataxia, and blindness can also occur.
VII. Gastrointestinal signs (vomiting, anorexia, weight loss, diarrhea) also may occur with lead toxicity.

Diagnosis

I. Presumptive diagnosis is based on history, accessibility to toxic compounds, and concurrent nervous and systemic clinical signs.
II. Occasionally, toxins cause concurrent clinicopathologic abnormalities (see Chapters 125 and 126).
III. Definitive diagnosis is made by toxicological testing.

Differential Diagnosis

I. Metabolic neuropathies
II. Paraneoplastic neuropathies

III. Inflammatory neuropathies
IV. Idiopathic neuropathies

Treatment and Monitoring

I. Nonspecific treatments are directed at eliminating further exposure, reducing further absorption, and alleviating clinical signs.
   A. Oral administration of activated charcoal can reduce gastrointestinal absorption of ingested toxins.
   B. Bathing can eliminate further topical absorption of OP.
II. Some specific treatments are described for the various toxins in Section 18.

VASCULAR DISORDERS

Definition

I. The most common cause of vascular neuropathies is aortic thromboembolism.
II. Thromboembolism occurs at the level of the aortic trifurcation, resulting in dysfunction of the muscles of the pelvic limbs, as well as the sciatic and femoral nerves.

Causes and Pathophysiology

I. In cats, the most common underlying disease is dilated cardiomyopathy.
   A. The origin of the embolus is usually a thrombus attached to an endocardial surface.
   B. Abyssinian, Birman, ragdoll, and male cats were overrepresented in one study (Smith et al., 2003).
II. In dogs, the most common underlying disease is a protein-losing glomerulopathy.
III. Arterial thromboembolism also occurs as a complication of hyperthyroidism and neoplasia (Sykes, 2003).
IV. Ischemia is produced by vasoconstriction of collateral circulation induced by serotonin and thromboxane A_2 released from platelets trapped in the thrombus.

Clinical Signs

I. Clinical signs are typically acute and include paresis and/or paraplegia with cold extremities, weak or absent femoral pulses, firm painful muscles, and loss of nociception.
II. The nail beds are cyanotic and fail to bleed when cut.
III. Occasionally, the same clinical signs can occur in the left thoracic limb as a result of thromboembolism involving the left brachycephalic artery.

Diagnosis

I. The diagnosis of feline cardiomyopathy is discussed in Chapter 10.
II. The diagnosis of protein-losing glomerulopathy is discussed in Chapter 48.
III. Common biochemical abnormalities in the acute phase include hyperglycemia, azotemia, and abnormally high serum concentrations of muscle enzymes (Smith et al., 2003).
IV. Confirm the diagnosis by aortography or Doppler ultrasonography of the aorta and its main branches.

Differential Diagnosis

I. Metabolic or toxic neuropathies
II. Inflammatory or immune-mediated neuropathies
III. Neoplastic polyneuropathies

Treatment and Monitoring

I. Treatment primarily involves supportive care.
II. Thrombolytic therapy is occasionally pursued with a variety of drugs (see Chapters 10 and 68).
III. Thrombolytic therapy can result in acute reperfusion injury.

NEOPLASIA

Paraneoplastic Neuropathies

Definition and Causes

I. A variety of cancers have been associated with both subclinical and clinical polyneuropathies.
II. Subclinical neuropathies have been associated with bronchogenic carcinoma, mammary gland carcinoma, osteosarcoma, thyroid adenocarcinoma, and mast cell tumors (Braund, 1990).
III. Clinical signs have been seen with bronchogenic carcinoma, mammary adenocarcinoma, malignant melanoma, insulinoma, lymphosarcoma, metastatic hemangiosarcoma, and leiomyosarcoma.

Pathophysiology

I. The current hypothesis is that the polyneuropathy results from an immune reaction primarily directed against the cancer that involves antibodies reacting with an antigen common to the nervous system and the tumor.
II. In humans, a variety of antineural, antimyelin basic protein, and antimyelin-associated glycoprotein antibodies, known as *neural onconeuronal antibodies*, have been identified in which there is a common antigen between cancer cells and nervous tissue cells (Cuddon, 2002).

Clinical Signs

I. Neuropathic signs may precede, develop with, or follow the identification of the underlying neoplasia.
II. Clinical signs consist initially of paraparesis, with slow progression to tetraparesis.
III. Clinical signs include hyporeflexia, hypotonia, and varying degrees of muscle atrophy.
IV. A specific syndrome solely involving multiple cranial nerves, particularly CN V, has been reported with lymphoma and leukemias (Carpenter et al., 1987).
   A. Signs include atrophy of the temporalis and masseter muscles, jaw weakness, inability to close the mouth, sensory deficits of the face, and deficits of the palpebral and corneal reflexes.
   B. Other commonly affected nerves are CNs VII and VIII.

Diagnosis

I. Diagnosis is by exclusion of other causes of neuropathies in animals with cancer.

II. Electrophysiology supports the diagnosis of a peripheral neuropathy.
III. Peripheral nerve biopsies show varying degrees of demyelination and axonal loss.

Differential Diagnosis

I. Metabolic or toxic neuropathies
II. Inflammatory neuropathies
III. Idiopathic neuropathies

Treatment and Monitoring

I. Direct treatment at the underlying neoplasia.
II. Successful treatment of the neoplasia may result in resolution of clinical signs (Mariani et al., 1999).
III. Unfortunately, not all clinical signs remit with resolution of the underlying cancer.

Insulinoma-Related Neuropathy

Definition and Cause

I. Clinical signs of generalized weakness can occur as a result of hypoglycemia from a functional insulinoma.
II. Subclinical polyneuropathy also has been reported with insulinomas (Braund et al., 1987).

Pathophysiology

I. Insulinoma is an insulin-secreting neoplasm of the beta islet cells of the pancreas that causes hyperinsulinemia and subsequent hypoglycemia.
II. Unlike neurons of the CNS, the peripheral nervous system can use not only glucose, but also amino acids and fatty acids as energy substrates.
III. Although the exact pathophysiology of the polyneuropathy is unknown, it may be a consequence of decreased energy metabolism secondary to hypoglycemia.
IV. The primary pathology is axonal degeneration affecting the distal axon of motor nerves.
V. Demyelination and remyelination have also been observed.

Clinical Signs

I. Clinical signs occur from both the effects of hypoglycemia and the polyneuropathy.
II. Signs of hypoglycemia include depression, lethargy, and seizures (see Chapters 46 and 73).
III. Signs associated with the polyneuropathy include appendicular weakness, exercise intolerance, collapse, and decreased to absent reflexes.
IV. Occasionally, CN dysfunctions (e.g., facial weakness, atrophy of the musculature of the head) have been seen.

Diagnosis

I. Presumptive diagnosis is made by identifying hypoglycemia and elevated serum insulin levels in dogs with appendicular weakness, and hypo- or areflexia.
II. Electrophysiological findings include fibrillation potentials and positive sharp waves, with mild decreases in NCV.
III. Definitive diagnosis requires histopathologic evaluation of peripheral nerves.
IV. Histopathologic changes include axonal degeneration and secondary demyelination.

Differential Diagnosis

I. Metabolic or toxic polyneuropathies
II. Inflammatory or immune-mediated polyneuropathies
III. Other paraneoplastic polyneuropathies

Treatment and Monitoring

I. Treatment is directed at correcting the hypoglycemia and eliminating the underlying neoplasia.
   A. Surgical removal of the neoplasm is the primary method of treatment (see Chapters 46 and 73).
   B. Hypoglycemia also can be controlled through dietary alterations, including diets high in fiber and low in carbohydrates, frequent feedings, and glucocorticoids (see Chapter 46).
II. Resolution of clinical signs requires weeks to months.
III. Occasionally, clinical signs persist despite euglycemia.

Peripheral Nerve Sheath Tumors

Definition and Cause

I. Peripheral nerve sheath tumors (PNSTs) arise from cells surrounding peripheral nerves.
II. The exact cell of origin is usually unknown.
III. Other terms, such as *neurofibroma, neurofibrosarcoma, schwannoma,* and *malignant schwannoma,* have also been used to describe these tumors.

Clinical Signs

I. Signalment is suggestive.
   A. Dogs are most commonly affected.
   B. Affected dogs range in age from 3 to 13 years, with a median of 9 years (Brehm et al., 1995).
   C. No breed or sex predilection has been reported.
   D. Cats are rarely affected.
II. The most common sign is chronic progressive, unilateral limb lameness.
   A. Thoracic limbs are more commonly affected than pelvic limbs.
   B. The affected limb typically shows signs consistent with LMN disease, such as muscular atrophy, decreased to absent segmental reflexes, and hypotonia.
III. Occasionally, the only clinical sign is pain.
IV. Hemiparesis or tetraparesis can be seen with neoplasia that encroaches on the spinal cord.
V. PNSTs can involve the cranial nerves (Zachary et al., 1986).
   A. The trigeminal nerve is most commonly affected and can result in ipsilateral sensory and motor deficits (atrophy of the muscles of mastication).
   B. Tumors arising from other CNs are rare.

Diagnosis

I. Diagnosis is most commonly made with imaging studies.
   A. Magnetic resonance imaging (MRI) can be used to visualize PNSTs arising from the brachial or lumbar plexus, and from spinal nerves.

B. MRI can also define the extent of the disease (e.g., location in the spinal canal, involvement of the spinal cord) (Platt et al., 1999).
C. Computed tomography (CT) can be used to diagnose a PNST involving the brachial plexus.
D. Ultrasonography can identify tumors involving the brachial plexus.
E. Myelography can identify a PNST within the vertebral canal based on its typical intradural-extramedullary myelographic pattern.

II. Electrophysiological testing defines which nerves are affected but abnormalities are nonspecific.
III. Tumors in the brachial plexus can be palpated occasionally.
IV. Pain at the site of the tumor can often be detected.
V. Tumors involving the thoracic (T)1-T3 spinal nerves or brachial plexus can cause ipsilateral Horner's syndrome.
VI. Surgical biopsy or resection is ultimately needed for a definitive diagnosis.

Differential Diagnosis

I. The most important differential diagnosis is musculoskeletal disease.
II. Lateralized intervertebral disc disease can result in similar clinical signs.
III. Other neoplastic processes compressing a spinal nerve or nerves of the brachial–lumbar plexus must be ruled out.

Treatment

I. Surgical resection via amputation is the treatment of choice.
II. For PNSTs involving the spinal nerves, hemilaminectomy combined with amputation may be needed (Bailey, 1990; Brehm et al., 1995).
III. Adjunctive treatment with postoperative radiation therapy may be beneficial.
IV. Radiation therapy also may be a treatment option for nonresectable PNSTs.

Monitoring of Animal

I. Prognosis varies with extent of disease.
II. Long-term survival can occur with complete resection of PNSTs, which is typically accomplished with tumors located distally on the limb.
III. For PNSTs involving a nerve plexus, the median relapse-free period is 7.5 months and the median survival time is 12 months (Brehm et al., 1995).
IV. For PNSTs involving the spinal nerves, the median relapse-free period is 1 month and the median survival time is 5 months (Brehm et al., 1995).

Secondary Peripheral Nerve Tumors

Definition and Causes

I. Occasionally, tumors of nonneural origin invade or compress peripheral nerves.
II. The most common secondary peripheral nerve tumors are related to hematopoietic neoplasia.
III. Small cell carcinoma of the lung compressing cervical (C) 8 and T1 spinal nerves has been reported (Ferreira et al., 2005).

Clinical Signs

I. Clinical signs relate to the nerves being affected.
II. Hematopoietic neoplasia commonly affects the trigeminal nerve (CN V) resulting in sensory–motor deficits of the head and atrophy of the muscles of mastication.

Diagnosis

I. Definitive diagnosis requires cytological or histopathologic confirmation of neoplastic involvement of nerves.
II. With cranial nerve involvement, CSF analysis may provide a cytological diagnosis of hematopoietic neoplasia.
III. MRI may demonstrate contrast enhancement of peripheral nerves.
IV. In animals with established hematopoietic neoplasia, presumptive diagnosis can be made based on clinical findings of cranial nerve dysfunction, particularly involving the trigeminal nerve.

Differential Diagnosis

I. The most important differential diagnosis is PNST.
II. Musculoskeletal disease can also manifest with clinical signs similar to secondary tumors compressing or invading spinal nerves.

Treatment and Monitoring

I. Treatment is dictated by the histopathologic diagnosis of the secondary tumor.
II. Treatment of hematopoietic tumors is discussed in Chapters 69 and 72.

TRAUMATIC DISORDERS

Brachial Plexus Avulsion

Definition and Causes

I. Common causes of nerve injury include road traffic accidents, gunshot wounds, bites, lacerations, stretching injuries, fractures, and iatrogenic damage from surgical procedures or injections.
II. Avulsion of the nerve roots forming the brachial plexus, as a result of a road traffic accident or falls from a height, is the most common traumatic neuropathy in the dog and cat.
III. Three types of nerve damage can be distinguished, depending on the degree of structural damage.
A. Neurapraxia is a transient, physiologic failure of nerve transmission in the absence of structural damage.
B. Axonotmesis is disruption of the axons, with the endoneurial and Schwann cell sheaths remaining intact.
C. Neurotmesis is complete severance of all structures of the nerve.

Pathophysiology

I. As long as the cell body of the neuron remains intact, damage to the axon results in degeneration of the distal segment, which is known as *Wallerian degeneration.*

II. Regeneration can occur in a proximal to distal direction.
III. Peripheral nerves regenerative at a rate of approximately 1 to 2 mm/day.
IV. The damage most often occurs at the level of the spinal roots where resistance to stretch is less than in peripheral nerves, owing to the lack of perineurium (Summers et al., 1995).

Clinical Signs

I. Clinical signs vary with the severity of the injury and depending on which peripheral nerves are involved.
II. Avulsion of the cranial plexus roots (C6 to C7 nerve roots) causes certain signs.
   A. Avulsion of the cranial plexus results in a loss of shoulder movement and elbow flexion, although the animal can still bear weight on that limb, as the extension of the elbow is spared.
   B. The cutaneous sensation may be lost in the dorsum of the paw and the cranial and lateral antebrachium.
III. Avulsion of the caudal plexus roots (C8 to T2 nerve roots) causes the following:
   A. Avulsion of the caudal plexus results in carriage of the limb with the elbow and shoulder flexed and inability to bear weight because of paralysis of the triceps brachii muscle (elbow extension).
   B. The elbow is dropped and knuckling of the carpus occurs with ambulation.
   C. Cutaneous sensation may be lost distal to the elbow.
IV. Complete avulsion of all plexus roots (C6 to T2 nerve roots) causes a flaccid limb with inability to bear weight and loss of cutaneous sensation in the entire limb.
V. Many dogs with brachial plexus avulsion also have ipsilateral Horner's syndrome, and/or loss of cutaneous trunci reflex.

Diagnosis

I. Diagnosis is made based on history and clinical findings.
II. Identifying specific areas of cutaneous sensation loss (analgesia) in regions of skin innervated by specific nerves (autonomous zones; see Table 21-3) can provide information regarding the involvement of particular nerves (Bailey et al., 1982).
III. EMG helps to document the extent of muscle denervation and confirms the distribution of nerve injury, although changes may not be seen for 7 to 10 days after the injury.

Treatment and Monitoring

I. Treatment for most injuries is conservative and relies mainly on aggressive physiotherapy.
II. Serial evaluation of radial motor NCV may be a useful prognostic indicator, with early decreased conduction velocity indicating a poor prognosis (Faissler, 2002).
III. Carpal arthrodesis may be indicated if triceps function is intact (the animal can extend the elbow and thereby weight support), but the animal is knuckling.
IV. Prognosis varies depending on the degree of dysfunction.
   A. The prognosis is good for animals with cranial brachial plexus avulsion that retain the ability to bear weight and have intact cutaneous sensation.
   B. Animals with complete or caudal brachial plexus avulsion have a guarded to poor prognosis, especially if cutaneous sensation has been lost.
      1. If no improvement occurs during the first 2 months, recovery is unlikely.
      2. Amputation is recommended in these cases, especially if complications such as self mutilation from paresthesia, joint contractures, or trophic ulcers develop.

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CHAPTER 26

Introduction

Lisa E. Moore

APPROACH TO CLINICAL PROBLEMS

Gastrointestinal versus Systemic Disease

I. In animals with signs of gastrointestinal (GI) disease, it is important to determine whether the signs are related to a primary GI disease or some other systemic disease.
II. This distinction is sometimes difficult, but usually can be made.
III. The distinction is important so the animal with systemic disease does not undergo unnecessary procedures, such as endoscopy or exploratory laparotomy.
IV. The presence of clinical signs other than those related to the GI tract often indicates a systemic disease.
    A. For example, polyuria and polydipsia do not usually accompany primary GI disease.
    B. Joint swelling may indicate an orthopedic or infectious disease.
V. Once it has been decided that the animal is suffering from primary GI disease, localizing the signs to a specific area of the GI tract is the next step.

Initial Evaluation

I. A complete history and physical examination are the foundation of any diagnostic work-up.
II. Information regarding travel history, environment, and vaccinations is important.
III. Whether any other animals or people in the household have or are affected by similar clinical signs can be important.
IV. Dietary history is especially important when dealing with intestinal problems.
V. Dogs and cats with GI disease may not have any abnormalities on physical examination.
VI. A rectal examination is part of the physical examination of any animal with diarrhea.

Minimum Database

I. Laboratory tests may not be necessary in acute cases, but are imperative in animals with chronic signs.
II. A thorough work-up includes a complete blood count (CBC), serum chemistry profile, urinalysis, fecal examination (both direct and flotation), and abdominal radiography.
III. If systemic disease is present, abnormalities are often found.
    A. Azotemia if the animal is vomiting from renal failure
    B. Electrolyte changes if the animal has hypoadrenocorticism

Further Testing

I. Once a minimum database has been performed, it is usually clear as to whether or not the animal has a primary GI or systemic disease.
II. If it is still unclear, additional tests are appropriate.
    A. Abdominal ultrasonography
    B. Endocrine testing
    C. Contrast radiography

LOCALIZATION AND DEFINITIONS

Vomiting versus Regurgitation

I. It is important to differentiate these signs as the diagnostic work-up for the two problems is quite different.
II. Vomiting is the forceful, reflexive ejection of stomach contents, and it is accomplished by contraction of the muscles of the diaphragm and abdomen.
    A. Vomiting is preceded by signs of nausea, including restlessness, depression, hypersalivation, lip licking, and frequent swallowing.
    B. It is an active process.
III. Regurgitation is the expulsion of ingesta from the esophagus or pharynx.
    A. It is a passive event, with no or little abdominal effort.

B. Generally, few if any prodromal signs are noted, but drooling may be present because of an inability to swallow saliva.
C. Regurgitated food is undigested and may be regurgitated at any time (immediately after eating or many hours later).
D. The ingesta may be tubular in shape, but this is not pathognomonic.

Small versus Large Bowel Diarrhea

I. Small intestinal diarrhea may vary from slightly loose to watery.
   A. The stool may be foul smelling and may contain melena or undigested food.
   B. The volume of stool is increased, and a mild to moderate increase in frequency of bowel movements (2 to 5 times a day) occurs.
   C. Urgency is rare.
   D. Weight loss is common.
   E. Other signs can include flatus, borborygmus, halitosis, vomiting, loss of appetite, or polyphagia.
II. Large intestinal diarrhea may vary from formed to loose.
   A. Mucus and/or fresh blood are common.
   B. Undigested food is rare.
   C. The volume of stool may be normal to increased, and the frequency of bowel movements is increased (5 to 10 times per day), with multiple attempts to defecate each time.
   D. Owners may confuse the attempts to defecate as constipation.
   E. Urgency and tenesmus are common.
   F. Changes in appetite and weight loss are uncommon, but can occur with severe motility changes or with chronic disease.

Melena versus Hematochezia

I. Melena is the presence of digested blood in the stool.
   A. The stool has a black, tarry appearance.
   B. Blood may enter the intestinal tract from numerous sources, such as swallowed blood from dental disease, nasal disease, and hemoptysis or from upper GI bleeding.
   C. Melena does not necessarily indicate primary GI disease, because coagulopathies can also cause GI bleeding.
II. Hematochezia is the presence of fresh, red blood in the stool.
   A. It may occur in the form of streaks on or in the stool, or the entire feces may be bloody and include clots and/or mucus.
   B. Hematochezia suggests involvement of the colon, rectum, or anus.

Other Clinical Signs

I. Halitosis can result from a variety of disorders, including uremia and oral, pharyngeal, esophageal, and gastric diseases.
II. Halitosis can be affected by diet (high protein, poorly digested protein).
III. Other signs of intestinal disease include ptyalism, dysphagia, retching, gagging, difficulty eating, borborygmus, flatulence, ascites, and abdominal pain.

CHAPTER 27

Diseases of the Oral Cavity and Pharynx

Mark E. Hitt | Debra L. Zoran

CONGENITAL/DEVELOPMENTAL DISORDERS

Debra L. Zoran

See Table 27-1.

INFECTIOUS AND INFLAMMATORY DISORDERS

Debra L. Zoran, Mark E. Hitt

Stomatitis, Gingivitis, and Glossitis

Definition

I. These disorders include inflammatory processes of the oral mucosa, tongue, and gingiva that result in ulceration, necrosis, and secondary infection.
   A. Stomatitis: inflammation of the mucous membranes of the mouth
   B. Glossitis: inflammatory lesions of the tongue
   C. Gingivitis: inflammation of the gingiva
   D. Faucitis: inflammatory lesions of the glossopalatine folds or angles of the mouth
   E. Cheilitis: inflammatory lesions of the lips
   F. Periodontitis: lesions of the periodontal membrane, gingiva, and alveolar bone
II. Many oral inflammatory diseases arise secondary to systemic diseases and may involve multiple, oral soft-tissue structures.
III. Progressive involvement and coalescence of multiple sites can occur.
IV. These inflammatory conditions are a frequent problem in cats and are increasing in dogs.
V. Chronic, unrelenting forms of gingivitis or stomatitis have a variety of names, including lymphoplasmacytic stomatitis, plasmacytic stomatitis, chronic ulcerative paradental stomatitis (CUPS), plasma cell gingivitis stomatitis, pharyngitis, and necrotizing stomatitis.
VI. Gingivostomatitis is generalized inflammation of the gingival and oral cavity (Lyon, 2005).

Causes

I. Dental plaque and calculus
II. Immune-mediated diseases
   A. Pemphigus complex: pemphigus foliaceus, pemphigus erythematosus, pemphigus vulgaris
   B. Systemic lupus erythematosus (SLE)
   C. Drug eruptions and/or toxic epidermal necrolysis
   D. Food hypersensitivity
   E. Discoid lupus erythematosus, bullous pemphigoid
   F. Allergic contact dermatitis: plastic materials
   G. Idiopathic vasculitis
   H. Ulcerative gingivitis-stomatitis of Maltese terriers
III. Idiopathic disorders
   A. Feline gingivitis-stomatitis-pharyngitis complex
   B. Feline eosinophilic granuloma complex
   C. Eosinophilic granuloma of Siberian huskies
   D. Ulcerative eosinophilic stomatitis of Cavalier King Charles spaniels
IV. Immunodeficiency disorders
   A. Neutrophil function defects
   B. Neutropenia
   C. Prolonged, immunosuppressive drug therapy
V. Infectious diseases
   A. Bacteria
      1. Major anaerobic species: *Porphyromonas* spp. (formerly *Bacteroides* spp.), *Fusobacterium* spp., *Propionibacterium* spp., *Peptostreptococcus* spp., and *Clostridium* spp.
      2. Gram-positive aerobes: *Streptococcus* spp., *Staphylococcus* spp., *Corynebacterium* spp., *Actinomyces* spp.
      3. Gram-negative aerobes: *Escherichia coli, Pseudomonas* spp., *Proteus* spp., *Pasteurella* spp.
      4. Spirochetes
         a. Acute necrotizing ulcerative gingivitis (ANUG, Vincent's stomatitis, or trench mouth)
         b. Leptospirosis: *Leptospira canicola, Leptospira icterohaemorrhagiae*
      5. Intracellular bacteria: *Bartonella henselae* implicated
   B. Viral diseases
      1. Feline calicivirus: most common
      2. Feline immunodeficiency virus (FIV)
      3. Feline herpesvirus (FHV-1)
      4. Feline leukemia virus (FeLV)
      5. Canine adenovirus (CAV-2)
      6. Canine distemper virus or feline panleukopenia virus
      7. Feline syncytium-forming virus

TABLE 27-1

Congenital and Developmental Disorders

DEFECT	CAUSES	CLINICAL CHARACTERISTICS	DIAGNOSIS	TREATMENT	COMMENTS
Primary cleft palate (lip)	May be secondary to intrauterine trauma or insult Affected pups are born to affected parents	Often associated with secondary cleft palate in the dog May occur unilaterally or bilaterally No signs other than the physical defect	Physical examination	Surgical lip reconstruction	Animals should not be bred Higher incidence in brachycephalic breeds, beagles, cockers, and dachshunds
Secondary cleft palate (hard and soft palate)	Inherited or secondary to developmental insult Occurs in both dogs and cats	Inability to nurse; poor growth; milk drainage from nares; coughing, gagging, and sneezing during nursing Nasal discharge resulting from rhinitis may occur with time Aspiration pneumonia may be fatal	Physical examination of mouth reveals abnormal division of hard/soft palate	Surgical reconstruction of palate when animal is 2-4 months of age; nutritional and medical supportive care until then	Higher incidences in brachycephalic breeds, Shetland sheepdogs, schnauzers, Labrador retrievers, and German shepherd dogs
Malocclusion: prognathism	Genetic factors: normal in brachycephalic dogs and Persian cats Abnormal dentition (position of teeth or retained teeth) Trauma	Clinical appearance: long mandible with short maxilla May predispose to periodontal and gingival disease	Physical examination	Early removal of retained supernumerary or malpositioned deciduous teeth	Maltese terriers are predisposed to retained teeth
Malocclusion: brachygnathism	Genetic factors: long-haired dachshund, shar-pei Abnormal in any breed, but no known cause	Physical finding of shortened mandible with a long maxilla If severe, may prevent normal jaw function and eating	Physical examination	No specific treatment available	
Microcheilia	Unknown cause	Physical finding of a reduced oral fissure	Physical examination	None	Reported in miniature schnauzers
Lip-fold dermatitis	Congenital trait resulting in abnormal conformation of the lip fold in spaniel breeds	Chronic moist, fetid dematitis of lip folds	Physical examination	Resection of skin folds	Affected animals should not be bred Breed with a higher incidence: Brittany spaniel
Elongated soft palate	Brachycephalic breeds are predisposed	Associated with exercise and heat intolerance, and abnormal oropharyngeal function	Physical examination, radiography	Surgical removal of offending tissue	Breeds with a higher incidence: affenpinscher, chow chow, English and French bulldogs, Pekingese, and pugs

Data from Clark RW (ed): Medical Genetic and Behavioral Aspects of Purebred Cats. Forum Publications, Fairway, Kan, 1992; Clark RW (ed): Medical Genetic and Behavioral Aspects of Purebred Dogs. Forum Publications, Fairway, Kan, 1994; Norden DM: Normal development and congenital defects in the cat. p. 1248. In Kirk RW, Bonagura JD (eds): Current Veterinary Therapy XI: Small Animal Practice. WB Saunders, Philadelphia, 1992.

TABLE 27-1

Congenital and Developmental Disorders—*cont'd*

DEFECT	CAUSES	CLINICAL CHARACTERISTICS	DIAGNOSIS	TREATMENT	COMMENTS
Craniomandibular osteopathy	Developmental condition	Proliferation of bones of skull and mandible; painful swelling of mandible Reduced jaw motion results in reluctance to eat and depression	Physical examination and radiographic changes (exostosis of mandible, tympanic bulla, and calvarium)	Corticosteroids and nonsteroidal anti-inflammatory drugs may relieve signs but are not curative Surgery is of limited success in most cases	Breeds affected: West Highland white, Scottish, and Cairn terriers; Labradors; Great Danes; Doberman pinschers
Microglossia	Congenital defect reported in dogs	Excessive drooling, difficulty eating	Physical examination	None	Rare

8. Papovavirus
9. Feline infectious peritonitis (FIP) virus: rare
10. Multiple viral infections: FIV or FeLV and calicivirus or FHV-1

C. Fungal diseases
1. Blastomycosis *(Blastomyces dermatitidis)*
2. Candidiasis *(Candida albicans)*
3. Cryptococcosis *(Cryptococcus neoformans)*
4. Others: histoplasmosis, sporotrichosis, coccidioidomycosis, *Malassezia* spp. (rare)

VI. Metabolic diseases
A. Diabetes mellitus
B. Hypoparathyroidism
C. Uremia: most common cause
D. Hypothyroidism

VII. Neoplasia (see later in this chapter)

VIII. Nutritional disorders
A. Hypervitaminosis A: oral lesions in conjunction with bony exostosis
B. Niacin deficiency (pellagra)
C. Protein-calorie malnutrition
D. Riboflavin deficiency (Roe, 1991)
E. Calcium imbalances: periodontal disease

IX. Physiochemical and traumatic causes
A. Caustic or irritant chemicals
1. Acids, alkalis
2. Phenols
3. Petroleum products
4. Benzalkonium chloride

B. Antineoplastic therapies: chemotherapeutics, radiation therapy
C. Dilantin (diphenylhydantoin)
D. Cyclosporine: gingival hyperplasia that appears as gingivitis
E. Foreign bodies
1. Plant material
2. Fiberglass
3. Bone fragments
4. Quills, claws
5. Rubber bands, string, or Christmas tree tinsel

F. Heavy metals: thallium, mercury
G. Insect bites and stings: bees, spiders, scorpions, ants, etc.
H. Irritant plants: dieffenbachia, poinsettia, philodendron
I. Electric cord burns
J. Persistent overgrooming (cats)
K. Trauma

Pathophysiology

I. A variety of factors influence the pathogenesis of inflammatory oral disease, including the many microorganisms in the mouth and the fact that the oral cavity is subject to trauma, abrasion, and frequent changes in hydration and temperature.

II. Most inflammatory diseases of the oral cavity have an immunological response that is excessive, persistent, or aberrant (Lyon, 2005).

III. Primary defenses against oral disease are the epithelial surface, saliva, and the local (inflammatory) and systemic immune responses (humoral and cell-mediated immunity).

IV. Depression of oral defense mechanisms allows secondary infections by organisms that are not normally pathogenic (Tenorio et al., 1991).
A. Acquired immunodeficiency diseases (e.g., FIV) and chronic corticosteroid use are important causes.
B. Long-term antibiotic treatment can alter the normal microflora, creating resistant species and allowing the overgrowth of bacteria (spirochetes) or *Candida* spp.
C. Chronic systemic diseases alter the replication, exfoliation, and maturation of epithelial cells, predisposing these tissues to disease.
D. The presence or persistence of periodontal disease can also lead to chronic infection and immunological stimulation.

V. Uremia causes oral ulceration by several mechanisms.
   A. Oral microbes degrade urea to ammonia, and the high systemic concentration of urea leads to production of cytotoxic levels of ammonia.
   B. Hyperammonemia results in decreased rates of tissue repair, and reduced platelet (increased bleeding and ulcerations) and immune function.
VI. Animals with diabetes mellitus often develop oral infections from immune compromise, which is exacerbated by the presence of xerostomia (dry mouth) or dehydration.
VII. Immune-mediated diseases cause oral lesions by production of autoantibodies to the normal epithelial components, resulting in destruction of normal mucosa, with concurrent ulcers, erosions, blisters, and inflammation.

Clinical Signs

I. A careful history of the signalment, onset, and duration of clinical signs is important.
II. It is also important to distinguish whether the disease process is either localized to the oral cavity or a manifestation of systemic disease.
III. The most common presenting complaints that may be associated with stomatitis, gingivitis, and glossitis include the following:
   A. Anorexia, reduced appetite, interest in food but refusal to eat
   B. Abnormal or exaggerated chewing motions, "chattering" teeth
   C. Halitosis
   D. Ptyalism (drooling)
   E. Bleeding from the mouth or gums
   F. Dysphagia
   G. Vomiting, retching, gagging, regurgitation
   H. Face rubbing, head shaking
   I. Nasal discharge, sneezing
   J. Fever, depression, regional lymphadenopathy

Diagnosis

I. General anesthesia may be required for a complete examination if the animal is fractious or in pain.
   A. Feline gingivitis-stomatitis-pharyngitis complex
      1. Focal, regional, or diffuse lesions
      2. Generalized hyperemia of mucous membranes and lips
      3. Severe gingival recession around teeth and surrounding bone (teeth may be loose)
      4. Severe oral ulceration
      5. Fever, depression, weight loss from inappetence
      6. Pain when opening the mouth, especially with faucitis
   B. Feline eosinophilic granuloma complex (see later in this chapter)
   C. Eosinophilic granuloma of Siberian huskies, Cavalier King Charles spaniels, and other breeds (rare)
      1. Proliferative eosinophilic lesions of the tongue occurring primarily in young dogs
      2. Other signs: difficult prehension or swallowing, drooling, and oral pain
   D. ANUG
      1. Acute onset of severe halitosis; gingivitis; oral ulceration of tongue, buccal mucosa, and palate
      2. Lesions possibly covered with a gray pseudomembrane of necrotic tissue and purulent exudate
      3. Localized or systemic immunodeficiency probably necessary for development
   E. Leptospirosis
      1. *L. canicola:* severe generalized hyperemia of mucous membranes, oral ulceration and hemorrhage, gingival petechiae, glossitis, lingual necrosis
      2. *L. icterohaemorrhagiae:* severe generalized hyperemia of mucous membranes, oral hemorrhage, gingival petechiae
   F. FHV-1
      1. Acute vesicular to ulcerative, focal to diffuse glossitis and stomatitis
      2. Rhinitis, conjunctivitis, keratitis, pharyngitis
      3. Persistent infections with recrudescence
   G. Calicivirus
      1. Oral vesiculation and ulceration of the tongue, palate, and fauces are the most common clinical manifestations.
      2. Transient fever, limping, and focal interstitial pneumonia occur in some infected cats.
   H. FeLV: chronic proliferative gingivitis, stomatitis, oral ulceration
   I. FIV
      1. Chronic gingivitis, stomatitis, periodontitis
      2. Acute, rapidly progressive gingival necrosis
      3. More severe and persistent with concurrent calicivirus
   J. Candidiasis
      1. Creamy, plaquelike lesions on the tongue, oral mucosa, lips, mucocutaneous junctions
      2. Inflammation and ulceration of mucosa beneath the lesions
   K. Blastomycosis: ulcerative, granulomatous plaques on tongue, gingiva, palate
   L. Cryptococcosis: fleshy, proliferative lesions on the palate, gingiva, lips, or tongue
   M. Phycogranulomatosis
      1. Phycogranulomatosis is a chronic, localized to diffuse glossitis surrounding embedded plant material.
      2. In cats, the lingual frenulum is a common location for awns or burrs to lodge.
   N. Diphenylhydantoin *(Dilantin):* gingival hyperplasia in both cats and dogs
II. Hematology is usually nonspecific.
   A. Anemia: chronic oral hemorrhage, anemia of chronic disease or associated with FIV and FeLV
   B. Leukocytosis: chronic inflammation or infection
   C. Eosinophilia: eosinophilic granuloma complex
III. Other laboratory tests are necessary to differentiate causes.
   A. Biochemical profile
   B. Thyroid function tests (see Chapter 42)
   C. Virological testing for FIV, FeLV, FHV-1, etc.
   D. Immunological testing (see Chapter 76)

E. Cytology
   1. Bacterial agents, especially spirochetes, can be identified.
   2. Fungal elements from *Blastomyces* spp. or *Histoplasma* spp. may be found.
   3. Neoplasia may be detected.

F. Culture
   1. Routine bacterial culture of oral lesions is not recommended, because most cultures reveal normal microbial flora.
   2. If routine antimicrobial therapy is ineffective, culture and sensitivity testing can be used to select antibiotics.

IV. Biopsy is very important in distinguishing a primary cause and appropriate therapy.
   A. Histopathology is essential to differentiate similar-appearing diseases (e.g., squamous cell carcinoma) before initiation of therapy.
   B. Specialized analysis of histopathologic specimens is done for immune-mediated disorders.

Differential Diagnosis

I. Oral neoplasia, especially squamous cell carcinoma (SCC)
II. Eosinophilic granuloma complex

Treatment

I. The primary objective is to identify and remove or treat the underlying cause.
II. The first step is to achieve a clean, healthy periodontium via dental prophylaxis, periodontal debridement, and antibacterial therapy.
III. Bacteria alone may be the primary cause of gingivitis or stomatitis, and it is important to determine if bacteria are a primary or secondary cause.
IV. Because secondary bacterial overgrowth is a common occurrence, symptomatic therapy is indicated.
   A. Amoxicillin 22 mg/kg PO, SC, IM TID
   B. Amoxicillin-clavulanic acid
      1. Dogs: 12.5 to 25 mg/kg PO BID
      2. Cats: 62.5 mg PO BID
   C. Clindamycin 5 to 10 mg/kg PO BID
   D. Cephalexin 22 mg/kg PO, IM, SC TID
   E. Doxycycline 5 mg/kg PO BID
   F. Enrofloxacin 4 mg/kg PO SID (cats) and 5 to 10 mg/kg SID (dogs)
   G. Metronidazole 5 to 15 mg/kg PO BID to TID, then SID to maintain remission
V. Antifungal therapy may be indicated.
   A. Ketoconazole 10 to 15 mg/kg PO BID
   B. Itraconazole 5 to 10 mg/kg PO SID
   C. Fluconazole 2.5 mg/kg PO BID
VI. Antiviral therapy with interferon-γ has been anecdotally beneficial in some cats with retroviral infections.
VII. In cats, corticosteroid therapy is commonly used to treat gingivitis and stomatitis, but other immunosuppressive drugs may be needed in dogs or cats with some forms of immune-mediated or inflammatory diseases or for adverse reactions to corticosteroids therapy (see Lymphoplasmacytic Stomatitis).
VIII. Cyclosporine 1 to 4 mg/kg PO SID or divided BID has been used (anecdotally) with success in some cats, but improvement takes time (4 to 6 weeks) and requires careful monitoring of drug levels.
IX. Nutritional support is important.
   A. Canned diets or soft, blenderized foods may be tolerated best.
   B. Nutritional support in the form of esophagostomy or nasogastric tube feeding may be necessary in cats or dogs with oral pain and prolonged anorexia.
   C. Vitamin supplementation with vitamins C and E may be useful to promote epithelial regeneration, tolerance to inflammation, and healing.
   D. If balanced foods are fed, additional supplementation is generally unnecessary; however, if homemade diets are fed, vitamin and mineral supplements are indicated.
   E. Zinc supplementation in Siberian huskies and other sled dog breeds may be helpful.
X. Oral hygiene is maintained through frequent dental scaling (every 3 to 6 months) and oral cleansing, especially in cats with recurrent or poorly controlled disease.
   A. Oral cleansing to remove necrotic tissue and debris enhances recovery.
   B. Chlorhexidine (0.2%) rinses or gel applications may be used.
XI. Use of various products to enhance or modulate the immune system's response to chronic viral infections (e.g., bovine lactoferrin, interferon) has been reported, but no clear efficacy has been documented.
XII. Laser thermoablation (carbon dioxide laser) is used to reduce chronic proliferative tissue in the oral cavity (especially fauces of cats).

Monitoring of Animal

I. Adequate nutrition and hydration are essential for normal healing and successful management of oral disease.
II. Avoid prolonged antibiotic therapy or frequent changing of antibiotics to prevent development of candidiasis and/or resistant bacterial species.
III. Maintenance of oral hygiene through dental care and oral washes is very important.

Tonsillitis

Definition

I. Tonsillitis is inflammation of the tonsils and surrounding pharyngeal structures, with secondary lymphoid hyperplasia.
II. Primary tonsillitis is rare in dogs and is usually seen in young, small-breed dogs.

Causes

I. Primary tonsillitis may be a manifestation of normal pharyngeal defense mechanisms as the tonsil is exposed to infectious agents.

II. Secondary tonsillitis can be caused by a variety of insults.
  A. Chronic vomiting or regurgitation
  B. Chronic coughing, gagging, or retching
  C. Chronic nasopharyngeal disease or nasal discharge
  D. Foreign body penetration

Pathophysiology

I. Microorganisms that penetrate the tonsillar epithelium are phagocytized and processed by macrophages, presented to B and T lymphocytes, and subsequently stimulate both humoral and cell-mediated immune responses.
II. Lymphoid hyperplasia and reactivity occur when chronic infection overwhelms the tonsillar defense mechanisms.

Clinical Signs

I. Fever, depression
II. Head shaking
III. Dysphagia, repeated attempts to swallow
IV. Anorexia

Diagnosis

I. Clinical signs, history, and direct visualization of enlarged, hyperemic, friable tonsils, and pharyngitis are suggestive; however, the tonsils do not always protrude from the crypts.
II. Cultures are of questionable value because the most common organisms associated with tonsillitis are also the normal microflora of the mouth (*Porphyrmonas* spp., *E. coli, Staphylococcus aureus, Staphylococcus albus*, hemolytic streptococci, diplococci, *Proteus* spp., *Pseudomonas* spp.).
III. Cytology may be useful to rule out neoplasia and other differential diagnoses.
IV. Radiography helps identify penetrating radiopaque foreign bodies (e.g., bone fragments).
V. Anesthesia may be necessary for a complete examination.
VI. Ultrasonography of adjacent lymph nodes and salivary glands may be helpful.

Differential Diagnosis

I. Neoplasia: SCC, lymphosarcoma
II. Underlying disorders that cause chronic vomiting, regurgitation, or coughing

Treatment and Monitoring

I. Where possible, identify and correct the underlying disorder.
II. Broad-spectrum antibiotic treatment for 5 to 7 days is curative in most cases of primary tonsillitis.
  A. Amoxicillin, amoxicillin-clavulanic acid, tetracycline/doxycycline, clindamycin, or metronidazole may be given.
  B. Avoid long-term antibiotic therapy and frequent changes in antibiotics because they promote bacterial resistance and fungal overgrowth.
III. Tonsillectomy is rarely indicated unless the enlarged tonsils interfere with chewing or swallowing, or if tonsillar neoplasia has not been ruled out.

IDIOPATHIC DISEASES

Mark E. Hitt

Lymphoplasmacytic Stomatitis

Definition

I. Lymphoplasmacytic stomatitis is a chronic proliferative inflammatory disorder of the oropharyngeal mucosa variably affecting the gingiva; palatoglossal arches (faucitis); base of the tongue; larynx; and palatine, nasal, and caudal pharynx.
II. Mature cats (>12 months of age) are most frequently affected.
III. Dogs are diagnosed with similar pathology, but less often.
IV. Synonyms include plasma cell gingivitis and stomatitis, lymphoplasmacytic glossopharyngitis, and lymphocytic laryngo-pharyngitis.

Causes and Pathophysiology

I. It is considered an idiopathic condition after chronic viral, bacterial, and mechanical/traumatic factors have been ruled out.
II. Hypersensitivity reactions to oral or dental tissues with bacterial antigens acting as haptens have been hypothesized as the cause.

Clinical Signs

I. Signs are related to inflammation, pain, and proliferation of tissue.
II. Predominant signs include distorted masticatory movements, halitosis, inappetence, bleeding from gums, oral dysphagia, and ptyalism.
III. Oral examination reveals various lesions, including raised, erosive, proliferative, and/or erythematous lesions that may have concurrent ulcerative and proliferative components.
  A. Usually lesions are found at the palatoglossal arches (faucitis), around the teeth (paradental), and along the caudal aspects of the frenulum of the tongue.
  B. Additional affected areas may include the caudal pharynx, nasopharynx, laryngeal mucosa, commissure of the buccal mucosa, and tongue.

Diagnosis

I. Diagnosis is based on biopsy and histopathologic evaluation of the lesions.
  A. Surgical, endoscopic, and rongeur cup-type biopsies are acceptable.
  B. Cytological samples are often nondiagnostic because of the abundant cellular and bacterial debris on the surface of the lesions.
II. Histologic findings include a variable mixture of lymphocytes and plasma cells, with predominance of lymphoid cells under an eroded epithelium.
  A. Additional inflammatory cells (eosinophils, macrophages, neutrophils) can be present.

B. Repeated biopsy of chronic or relapsing cases is advised because of concern for oral neoplasia.

III. Clinical pathologic information is often helpful.
   A. A complete blood count (CBC) may reveal leukocytosis and mild anemia of chronic disease.
   B. Elevation of serum globulins and serum electrophoresis may support a polyclonal gammopathy reflective of a chronic lymphoid inflammatory response.
   C. Bacterial cultures for aerobes and anaerobes and Gram staining are not initially performed because of overlap between normal flora and pathogenic organisms; however, they may be helpful in chronic cases.

Differential Diagnosis

I. Eosinophilic granuloma complex and/or plaques: lesions more localized to the hard palate, philtrum, lips, and tongue
II. Neoplasia: especially SCC, lymphosarcoma
III. Linear foreign body wrapped at the base of the tongue and penetrating foreign bodies lodged in the mucosa (e.g., plant awns, burrs)
IV. Severe pyorrhea associated with bacterial infections and periodontitis
V. Chronic viral infections: FeLV, FIV, caliciviruses, FHV-1
VI. Adverse drug reactions
VII. Immune-mediated diseases: SLE, pemphigus complex, Stevens-Johnson syndrome
VIII. Inflammation from persistent vomiting, reflux of gastric acid and bile
IX. Eosinophilic granuloma of Siberian huskies
X. Eosinophilic stomatitis of Cavalier King Charles spaniels

Treatment

I. Treatment involves aggressive antiinflammatory or immunosuppressive medications.
II. The disorder is a persistent condition requiring long-term control.
III. Formulation of medications into liquids may be preferable.
IV. Oral hygiene is helpful for treating halitosis and removing superficial debris.
V. Antiinflammatory and immunosuppressive drugs include the following:
   A. Prednisone/prednisolone 2 mg/kg PO SID to BID, then tapered to lowest effective dose
   B. Methylprednisolone acetate 2 to 4 mg/kg IM at 2- to 6-week intervals in cats, as tolerated
   C. Megestrol acetate 0.25 mg/kg PO QOD for three doses, then once or twice weekly, as needed in cats only
      1. Do not use in unspayed females, in diabetics, or concurrently with corticosteroids.
      2. Use with caution because of severe potential side effects.
   D. Azathioprine 1 to 2 mg/kg PO SID to QOD in dogs; used concurrently with corticosteroids
   E. Chlorambucil 0.25 to 0.33 mg/kg PO every 72 hours initially in cats and 0.1 to 0.2 mg/kg PO SID to QOD in dogs; used concurrently with corticosteroids
   F. Aurothioglucose 1 mg/kg IM weekly for 10 to 20 weeks, then tapered to once monthly; response possibly delayed for 1 to 3 months
   G. Cyclosporine 2 to 5 mg/kg PO BID initially, then SID or QOD, but anecdotal or literature recommendations inconclusive at this time
VI. Antibiotics are often helpful initially and intermittently as secondary infections recur (see Stomatitis, earlier in this chapter).
VII. Laser fulguration, used carefully in conjunction with immunosuppressive therapy, is reported to help in some cases with marked proliferative lesions.
VIII. Dental extraction is an aggressive treatment.
   A. It is advised only after medications have been tried, or after owner compliance fails and client frustration is high.
   B. It is generally effective.
IX. Response to treatment is variable.
   A. Response to therapy may take weeks to assess.
   B. Lymphoplasmacytic stomatitis is a chronic condition that may be kept in remission, but is not often cured.
   C. Combinations of corticosteroids and immunosuppressive agents have usually provided the most success.

Monitoring of Animal

I. Clients must be advised that initial, frequent reassessments every 2 to 3 weeks to every 1 to 3 months are necessary to safely monitor and guide the use of immunosuppressive drugs.
II. Long-term monitoring of CBC, platelet counts, serum chemistries, and urinalyses are advised at 1- to 3-month intervals to assess for potential adverse effects of medication and chronic inflammation that may include anemia, leukopenia, thrombocytopenia, hepatopathy, and increased risk of bacterial infections.

Oral Feline Eosinophilic Granuloma Complex

Definition and Cause

I. Two forms of eosinophilic granuloma complex affect the oral cavity.
   A. Indolent or "rodent ulcer"–type erosions, often on the upper lip
   B. Eosinophilic granulomas anywhere in the oral cavity
II. These lesions are considered idiopathic because the cause is not well defined.
III. They involve an accumulation of a dense matrix of mixed inflammatory cells, which may have a predominance of eosinophils in fibroproliferative tissue.
IV. They occur as erosions, plaques, or proliferative lesions.

Clinical Signs

I. The clinical signs are the same as those of idiopathic lymphoplasmacytic gingivostomatitis.
II. Lesions are generally more focal than those seen in lymphoplasmacytic disease.

Diagnosis

I. Diagnosis is based on biopsy and histopathologic evaluation.
II. Surgical, endoscopic, and rongeur cup-type biopsies are acceptable.
III. Cytological samples are often nondiagnostic because of the abundant cellular and bacterial debris on the surface of the lesions.

Differential Diagnosis

I. SCC
II. Linear string foreign body
III. Lymphoplasmacytic oropharyngeal disease

Treatment

I. Use corticosteroids (prednisone, prednisolone, dexamethasone, triamcinolone) initially PO and/or intralesionally.
II. Try megestrol acetate at 0.25 to 0.5 mg/kg PO SID for 3 days, then once or twice weekly for several weeks until resolution.
III. Radiation, laser surgery, or cryotherapy can be effective for nonresponsive rodent ulcers.

PHARYNGEAL AND SWALLOWING DISORDERS

Mark E. Hitt

Oropharyngeal Dysphagia Disorders

Definition

I. Dysphagia is defined as difficulty in swallowing.
II. An abnormal oropharyngeal phase of swallowing can occur at several points.
  A. Oral stage: prehension in the oral cavity, bolus formation at the base of the tongue, and initiation of swallowing reflex
  B. Pharyngeal stage: rapid contractions of pharynx to direct the bolus aborally toward the cricopharyngeal passage
  C. Cricopharyngeal stage: coordinated relaxation of the upper esophageal sphincter (UES), propulsion of the bolus by the tightened pharynx into the proximal esophagus, and retightening of the UES and relaxation of the pharynx

Causes and Pathophysiology

I. Dysphagia is clinically difficult to separate into the specific stages.
  A. Visual observation can be difficult to assess.
  B. There are many overlapping causes involving more than one phase of swallowing.
II. Oral and pharyngeal dysphagia may arise from the following:
  A. Hypoglossal nerve dysfunction
    1. Hydrocephalus or other causes of increased intracranial pressure
    2. Trauma to the hypoglossal nerves (central or peripheral)
    3. Neoplasia affecting the cranial nerve nucleus
  B. Systemic neuromuscular disease
    1. Myasthenia gravis: focal or generalized
    2. Endocrine neuropathies
      a. Hypothyroidism
      b. Hyperadrenocorticism
      c. Hypoadrenocorticism
    3. Myopathies
      a. Familial myopathies (see Chapter 82)
      b. Muscular dystrophy-like disease of Bouviers des Flandres
    4. Immune-mediated myositis (inflammatory myopathies)
      a. Masticatory myositis
      b. Eosinophilic myositis
      c. Myositis associated with SLE
  C. Infectious causes
    1. Rabies virus
    2. Submucosal abscess: foreign bodies, bite wounds
    3. Borreliosis (Lyme disease): effects on cranial nerves (rare)
  D. Traumatic and physical obstruction
    1. Skeletal disorders and fractures
    2. Dental disease
    3. Gastroesophageal-pharyngeal reflux: bile or stomach acids
    4. Craniomandibular osteopathy
    5. Tumors of the oropharynx
    6. Pharyngeal mucocele
    7. Inflammatory nasopharyngeal polyps in cats
    8. Retropharyngeal lymphadenopathy from regional infection or metastasis: tonsillar carcinoma, thyroid carcinoma
    9. Pharyngeal mucosal laxity (collagen weakness) associated with hyperadrenocorticism in small and toy breeds of dogs (rare)
    10. Brachycephalic syndrome (see Chapter 15)
    11. Oropharyngeal foreign bodies
III. The etiology of cricopharyngeal dysphagia is variable.
  A. Failure to coordinate (asynchronous) the relaxation of the UES (achalasia) with cricopharyngeal contraction is an idiopathic congenital condition.
  B. Acquired or congenital strictures in the region of the cricopharynx and UES may result from the aforementioned causes.
IV. The mechanism of dysphagia varies and may be a dysfunction of anatomy, an asynchronous coordination of events, or may arise from obstruction.

Clinical Signs

I. Oral dysphagia
  A. Prehensile dysfunction may be noted.
    1. Drooling, dropping food from mouth
    2. Exaggerated efforts to toss food back into the oral cavity

B. Tongue fails to propel material aborally and has poor retractile strength when grasped.
C. Asymmetry of muscular or skeletal anatomy may be noted on examination.

II. Pharyngeal dysphagia
A. Prehension is normal, but there are repeated efforts at swallowing.
B. Gagging and coughing of saliva or a food bolus may occur.
C. Liquids may be swallowed more easily, but a post-swallowing cough or "clearing of the throat" is often reported.
D. Rhinitis and nasal discharge are often noted.
E. Aspiration pneumonia, pneumonitis, and/or tracheobronchitis with associated coughing, fever, or chronic pulmonary disease may be present.
F. Signs of systemic disorders may be present.

III. Cricopharyngeal dysphagia
A. In puppies the time of onset (achalasia) is usually at weaning.
B. Repeated efforts are made to swallow the same bolus of food.
C. Aspiration pneumonia and nasal discharge are common complications.

Diagnosis

I. Complete neurological and musculoskeletal examinations are imperative.
II. Take a careful history and observe any swallowing attempts.
III. Evaluate standard hematological and biochemical tests to identify predisposing disorders.
IV. Serological evaluation of antinuclear antibody, acetylcholine receptor antibody, and masticatory myositis antibodies may identify immune-mediated disorders.
V. Electromyography is helpful in identifying cranial nerve dysfunction but may be difficult to perform and interpret.
VI. Radiography and imaging techniques may be indicated.
A. Swallowing a positive contrast medium under videofluoroscopy is an ideal technique for evaluation of dysphagia.
B. Iohexol mixed with water, barium suspension, or barium mixed with food all have merit as contrast media (different textures).
C. Cervical region soft tissue and musculoskeletal abnormalities may be detected on survey radiographs.
D. Thoracic radiography may identify megaesophagus or detect mass lesions (e.g., thymoma, lymphosarcoma, heart base tumors).
E. Abdominal radiography may identify causes of gastric acid reflux or reveal evidence of more widespread dysautonomic gastrointestinal function.
F. Ultrasonography of the soft tissues of the cervical and ventral pharyngeal region helps identify tumors, cysts, abscesses, and asymmetry in the region.
G. Magnetic resonance imaging and computed tomography may localize tumors.

Differential Diagnosis

I. See causes listed earlier
II. Megaesophagus (see Chapter 30)
III. Retropharyngeal lymphadenopathy or abscess
IV. Meningitis with neck pain
V. Musculoskeletal disorders: temporomandibular joint disease, fractures
VI. Trigeminal neuralgia
VII. Retrobulbar abscess
VIII. Idiopathic polyneuropathy of Dalmatians and other breeds
IX. Laryngeal paralysis

Treatment

I. Treatment for dysphagia relies on determining the underlying cause(s).
II. Symptomatic treatment includes nutritional support.
A. Elevated feeding with trials of various textures of foods is often unrewarding for dysphagia.
B. Percutaneous endoscopic gastrostomy (PEG) tubes are superior to nasoesophageal and pharyngoesophageal tubes.
C. PEG tubes may be replaced for long-term feedings with low-profile gastrostomy (button) tubes.
D. Myotomy of the cricopharyngeal muscle is performed for cricopharyngeal achalasia, but for other dysphagias it may increase the risk of aspiration pneumonia.
III. See Chapter 18 for treatment of aspiration pneumonia.

Monitoring of Animal

I. Spontaneous improvement has been noted in a few cases of cranial nerve neuropathies, but neuropraxias (trauma causing dysfunction of the nerves) and musculoskeletal injuries may require months to improve.
II. Prognosis is guarded to poor if a specific cause cannot be identified because of the risk of aspiration pneumonia and the debilitation that ensues from malnutrition.

NEOPLASIA

Debra L. Zoran

Epulis

Definition and Cause

I. Gingival proliferations of tissue that are benign and do not significantly invade bone are termed *epulides*.
II. Classification of epulides is controversial, but they are most commonly grouped as ossifying epulis, fibromatous epulis, or squamous or acanthomatous epulis.
A. Acanthomatous epulis may be a form of basal cell carcinoma, may be fixed to bone at the gum line, and is considered to be more aggressive than fibromatous or ossifying epulides.
B. Synonyms for acanthomatous epulis are adamantinoma and ameloblastoma.

III. Epulides are common in dogs (20% of oral tumors), but are rare in cats (Withrow, 2001).
IV. No known causes or risk factors have been identified.

Pathophysiology

I. Ossifying and fibromatous epulides are firm or pedunculated, nonulcerating, and noninvasive tumors that can occur as single or multiple growths.
II. An epulis is usually ≤1 to 4 cm and is attached to the gingiva at the gum line, but they do not invade bone in most cases.
III. Acanthomatous epulis is locally aggressive, often associated with marked bony lysis, more commonly affects the rostral mandible, and rarely metastasizes (Withrow, 2001).

Clinical Signs

I. Because of their location, masses are often discovered before signs develop.
II. Dogs may have anorexia, drooling, oral hemorrhage, dysphagia, and halitosis.
III. Epulides are most commonly observed in geriatric dogs but can occur at any age (Diebielzig et al., 1979).

Diagnosis

I. Surgical biopsy is diagnostic, but fine-needle aspirate or a scraping may also be useful to rule out other malignant tumor types.
II. Histologically, acanthomatous epulis may closely resemble SCC.
III. Regional metastasis is more common with SCC, so careful examination of regional lymph nodes (aspirate) is important (Verstraete et al., 1992).

Differential Diagnosis

I. Severe gingival hypertrophy
II. Oral papillomas
III. SCC
IV. Fibrosarcoma
V. Other oral neoplasms: chondroma, osteoma, hemangioma, lipoma
VI. Other dental neoplasms: odontoma, ameloblastoma

Treatment and Monitoring

I. Treat fibromatous and ossifying epulides with surgical excision.
II. Because epulides arise from the periodontal ligament, excision at the level of the gingiva is often incomplete and the tumor may regrow.
III. Partial maxillectomy or mandibulectomy is often necessary to prevent local recurrence of acanthomatous epulis.
   A. The prognosis is guarded to good (Withrow, 2001).
   B. Cryosurgery is not recommended because local recurrence is common.
   C. Radiation therapy is also an effective treatment method.
IV. Successful use of chemotherapy using doxorubicin and cyclophosphamide has been reported, but is not done unless repeated local recurrences develop.
V. Intralesional bleomycin has been successful in a few dogs, but is not recommended as the first therapeutic choice.

Oral Papillomatosis

Definition and Causes

I. Multiple, benign cauliflower-like growths arising from squamous epithelium affect the lips, buccal mucosa, gingiva, tongue, and pharyngeal structures.
II. Papillomas are seen primarily in young dogs (<1 year), with no breed or sex predilection.
III. The tumors are induced by canine oral papillomavirus (papovavirus) and are contagious.
IV. They are not related to nonviral, cutaneous papillomas that are common in geriatric dogs.

Pathophysiology

I. The incubation period following viral infection is approximately 4 to 8 weeks.
II. Tumor growth lasts 1 to 5 months.
III. Spontaneous regression occurs over 6 to 12 weeks (Calvert, 1990).
IV. Regression is accompanied by lifelong immunity.

Clinical Signs

I. Dogs may be asymptomatic, but multiple or large papillomas, dysphagia, ptyalism, halitosis, or other signs of oral disease (e.g., inappetence, face rubbing) may be observed.
II. Lesions vary in appearance from large, gray, pedunculated masses to small, white, smooth nodules.
III. Regressing lesions appear dark and shriveled, and regression may take 1 to 2 weeks.

Diagnosis

I. Clinical signs and gross appearance in a young dog are suggestive.
II. Surgical biopsy and histopathology confirm the diagnosis.

Differential Diagnosis

I. Transmissible venereal tumor (TVT)
   A. Lesions are typically present on external genitalia as well as the mouth.
   B. TVT is usually sessile and more often ulcerated.
   C. Biopsy is diagnostic.
II. SCC: often presents as sessile, ulcerated masses with bony lysis
III. Epulis

Treatment and Monitoring

I. Treatment is usually not recommended if only a few papillomas are present.
II. If large or multiple growths cause persistent clinical signs or do not regress, treatment is indicated.
III. Several methods are effective, including surgical excision, cryotherapy, and electrosurgery.
IV. The efficacy of autologous wart vaccines is questionable, and they are not recommended.

Squamous Cell Carcinoma

Definition

I. SCC is a malignant neoplasm of squamous epithelium.
II. SCC is the most common oral neoplasm of cats (70% of all oral tumors) and the second most common (20% to 30%) oral tumor in dogs (Stebbins et al., 1989; Withrow, 2001).
III. Although tumors of the tongue are rare, SCC of the tongue is the most common lingual cancer.
IV. It is most commonly seen on the ventrolateral surface of the tongue in cats, and is associated with extensive involvement of bone.
V. In dogs, SCC is commonly seen in the tonsillar crypt or gingival mucosa (Withrow, 2001).
VI. Gingival SCC may arise adjacent to the incisors and premolars of the lower jaw; near the molars in the upper jaw; on the hard palate; and on the buccal and labial mucosa (Smith, 2005).

Causes

I. There is no known cause of SCC.
II. Conditions that may be associated with an increased incidence of SCC include the following:
  A. Chronic periodontal disease
  B. Eosinophilic ulcer
  C. Oral papillomatosis
III. Dogs living in an urban environment have a higher incidence (10:1) of tonsillar SCC.

Pathophysiology

I. The biological behavior of SCC varies by the species affected and the location within the oral cavity.
  A. SCCs of the tongue and tonsil are aggressive forms that tend to metastasize early to regional (retropharyngeal or mandibular lymph nodes) and distant (lungs) sites (Withrow, 2001).
  B. SCC of the gingival tissues is locally aggressive (bony invasion in 77%) and superficially ulcerative but is slowly progressive (10% regional metastasis, 3% distant sites) (Smith, 2005).
  C. Small, rostrally located, gingival SCCs tend to have the best prognosis (Ogilvie and Moore, 1995).
II. Generally, SCC tends to occur with greater frequency in white dogs and cats, even though lack of protective pigment may have less effect in the mouth.

Clinical Signs

I. SCC of the tongue
  A. In cats, the tumor arises at the base of the tongue and may initially appear as a small, raised ulcer or erosive lesion.
  B. Canine SCC of the tongue is more likely to arise on the dorsal surface.
  C. The animal may be asymptomatic or show severe dysphagia, difficulty in prehension of food, oral hemorrhage, excessive licking movements, ptyalism, and gagging.
  D. Lingual forms are usually seen in older dogs and cats.
II. SCC of the tonsil (Evans and Shoter, 1988)
  A. It is most often seen in old (mean age, 10 to 12 years), male (2:1) dogs (Spodnick and Page, 1995).
  B. Palpation of enlarged mandibular or retropharyngeal lymph nodes in an older dog indicates the need for a careful examination of the tonsils and caudal oropharynx.
  C. The tumor is typically a unilateral, firm mass deeply attached in the tonsillar crypt and may be associated with subcutaneous swelling, severe dysphagia, and pain.
  D. It rapidly metastasizes to the retropharyngeal lymph nodes, so the disease should be considered systemic at the time of diagnosis.
III. SCC of the gingiva
  A. The mean age of occurrence is slightly younger (7 to 9 years old) than for tonsillar SCC.
  B. Lesions may present as nonhealing ulcers in the gingiva adjacent to teeth or as proliferative, expansile masses without ulceration.
  C. Both single and multiple masses are reported.

Diagnosis

I. Surgical biopsy of the mass and enlarged lymph nodes with histopathology is required for diagnosis.
  A. Cytology is often unrewarding because of the accompanying necrosis and inflammation.
  B. Any nonhealing, ulcerated region in the oral cavity should be biopsied to rule out SCC.
II. Stage all animals with oral masses through blood tests, three radiographic views of the thorax, ± oral radiography, and cytological and histopathological testing.

Differential Diagnosis

I. SCC of the tongue
  A. Sublingual foreign body
  B. Eosinophilic granuloma complex
  C. Other less common neoplasms: granular cell myoblastomas (second most common tongue tumor), fibrosarcoma, malignant melanoma, mast cell tumor, lymphosarcoma
II. SCC of the tonsil
  A. Lymphosarcoma
  B. Salivary gland adenocarcinoma (rare)
  C. Tonsillitis or tonsillar abscess
III. SCC of the gingiva
  A. Chronic gingivitis, periodontitis
  B. Eosinophilic granuloma complex
  C. Epulis
  D. Other neoplasms: fibrosarcoma, osteosarcoma, malignant melanoma
  E. Osteomyelitis (especially in cats)
IV. SCC of the palatine mucosa
  A. Plasmacytic gingivitis-stomatitis complex
  B. Salivary gland adenocarcinoma

Treatment

I. Attempt to rule out metastatic disease first, because some SCCs have metastasized at the time of diagnosis.

II. Surgical excision is the initial treatment of choice, but tumor removal may be difficult because of extensive invasion of underlying tissue and bone.
   A. Hemimandibulectomy or total maxillectomy/mandibulectomy has the greatest success rates for gingival SCC, but when the tumor is large and surgical margins are incomplete, concurrent radiation therapy is indicated (Ogilvie and Moore, 1995; Smith, 2005).
   B. SCC of the tongue is amenable to surgical removal in 40% to 60% of canine cases, but the percentage is lower in cats because of its usual location on the ventral surface of the base of the tongue (Guilford, 1996).
   C. For tonsillar SCC, surgical debulking is only palliative and is typically used in conjunction with radiation therapy.
      1. Radiation therapy and hyperthermia after surgical debulking have provided the best long-term results (Ogilvie and Moore, 1995; Smith, 2005).
      2. Radiation therapy of caudal tumors has a poorer response rate and greater chance of radiation-induced bone necrosis and fistula formation.

III. Cisplatin alone or combined with doxorubicin (dogs), and doxorubicin with cyclophosphamide (cats) may be tried in animals that are not candidates for surgical resection or radiation therapy, or for whom palliation is the treatment choice.

Monitoring of Animal

I. Monitor oral and thoracic radiographs periodically to assess disease progression.
II. Because of the rapid growth of tonsillar SCC, owners must be made aware of the potential for airway obstruction.
III. Nutritional support of the animal is an important part of treatment.
   A. Aggressive forms of nutritional support, such as PEG or esophagostomy tube insertion, may be used for SCC or any oral malignancy.
   B. Special diets, such as soft, blenderized foods, or canned diets may improve food consumption.

Malignant Melanoma

Definition and Cause

I. Malignant melanoma is a neoplasm of melanocytes within the epidermis; however, not all melanomas (up to one third) contain melanin.
II. Melanoma is the most commonly reported oral tumor in dogs; however, it is rare in cats.
III. There is no known cause.
IV. Certain breeds appear to be more susceptible, especially black-coated dogs (e.g., black cocker spaniel, Scottish terrier).
V. The tumor is also common in poodles, dachshunds, and golden retrievers.

Pathophysiology

I. Most oral melanomas are malignant, and melanomas of the mucocutaneous junction are invariably malignant.
II. Major sites are the pigmented gingiva, buccal mucosa, and palate.
III. The tongue is a less common site.
IV. Melanomas are locally aggressive tumors.
   A. Smaller tumors (<2 cm diameter) are associated with longer survival times (Harvey et al., 1981).
   B. Metastasis to regional sites (lymph nodes) occurs early in dogs.
   C. The time to metastasis to distant sites (lungs, brain, kidney) is variable, with lung metastasis most common (Smith, 2005).

Clinical Signs

I. The mean age for melanoma in dogs is 10 to 12 years (Spodnick and Page, 1995).
II. There is no apparent sex predilection for oral melanoma in dogs (Hahn et al., 1994).
III. Female cats may be predisposed, but the numbers reported are small.
IV. Signs depend on location and size of the tumor and include halitosis, dysphagia, difficulty chewing or painful chewing, face rubbing, oral hemorrhage, drooling, and inappetence.
V. Melanomas are typically pigmented, but amelanotic melanomas have a pinkish-white appearance, are friable and necrotic, and bleed very easily.
VI. Tumors may be dome shaped or sessile.
VII. Local invasion of bone is common.

Diagnosis

I. Excisional biopsy with histopathology is diagnostic, although amelanotic melanomas are often reported histologically as anaplastic sarcomas.
II. A complete work-up includes a hemogram, biochemical profile, urinalysis, thoracic and oral radiography, and regional lymph node aspirates or biopsy for staging of the disease.
III. Animals with no evidence of distant metastasis are considered candidates for aggressive therapy.

Differential Diagnosis

I. Fibrosarcoma
II. SCC
III. Hemangiosarcoma
IV. Other anaplastic sarcomas

Treatment and Monitoring

I. Prognosis is guarded to poor, because the tumor may have metastasized by the time of diagnosis (1-year survival is 25%).
II. Radical surgical excision (margins ≥2 cm) via maxillectomy or mandibulectomy is the most common treatment.
III. Cryosurgery may be indicated for lesions <2 cm in diameter that are fixed or minimally invasive into bone.
IV. Radiation therapy may be useful, but large doses may be required.
   A. Concurrent hyperthermia enhances the effectiveness of radiation therapy.

B. Radiation therapy appears to be most effective with small tumors.
C. It is most often used for palliation of inoperable tumors.

V. Chemotherapy for metastatic disease is generally unrewarding.
A. Cisplatin 60 mg/m^2 IV every 3 weeks
B. Carboplatin 300 mg/m^2 IV every 3 weeks (Ogilvie and Moore, 1995)

VI. Immunotherapy may be considered along with chemotherapy for metastatic disease.
A. *Corynebacterium parvum* may be beneficial when used together with surgery.
B. Liposome-encapsulated muramyl tripeptide-phosphatidylethanolamine (L-MTP-PE) immunotherapy has been used but did not improve survival of dogs with in advanced stage (II, III) disease (Withrow, 2001).

VII. Recently a melanoma vaccine has been given limited approval by the U.S. Department of Agriculture.

Oral Fibrosarcoma

Definition and Cause

I. Oral fibrosarcoma is a malignant tumor of fibrocytes.
II. Fibrosarcoma is the second most common tumor of the oral cavity in cats (20%) (Spodnick and Page, 1995).
III. In dogs, oral fibrosarcoma is the third most common malignant tumor (10% to 20%), after melanoma and SCC (Spodnick and Page, 1995).
A. The median age of occurrence is 8 years, with large-breed dogs being overrepresented, especially golden retrievers and Doberman pinschers (Ciekot et al., 1994).
B. Males may be predisposed.
IV. Cats are usually older (mean age, 10 years).
V. There are no known causes or viral associations; it is not related to feline sarcoma virus.

Pathophysiology

I. Oral fibrosarcoma is a solid, fleshy tumor that arises from gingival or periodontal connective tissue, with gingival origin being the most common.
II. The most common sites are the maxillary gingiva and the hard palate in the area between the canine and carnassial teeth.
III. Fibrosarcomas are locally aggressive but only occasionally metastasize to the lungs in cats or old dogs.
IV. In young dogs, the tumor tends to act more aggressively and metastasizes to distant sites.

Clinical Signs

I. The presenting signs depend on the location and size of the tumor and may include dysphagia, ptyalism, anorexia or inappetence, halitosis, exaggerated chewing motions, difficulty chewing, and pawing at the mouth.
II. Fibrosarcomas may grow to be very large (>4 cm in diameter) (Todoroff and Brodey, 1979).

Diagnosis

I. Diagnosis is suggested by the age, breed, sex, and location.
II. Definitive diagnosis is made by excisional biopsy and histopathologic examination.
III. Staging of the tumor is important.
A. Oral radiography often underestimates the tumor margins.
B. Computed tomography is more accurate for determining the extent of bony involvement.

Differential Diagnosis

I. SCC
II. Malignant melanoma
III. Hemangiosarcoma
A. Low incidence of occurrence in the oral cavity
B. Breeds affected: German shepherd dog, golden retriever
IV. Other oral neoplasms
A. Osteosarcoma
B. Salivary gland adenocarcinoma
C. Mast cell tumors
D. Lymphosarcoma
E. Epulis
F. Undifferentiated carcinomas and sarcomas

Treatment

I. Wide surgical excision (partial or complete maxillectomy) is required to prevent local recurrence.
II. Radiation therapy as a single treatment modality is disappointing, unless large doses are used.
A. Megavoltage radiation may be more effective than orthovoltage radiation (Ogilvie and Moore, 1995).
B. Radiation combined with hyperthermia appears to improve local control (Brewer and Turrel, 1982).
III. Fibrosarcoma is unresponsive to cryotherapy.
IV. Combination therapy with surgical debulking, radiation, and/or chemotherapy (e.g., doxorubicin, dacarbazine, carboplatinum, cisplatin) may give the best long-term results.

Monitoring of Animal

I. Local recurrence occurs in 50% of the cases (Withrow, 2001).
II. Some fibrosarcomas are very slow growing, so 6- to 18-month survival times with good quality of life are possible.
III. Metastatic disease is slow to develop, but regional lymph node aspirates and thoracic radiographs are used to monitor disease progression and treatment success.

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CHAPTER 28

Dental Diseases

Ellen I. Logan

GENERAL CONSIDERATIONS

I. Primary dental diseases can be subdivided into conditions affecting the tooth or the periodontium.
II. Diseases that affect the tooth structure may cause pathologic conditions in the periodontal apparatus and/or oral mucosa.
III. Diseases affecting the periodontium may result in exfoliation of teeth.
IV. Diseases affecting the tooth (pulpitis) may cause periodontal pathology.
V. Dental diseases have local and systemic ramifications.

CONGENITAL/DEVELOPMENTAL DISORDERS

Absent or Supernumerary Teeth

Definition

I. Dogs and cats are diphyodont, erupting deciduous and permanent teeth, with published dental formulas representing teeth that are normally present in all dogs and cats.
II. Oligodontia (fewer teeth than normal) and polyodontia (supernumerary or excessive teeth) occur sporadically in dogs and cats.
III. Anatomically, the maxillary first premolars and the mandibular first and second premolars are absent in cats.

Causes and Pathophysiology

I. Anomalies of tooth development may be genetic.
II. They may result from primary dysplasias of the enamel organ.
III. They can occur secondary to insults, such as trauma, infection, toxicosis, or metabolic abnormalities.

Clinical Signs

I. Animals may be asymptomatic.
II. Missing teeth may predispose to soft-tissue trauma from occluding teeth and may reduce the self-cleaning mechanism of the oral cavity.
III. Supernumerary teeth may result in malocclusions and abnormal tooth-to-tooth or tooth–to–soft-tissue contacts.
IV. Early onset of periodontal disease (PD) occurs from plaque accumulation and retention.

Diagnosis

I. Oral examination: abnormal dental formula
II. Intraoral radiographs

Differential Diagnosis

I. Unerupted teeth
II. Exfoliation of teeth from spontaneous PD
III. Previous extraction
IV. Retained root
V. Soft-tissue impaction

Treatment and Monitoring

I. No treatment: asymptomatic animal, normal radiographic examination
II. Extraction: overcrowding and/or rotation of the teeth, tissue trauma, plaque retention
III. Periodontal management: daily plaque control, increased frequency of oral examination and professional prophylaxis
IV. Regular oral examinations
  A. Frequency may be quarterly to biannually, depending on severity and home care compliance.
  B. Evaluate for occlusion as well as tooth and periodontal health.

Retained Deciduous Teeth

Definition

I. A primary, or deciduous, tooth is still in place when the permanent tooth has erupted.
II. The condition is also known as *persistent primary teeth* or *pseudopolyodontia*.
III. It is common in small-breed dogs but can occur in all breeds of dogs and cats.

Causes

I. Congenital defect
II. Alterations in eruption of permanent teeth

Pathophysiology

I. Persistent primary (deciduous) tooth forces the permanent tooth to erupt in an abnormal location.
II. Displaced permanent teeth interfere with eruption and occlusion of other permanent teeth.

Clinical Signs

I. Malocclusion results in abnormal tooth-to-tooth and tooth-to-tissue contact.
II. Abnormal tooth wear and increased accumulation and/or retention of microbial plaque and oral debris may occur.

Diagnosis

I. Oral examination reveals erupted primary and permanent teeth in the same location.
II. With respect to incisors, maxillary permanent teeth erupt palatally to primary teeth, and mandibular permanent teeth erupt lingually to primary teeth.
III. For canine teeth, maxillary permanent teeth erupt mesially to primary teeth, and mandibular permanent teeth erupt lingually and distal to primary teeth.
IV. For premolar teeth, maxillary permanent teeth erupt palatally to primary teeth, and mandibular teeth erupt lingually to the primary teeth.
V. The maxillary fourth premolar erupts buccodistally to the last primary premolar.

Treatment and Monitoring

I. Extraction of primary tooth
II. Orthodontic correction if permanent tooth does not move to appropriate position and causes occlusal trauma
III. Biannual to annual oral examinations to evaluate occlusion, tooth, and periodontal health

Malocclusions

Definition

I. Dental occlusion refers to the position of each tooth and its relation to all other teeth.
II. Normal occlusion is classified as a scissors bite.
  A. The mandibular incisors occlude on the cingulum of the maxillary incisors.
  B. The mandibular canine tooth lies between the maxillary third incisor tooth and canine tooth, without touching either tooth.
  C. The maxillary premolar teeth interdigitate with the mandibular premolar teeth, forming a "pinking shears" pattern.
  D. The upper and lower dental arches are symmetrical.
III. Cats have a more uniform skull conformation than dogs, and malocclusions are rare, except in Persians.

Causes and Pathophysiology

I. Congenital or hereditary: breed predilection
II. Delayed eruption of deciduous or permanent teeth
III. Retained deciduous teeth
IV. Trauma affecting jaw growth or tooth eruption

Clinical Signs

I. Tooth malposition or abnormal bite
II. Tooth crowding or rotation
III. Soft-tissue defects from traumatic tooth contact
IV. Fractures or abnormal wear of teeth from improper tooth contact

Diagnosis

I. With Class I malocclusions, generally one or more teeth are malaligned or rotated.
  A. Anterior crossbite
    1. One or more of the mandibular incisors occlude anterior to the maxillary incisors.
    2. Remaining teeth occlude normally.
  B. Base-narrow (lingually displaced) canine teeth
    1. Mandibular canine teeth are displaced lingually.
    2. They occlude against the hard palate.
  C. Lance tooth
    1. The maxillary canine tooth erupts at an angle, creating interference with the mandibular canine tooth.
    2. The condition may be unilateral or bilateral.
II. Class II malocclusions (e.g., mandibular brachygnathism, overjet, retrusive mandible, distal mandibular excursion) occur when the mandibular premolars and molars are positioned distal to the maxillary premolars and molars.
III. Class III malocclusions (e.g., prognathism, undershot, underjet, protrusive mandible, mesial mandibular excursion) occur when the mandibular premolars and molars are positioned rostral to the normal position.
IV. Wry bite is abnormal occlusion caused by a difference in length of the two halves of the mandible and maxilla.

Differential Diagnosis

I. Tooth displacement from trauma, oral masses, or other causes
II. Open bite secondary to jaw fracture, tooth luxation, or trapped foreign body

Treatment

I. A functional, nontraumatic bite does not require treatment.
II. The primary goals of orthodontic treatment are to prevent abnormal wear or trauma to hard or soft tissues from improper contact, and to provide the animal with a comfortable, functional bite.
III. Malocclusions are generally inherited conditions and a signed release informing the owner of legal and ethical considerations should be obtained (Holmstrom et al., 2004c).
IV. Extraction or crown reductions are alternatives to classic orthodontic corrections.
V. The proper orthodontic procedure is determined by the class and severity of the malocclusion (Holmstrom et al., 2004c; Wiggs and Lobprise 1997a).

Monitoring of Animal

I. Instruct the owner to examine the appliance BID and flush the mouth with an oral hygiene solution (e.g., 0.12% chlorhexidine digluconate).
II. Prevent chewing on hard treats and toys, and provide a soft diet while the appliance is in place.
III. Weekly to biweekly oral examinations are used to monitor appliance stability and tooth movement.
IV. Examine at 2 weeks, 2 months, and 6 months after appliance removal to assess occlusal stability.
V. Radiographic evaluation is done 6 months posttreatment to evaluate tooth and root vitality.

Enamel Hypoplasia/Hypocalcification

Definition and Causes

I. Defects in enamel formation may result in pitting and discoloration of the enamel surface of the permanent teeth.
II. Causes include nutritional, metabolic, toxic, or traumatic insults to ameloblasts.

Pathophysiology

I. Injured ameloblasts do not adequately produce or mineralize enamel.
II. Removal of the insult allows subsequent ameloblasts to begin making normal enamel.

Clinical Signs

I. Affected teeth have varying patterns of enamel defects, including isolated opaque spots, pits, and deep horizontal indentations (severe cases).
II. Fractures may occur from weakened tooth structure.

Diagnosis

I. History of illness during gestation, insult, or trauma during tooth development
II. Oral examination: discolored teeth, irregular or pitted teeth, increased plaque or calculus retention on irregular tooth surfaces

Differential Diagnosis

I. Enamel staining
II. Caries
III. Amelogenesis imperfecta: genetic enamel disorder

Treatment

I. Treatment depends on the extent of the lesions.
II. Smooth the tooth surface by removing sharp irregularities and diseased enamel.
III. Restoration of focal defects with composite or glass ionomer may be beneficial, although results are reported to be short-lived (Wiggs and Lobprise, 1997a).
IV. Fluoride application may decrease sensitivity and enhance enamel strength.

Monitoring of Animal

I. Monitor for further degeneration or complications with semiannual to annual examinations.
II. Recommend semiannual to annual professional prophylaxis and daily mechanical plaque control via brushing or feeding a dental food.
III. Do not allow excessive chewing on hard objects.
IV. Inform the owner that enamel degeneration may continue and necessitate future treatment.

Dentigerous Cysts

Definition and Causes

I. These cysts contain part or all of a tooth.
II. Abnormal tooth development or eruption causes epithelial-lined, cystic structures in the bone or tissues of the jaw.

Pathophysiology

I. They are typically benign but cause bony destruction.
II. They may lead to loss of adjacent teeth.
III. Malignant transformation has been reported.

Clinical Signs

I. Animals may be asymptomatic, depending on the size of cyst.
II. Swelling of the gingival tissue or oral mucosa may be detected.
III. Loosening or abnormalities of affected teeth can occur.

Diagnosis

I. History and oral examination: missing (unerupted) tooth, oral swelling
II. Intraoral radiography: embedded tooth or permanent tooth bud, bone loss
III. Histopathology: cystic epithelium

Differential Diagnosis

I. Impacted tooth
II. Oral neoplasia

Treatment and Monitoring

I. Surgical extraction of the affected tooth and thorough removal of the entire epithelial lining of the cyst wall is usually curative.
II. Postoperative evaluation is done at 1 week to evaluate healing.
III. Oral examination and intraoral radiography are repeated 12 months after treatment.

DEGENERATIVE DISORDERS

Attrition and Abrasion

Definition

I. Attrition is physiological wear of tooth surfaces from contact with occluding teeth during mastication.
II. Abrasion is abnormal wear of tooth surfaces from contact with an external object.

Causes

I. Attrition may result from malocclusion and abnormal wear from continuous tooth-to-tooth contact.
II. Abrasion may result from excessive chewing on hard materials, such as rocks or other hard objects.
   A. The incisor teeth in dogs may show marked wear from excessive chewing behaviors and excessive grooming associated with dermatological conditions.
   B. Abrasion may result from inappropriate use of power instrumentation or excessive brushing.

Pathophysiology

I. Excessive wear is not pathologic, unless the wear rate exceeds the rate of reparative dentin formation.
II. As a response to trauma, odontoblasts produce tertiary dentin as a reparative substance.

III. Rapid wear can lead to pulpal exposure and infection as well as compromised tooth strength.

Clinical Signs and Diagnosis

I. Oral examination reveals abnormal tooth wear.
II. Worn teeth have a shortened crown with a discolored occlusal surface and a central dark-brown or black dot.
III. The central occlusal area is probed with a dental explorer.
   A. If the central occlusal area is firm, then adequate reparative dentin is present.
   B. If the probe sinks into the central occlusal cavity, the pulp is exposed.

Treatment and Monitoring

I. No treatment is necessary if adequate tertiary dentin is protecting the pulp and the tooth is not excessively worn.
II. Pulp exposure requires appropriate endodontics or extraction (Niemiec, 2005).
III. Excessive damage may require smoothing of sharp edges, crown prosthesis, or extraction (Wiggs and Lobprise, 1997a).
IV. Prevention of further wear may require avoidance of hard toys or behavior modification to address inappropriate chewing.
V. Regular oral examinations (every 6 to 12 months) are required to monitor further tooth wear and status of dental health.

INFLAMMATORY DISORDERS

Periodontal Disease

Definition

I. Periodontal disease is the most common dental disease in adult dogs and cats.
II. It is pathology that affects the health of the periodontium, which includes the tissues that surround and support the tooth.
   A. The periodontium is composed of the gingiva, cementum, periodontal ligament, and alveolar bone.
   B. PD commonly refers to gingivitis and periodontitis.
      1. Gingivitis is inflammation of the gingiva and is reversible.
      2. Periodontitis includes gingivitis and inflammation and destruction of the remaining periodontal tissues, and is usually irreversible.

Causes

I. Several materials accumulate on tooth surfaces and participate in the pathophysiology of PD.
II. These substances are commonly referred to as *tooth-accumulated materials* or *dental substrates.*
   A. Acquired enamel pellicle is a thin film composed of protein and glycoproteins deposited from saliva and gingival crevicular fluid.
      1. Pellicle initially protects and lubricates the tooth surface.
      2. As pellicle ages, its constituents are modified and provide a framework for initial bacterial colonization.
      3. Within minutes after a dental polishing, approximately 1 million bacterial organisms are deposited per mm^2 of enamel surface.
   B. Microbial plaque is a soft adherent aggregate of bacteria, salivary glycoproteins, extracellular polysaccharides, and epithelial and inflammatory cells.
      1. Dental plaque has a specific composition and texture that changes with time so that a complex biofilm is formed.
      2. Supragingival plaque forms above the gingival margin.
      3. Growth and maturation of supragingival plaque are necessary for subsequent colonization of subgingival surfaces by gingival plaque.
      4. Subgingival plaque is formed entirely within the gingival sulcus.
   C. Calculus is mineralized plaque formed by the interactions of salivary and crevicular calcium, phosphate, and carbonate salts with existing plaque.
      1. Calculus accumulates supra- and subgingivally and thickens over time.
      2. Calculus provides a roughened surface that enhances plaque attachment and accumulation.
   D. Acquired dental stain is discolored pellicle, plaque, or calculus.
      1. Appearance is influenced by various nutritional, chemical, and microbial factors.
      2. Extrinsic staining is not pathologic; however, it is an important aesthetic concern to pet owners and is often the reason veterinary care is sought.
III. PD results from the accumulation and maturation of the dental plaque biofilm.

Pathophysiology

I. Plaque accumulation along the gingival margin induces inflammation in adjacent tissues.
II. Without plaque removal or control, gingivitis progresses in severity and local changes occur that allow subsequent bacterial colonization of subgingival sites.
III. Inflammatory mediators damage the integrity of the gingival margin and sulcular epithelium, allowing infiltration of bacteria.
IV. Bacteria release factors that interfere with normal host cell function or contribute to destruction of cells or cellular components.
V. The host attempts to limit invasion of the periodontal tissues, which may result in further destruction of local tissues from inflammatory cytokines.
VI. PD increases the risk of secondary systemic disorders.
   A. The pathogens associated with PD may cause systemic bacteremia.
   B. Pathogens stimulate an immune and nonimmune host response (e.g., inflammatory cytokines, inflammatory mediators) that may have systemic effects.

Clinical Signs

I. Plaque and calculus accumulation on supra- and subgingival tooth surfaces
II. Oral malodor (halitosis)
III. Gingival redness, swelling, bleeding
IV. Gingival recession
V. Periodontal pocket formation
VI. Increased tooth mobility or exfoliation

Diagnosis

I. Tentative diagnosis is made by a general oral and physical examination.
II. Definitive oral examination under sedation or anesthesia is used to determine the extent of disease and appropriate therapy.
  A. Use a periodontal probe-explorer to evaluate plaque and calculus coverage, gingival inflammation, furcation exposure, tooth mobility, pulp exposure, resorptive lesions, or other tooth abnormalities.
  B. Periodontal probing is done to determine the distance between the free gingival margin and apical extent of any gingival or periodontal pocket.
    1. Normal probe depth in dogs is 1 to 3 mm.
    2. Normal probe depth in cats is 1 mm.
    3. Probe depth may over- or underestimate the extent of periodontitis because of gingival recession or hyperplasia.
  C. Determine attachment loss by measuring the distance between the cemento-enamel junction and the apical extent of the periodontal pocket, as any loss indicates periodontitis.
  D. Dental charting is used to record pathologic findings and therapeutic procedures.
  E. Intraoral radiography identifies lesions that cannot be detected visually or manually, and determines the extent of certain pathologies.
  F. The degree of severity is determined for each tooth because an animal may have teeth in different stages of periodontal disease.
  G. PD may be classified as follows:
    1. PD 0: clinically normal, no gingival inflammation or periodontitis evident
    2. PD 1: gingivitis, inflammatory changes affecting only the gingivae
    3. PD 2: early periodontitis, <25% attachment loss
    4. PD 3: moderate periodontitis, 25% to 50% attachment loss
    5. PD 4: advanced periodontitis, >50% attachment loss

Differential Diagnosis

I. Stomatitis
II. Oral neoplasia
III. Systemic lupus erythematosus
IV. Pemphigus complex

Treatment

I. Removal of supra- and subgingival plaque and tartar
  A. Professional cleaning, hand-scaling, polishing, irrigation, root planing, subgingival curettage, and application of fluoride are done as warranted.
  B. Oral surgery to expose affected roots for treatment may be indicated with advanced periodontitis.
II. Correction of existing attachment loss (Holmstrom et al., 2004d; Wiggs and Lobprise, 1997c)
  A. Application of local antibiotic gel (Doxirobe)
  B. Gingival flap procedures
  C. Bone replacement procedures
  D. Guided tissue regeneration with membrane barriers to promote new bone
  E. Periodontal splinting
III. Tooth extraction
  A. For severe attachment loss
  B. If home care insufficient
IV. Home care
  A. Periodontal health care involves a combination of professional therapy and effective home care.
  B. Home care procedures must be tailored to fit the owner, animal, and pathologic condition.
  C. Mechanical home care is provided by brushing or dietary cleansing.
    1. Tooth brushing is highly effective, but compliance may be low.
    2. Dietary cleansing through proven dental foods is effective in many animals.
  D. Chemical tartar control is provided by oral preparations containing polyphosphates (e.g., hexametaphosphate).
  E. Products formulated with chlorhexidine, zinc, and fluoride provide varying levels of antimicrobial activity.
  F. Barrier agents are placed on the tooth surface to reduce bacterial attachment.
  G. Numerous professional and over-the-counter products are labeled for dental home care.
    1. Product recommendation is based on evidence to support product claims, ability of the owner to apply the product, acceptance by the pet, and the oral pathology present.
    2. The Veterinary Oral Health Council (VOHC) recognizes products that substantiate claims for plaque and/or tartar control.

Monitoring of Animal

I. Intervals for reexaminations are dictated by the degree of periodontal pathology, as well as specific therapies and home care procedures prescribed.
II. Recheck at 1 week to evaluate oral recovery and modify home care.
III. Taper frequency of rechecks to weekly, monthly, or longer intervals to assess oral health and determine appropriate periodontal management protocols.

Caries

Definition and Causes

I. Caries are areas of decay in the tooth structure.
II. They occur occasionally in dogs and rarely in cats.

III. Caries arise from the effects of oral bacteria on fermentable carbohydrates on the tooth surface.
IV. Rarely, they are associated with xerostomia (e.g., Sjögren's syndrome in dogs).

Pathophysiology

I. Fermentation of carbohydrates by oral bacteria produces acids that demineralize the enamel and dentin.
II. Factors that prolong retention of fermentable carbohydrates and bacterial plaque on the tooth surfaces predispose to the development of caries.
III. Caries may affect the tooth crown or root(s).

Clinical Signs

I. Signs of oral pain, such as changes in eating behavior and excessive salivation, may be noticed.
II. Tooth defects (dark spot on enamel, concavity, soft spot) may be noted on oral examination.

Diagnosis

I. Supra- and subgingival oral examination is done with a dental explorer.
   A. Defects and discoloration are carefully probed.
   B. Carious dentin is soft and the explorer sinks into the lesion and sticks slightly as the instrument is retracted.
II. Intraoral radiography is indicated to determine the extent of tooth destruction and define required treatments.
III. Radiolucent defects are seen radiographically, and involvement of the pulp tissue warrants endodontic therapy.

Differential Diagnosis

I. Attrition
II. Abrasion
III. Crown fracture
IV. Enamel hypocalcification
V. Resorptive lesions

Treatment

I. Restore mild to moderate defects with composite or glass ionomer.
II. Endodontic therapy and restoration are indicated if the defect extends into the pulp canal (Holmstrom et al., 2004b).
III. Tooth extraction is done for severe lesions.
IV. Application of a pit-and-fissure sealant on teeth with occlusal surfaces may be considered in high-risk cases (Hale, 1998).

Monitoring of Animal

I. Oral examination and intraoral radiography of treated teeth are performed 6 months postoperatively to evaluate stability of restoration and monitor for lesion progression.
II. Annual oral examination and intraoral radiography are used to detect new lesions.
III. Animals with enamel defects, poorly mineralized enamel, lower salivary pH, and diets high in fermentable carbohydrates are at greater risk for developing caries.

Resorptive Lesions

Definition and Causes

I. Noncarious tooth resorption is frequently diagnosed in cats.
II. The definitive etiology is unknown.
III. Proposed theories include chronic, excessive intake of vitamin D, occlusal stress, and cellular hyperactivity secondary to noxious stimuli that stimulate odontoclastic activity (DuPont, 2005).

Pathophysiology

I. Activated odontoclasts attach to and resorb dental tissues.
II. Lesions begin as a superficial resorption of tooth substance often at or close to the cemento-enamel junction.
III. A grading system for resorptive lesions is as follows:
   A. Stage 1: incipient lesion affecting only enamel
   B. Stage 2: lesion extending into dentin but not involving pulp
   C. Stage 3: lesion extending into the pulp
   D. Stage 4: significant destruction of tooth crown
   E. Stage 5: no remaining tooth crown, gingiva completely covers site
IV. Resorptive lesions may be type 1 or 2.
   A. Type 1 lesions have an identifiable root and periodontal ligament.
   B. Type 2 lesions have root resorption and loss of the periodontal ligament.

Clinical Signs

I. Many cats are asymptomatic.
II. Signs may include anorexia, ptyalism, lethargy, depression, dysphagia, halitosis, and discomfort during eating or an oral examination.

Diagnosis

I. General oral examination may demonstrate suspicious lesions.
   A. Hyperplastic gingival and/or granulomatous tissue may cover the defect.
   B. Surface lesions appear as a concavity in the enamel surface, often at the cemento-enamel junction.
   C. A pink spot may be noticed on the tooth crown.
   D. Advanced lesions located on the crown are readily evident.
II. Definitive oral examination is done under general anesthesia.
   A. Gross deposits of plaque or calculus may cover lesions.
   B. A dental explorer is used to detect resorptive lesions.
III. Intraoral radiography is indicated to determine extent of the lesions and assess the integrity of the periodontal ligament and periapical area.

Differential Diagnosis

I. Furcation (junction of roots) exposure from periodontal disease
II. Stomatitis
III. Caries

Treatment and Monitoring

I. Treatment is controversial because of the progressive nature of the lesions.
   A. Consider the stage and type of lesion.
   B. Discuss treatment options and prognosis with the client.
II. Current recommendations are as follows (DuPont, 2005):
   A. Stage 1 lesions
      1. Debride tissue from defects and etch with acid.
      2. Apply sealant and fluoride.
   B. Stage 2, 3, and 4 lesions
      1. Completely extract type 1 lesions.
      2. Amputate crowns of type 2 lesions when no other disease present
   C. Stage 2 or 3 lesions on canine teeth: restoration until lesion reaches stage 4
   D. Stage 5 lesions
      1. Extract root remnants of type 1 lesions.
      2. Type 2 lesions are monitored visually and radiographically (every 6 to 12 months) for continued resorption or changes requiring further treatment.
III. Perform follow-up oral examinations and intraoral radiography (every 6 to 12 months) to monitor for recurrence or progression.

Apical Abscess

Definition and Causes

I. It is localized infection at or around the tooth apex.
II. Typically it results from endodontic or periodontal disease.

Pathophysiology

I. Trauma or bacterial invasion of the pulp tissue causes pulpitis.
II. Pulpal swelling causes necrosis and extension of infection through the apical delta into surrounding alveolar bone.
III. Sequelae include osteomyelitis, cellulitis, sinusitis, and perforation to a fistulous tract.

Clinical Signs

I. In early stages, the animal may be asymptomatic.
II. Oral examination may reveal a fractured or discolored tooth, a loose tooth, a tooth that is painful on palpation, or purulent discharge in the oral mucosa or facial skin.
III. Advanced stages often demonstrate the following:
   A. Reluctance to chew on the affected side or to chew hard food
   B. Behavior changes associated with discomfort: inappetence, lethargy
   C. Oral malodor (halitosis)
   D. Facial lymphadenitis, localized cellulitis, or swelling
   E. Exophthalmos, pain upon retropulsion of globe or opening mouth with caudal tooth involvement
   F. Sinusitis, nasal discharge
   G. Cutaneous draining fistula over maxillary area or at site of prior enucleation
   H. Fever, occasional regional lymphadenopathy

Diagnosis

I. Tentative diagnosis is based on clinical signs and oral examination findings.
II. Definitive diagnosis is achieved with intraoral radiography.
   A. Thickening of the apical periodontal ligament
   B. Radiolucency surrounding the apical delta
   C. Bone loss and inflammatory changes as the lesion progresses

Differential Diagnosis

I. Resorptive lesions
II. Cysts
III. Neoplasia: squamous cell carcinoma, fibrosarcoma
IV. Other causes of cutaneous fistulas
V. Other causes of exophthalmos (see Chapter 103)

Treatment

I. Perform root canal of the affected tooth for early or mild infections of vital periodontal structures (Niemiec, 2005).
II. Tooth extraction and curettage of the affected area is necessary with large or chronic lesions.
III. Drain and explore any adjacent infection or fistulas (e.g., draining tract ventral to eye in dogs with carnassial tooth abscesses) (Niemiec, 2005).
IV. Systemic antibiotics are indicated in most cases.
V. Postoperative care includes appropriate pain medication and soft foods for several days.

Monitoring of Animal

I. Recheck 7 to 10 days postoperatively to monitor healing.
II. Intraoral radiography 6 to 12 months postoperatively if root canal was performed.
III. Avoid chewing on hard objects with potential to cause tooth fractures (e.g., bones, rocks, hooves).

Oronasal Fistula

Definition and Causes

I. It is a communication between the oral and nasal cavity.
II. Oronasal fistulae can be associated with any of the maxillary teeth.
III. The fistula may be congenital or result from trauma, severe periodontitis, or tooth extraction.
   A. Small-breed dogs are most often affected.
   B. Severe periodontitis of the maxillary canine tooth causes lysis of the bone separating the nasal and oral cavities.
   C. Base-narrow mandibular canine teeth may penetrate the hard palate.
   D. Severe endodontic disease may cause periapical lysis and abscessation.

Clinical Signs

I. Chronic rhinitis and/or sinusitis
II. Sneezing
III. Nasal discharge: possibly putrid or hemorrhagic

Diagnosis

I. Oral examination with a periodontal probe reveals a communication between the oral and nasal cavity.
II. Most fistulae occur in the area of the maxillary canine teeth.
III. Periodontal probing may cause hemorrhage from the ipsilateral nostril.

Differential Diagnosis

I. Periodontal disease
II. Neoplasia
III. Trauma or foreign body penetration

Treatment and Monitoring

I. If the tooth is still present, extracted it and repair the defect.
II. Use a single gingival flap technique when enough gingiva remains to provide a strong anchor for sutures.
III. Use a double gingival flap technique when the fistula is large or chronic in nature (with no remaining attached gingiva).
IV. Use guided tissue regeneration for repair of a deep palatal pocket without fistulation (Harvey and Emily, 1993; Holmstrom et al., 2004a).
V. Give a broad-spectrum antibiotic for 10 days.
VI. Feed a soft-food diet and restrict access to chew toys and hard treats for 2 weeks.

IMMUNE-MEDIATED DISORDERS

Stomatitis

See Chapter 27.

Lymphocytic Plasmacytic Gingivostomatitis

See Chapter 27.

NEOPLASIA

Epulis

See Chapter 27.

TRAUMATIC DISORDERS

Tooth Luxation or Avulsion

Definition and Causes

I. Partial or complete dislocation of a tooth from its alveolus
   A. Vertical luxation (intrusion) occurs when the tooth is pushed apically.
   B. Lateral luxation (extrusion) occurs when the tooth is displaced vertically.
   C. Complete displacement is termed *avulsion.*
II. Potential causes
   A. Trauma
   B. Severe periodontitis: luxation before complete exfoliation

Pathophysiology

I. Trauma causes injury to the periodontium, which results in tooth mobility and movement.
II. Periodontitis causes destruction of the supporting periodontium.

Clinical Signs

I. The animal may be asymptomatic, depending on the degree of luxation.
II. Excessive licking, ptyalism, head shaking, changes in eating behavior, and other signs of discomfort (inappetence, lethargy) may be present.

Diagnosis

I. Oral examination reveals tooth malposition or absence.
II. With intrusion, the tooth appears shorter and is immobile.
III. With extrusion, the tooth appears longer and is mobile.
IV. With avulsion, the owner may find an intact tooth, or a missing tooth may be noted.

Differential Diagnosis

I. Tooth fracture
II. Tooth exfoliation from PD

Treatment

I. Treatment varies depending on the severity of dislocation, health of associated periodontal tissues, time between occurrence and diagnosis, and any handling of an exfoliated tooth.
   A. Optimal results are obtained if the tooth is reimplanted within 30 minutes.
   B. Do not let an avulsed tooth dry out. Placement in saline is the best medium; milk may also be used.
   C. Handle tooth gently by its crown and do not remove periodontal ligament.
   D. Rinse carefully with sterile saline solution, and if severely contaminated, cleanse the tooth gently with sterile gauze moistened with saline.
II. Replacement and splinting in the normal position can be effective with proper cleansing and tooth handling.
   A. Fixation appliances are left in place for 4 to 6 weeks.
   B. Effective oral hygiene through flushing with water or 0.12% chlorhexidine solution is important to remove debris between the teeth and the appliance, and to control plaque accumulation and gingival inflammation.
   C. A broad-spectrum antibiotic is recommended to control infection.

Monitoring of Animal

I. Luxated and avulsed teeth often develop pulpal necrosis, so oral examination and intraoral radiography are performed at the time of appliance removal, and again at 6 and 12 months.
II. Endodontic therapy (root canal) is performed if signs of pulp pathology (tooth discoloration or periapical pathology) are present (Gorrel and Robinson, 1995).

Tooth Fracture

Definition and Causes

I. A break involving part or all of a tooth
II. May involve the enamel, dentin, crown, or root
III. Generally secondary to trauma

Clinical Signs

I. Some animals may be asymptomatic.
II. Increased tongue movement, ptyalism (possibly bloody), head shaking, changes in eating behavior (e.g., reluctance to eat hard foods, frequent trips to food bowl without eating), inability to close mouth, and other signs of discomfort (lethargy, anxiety) may be present.

Diagnosis

I. Oral examination and intraoral radiography
   A. Fractures involving part of the tooth crown (slab fractures) may not be detected until plaque and calculus are removed.
   B. Intraoral radiography is essential to determine extent of the fracture.
II. Crown fractures may affect enamel and/or dentin.
   A. Uncomplicated fractures have not entered the dentin, but pale pink pulp may be visible if the fracture is close to the pulp chamber.
   B. Complicated fractures expose the pulp chamber.
      1. Pulp hemorrhage occurs with a fresh fracture.
      2. An old fracture may have necrotic pulp and the tooth may be discolored.
III. Root fractures may occur at any point along the root surface and may be associated with a crown fracture.

Differential Diagnosis

I. Luxation
II. Caries
III. Enamel defects
IV. Resorptive lesions

Treatment

I. Treatment depends on the tooth and fracture type, age of fracture, and endodontic involvement.
II. Treat uncomplicated crown fractures by smoothing sharp edges and sealing the exposed dentin tubules.
III. Complicated crown fractures require endodontic therapy or tooth extraction.
   A. Treat fresh fractures (pulp still vital) with partial pulpectomy or vital pulpotomy with restoration (Niemiec, 2005).
   B. Old fractures in teeth with necrotic or inflamed pulp require standard root canal therapy and restoration.
IV. Treat root fractures without pulp involvement and extending <5 mm below the gingival margin with restorative dentistry.
V. Treat root fractures with pulp involvement and extending >5 mm below the gingival margin with tooth extraction.
VI. A horizontal root fracture in the coronal part of the root typically requires extraction.
VII. To maintain jaw stability, treat a horizontal root fracture in the coronal part of the mandibular canine tooth by removal of the coronal portion and endodontic therapy.
VIII. A horizontal root fracture located midroot or apically usually heals if the tooth is immobilized.
   A. In a midroot fracture, if the pulp becomes necrotic or the fracture does not heal, endodontic treatment is indicated.
   B. Remove the apical segment if there is radiographic evidence of periapical pathology.

Monitoring of Animal

I. Perform oral examination and intraoral radiography at frequent intervals to monitor healing and pulp health.
II. Perform oral examination and intraoral radiography 6 to 12 months postoperatively for partial pulpectomy and vital pulpotomy procedures; evidence of necrotic pulp with periapical changes requires root canal therapy.
III. Perform oral examination and intraoral radiography 6 to 12 months after standard root canal therapy; any evidence of periapical pathology requires further endodontic therapy (repeating the root canal or surgical endodontics) or tooth extraction.
IV. Oral examination and intraoral radiography are indicated 6 to 12 months postoperatively for root fractures to evaluate healing.

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CHAPTER 29

Diseases of Salivary Glands

Jill Lurye

INFLAMMATORY DISORDERS

Ptyalism

Definition

I. Excessive salivary secretion
   A. Typically occurs secondary to an underlying condition
   B. Also referred to as *sialorrhea, hypersialism,* and *hypersialosis*
II. Differentiated from pseudoptyalism in which there is excessive release of saliva that has accumulated within the oral cavity

Causes

I. Conformational disorder of the lips
   A. Most common in giant-breed dogs
   B. May be considered normal in some breeds: bloodhound, Great Dane
II. Salivary gland disorders: see later sections
III. Oral or pharyngeal abnormalities
   A. Neoplasia
   B. Foreign body
   C. Stomatitis, gingivitis: may be viral induced in cats
   D. Functional or neurological disorder of the pharynx
IV. Esophageal or gastrointestinal (GI) abnormalities
   A. Neoplasia
   B. Foreign body
   C. Esophagitis
   D. Esophageal stricture
   E. Megaesophagus
   F. Hiatal hernial
   G. Gastroesophageal reflux
   H. Gastric ulceration
   I. Gastric distension, dilatation, volvulus
V. Metabolic disorders
   A. Hepatic encephalopathy: especially common in cats with portosystemic shunts
   B. Uremia
VI. Drugs and toxins
   A. Caustic plants or chemicals
   B. Organophosphates, cholinergic drugs, pyrethrin, pyrethroids
   C. Oral, otic, or ophthalmic medications with disagreeable taste: especially cats
VII. Neurological and behavioral disorders
   A. Anxiety
   B. Vestibular disease and associated nausea
   C. Disorders of swallowing or decreased jaw tone
   D. Seizures resulting in reduced swallowing or autonomic discharge that stimulates salivation
   E. Clostridial toxins: botulism, tetanus
   F. Certain infections: rabies, pseudorabies

Pathophysiology

I. Anatomical, mechanical, inflammatory, or functional abnormalities can result in dribbling of saliva or prevent normal swallowing, which makes normal saliva production appear excessive.
II. Excess production may occur as a result of primary salivary gland disease or stimulation from other causes.
   A. Excitation of the salivary nuclei in the brainstem or higher centers may lead to increased salivation.
   B. Diseases affecting the oropharyngy, esophagus, or stomach may also stimulate excessive salivation.

Clinical Signs

I. Excessive salivation is the primary sign.
II. Alterations in salivary gland size, shape, or presence of pain may be noted with primary salivary gland diseases.
III. Pawing at the face or facial pain may occur with oral or pharyngeal diseases.
IV. Blood in the saliva is suggestive of oral, pharyngeal, or esophageal abnormalities.
V. Halitosis may occur with oral cavity disease, or less commonly with esophageal and gastric abnormalities.
VI. Anorexia may indicate oral, GI, or systemic causes of the ptyalism.
VII. Dysphagia or changes in eating behavior may occur with oral or neurological diseases.
VIII. Regurgitation may occur with underlying esophageal diseases.
IX. Vomiting is suggestive of GI or systemic illness.
X. Neurological signs can be focal or diffuse.
   A. Signs consistent with vestibular disease or cranial nerve abnormalities may indicate a primary neurologic cause for the ptyalism.
   B. More generalized neurological signs may occur from drug or toxin exposure, or with hepatic encephalopathy.

Diagnosis

I. Physical examination may reveal the following:
   A. Palpation of salivary glands: unilateral or bilateral enlargement, irregular borders, pain, heat
   B. Oral examination: masses, periodontal abnormalities, stomatitis, foreign bodies, pharyngeal abnormalities
   C. Cranial nerve and neurological examination: abnormal jaw tone, abnormal tongue movement, muscle atrophy, abnormal swallowing reflex
   D. Changes consistent with systemic disease: cachexia, abdominal pain, abdominal masses, abnormal behavior

II. Laboratory findings are usually nonspecific.
   A. Complete blood count (CBC) is often normal.
      1. Infections or immune-mediated disease may cause leukocytosis.
      2. Microcytosis may be present with portosystemic shunts.
      3. Cats infected with feline leukemia virus (FeLV) or feline immunodeficiency virus (FIV) may have leukopenia or anemia.
   B. Biochemistry profile is often normal.
      1. Renal disease may be evident with azotemia and hyperphosphatemia if uremia is causing the ptyalism.
      2. Hepatic disease may be evident (e.g., elevated hepatic enzymes; low blood urea nitrogen, albumin and glucose levels; alterations in cholesterol and bilirubin levels).
      3. Severe ptyalism may result in acidosis and hypokalemia from excessive loss of bicarbonate and potassium in saliva.

III. Additional diagnostic tests include the following:
   A. Perform fasting and postprandial bile acids when hepatic encephalopathy is suspected.
   B. Radiographic imaging of dentition, oral cavity, neck, and thorax may be indicated if dental disease, neoplasia, or a foreign body is suspected.
   C. Abdominal ultrasonography is useful if GI, hepatic, or renal diseases are suspected.
   D. Endoscopic evaluation and biopsies may be done if esophageal, gastric, or intestinal diseases are likely.
   E. Fine-needle aspirate and cytology, or biopsy and histopathology of salivary glands, oral lesions, or masses may be helpful.

Differential Diagnosis

I. Determining the cause of ptyalism requires a thorough history and physical examination, including complete oral and neurological evaluations, and certain laboratory tests.

II. History, clinical signs, physical and laboratory findings may differentiate oropharyngeal, GI, neurologic, metabolic, or toxic disorders from primary salivary disease.

Treatment

I. Definitive treatment of the underlying disorder is often required for resolution of ptyalism (see Causes).

II. Symptomatic treatment may help reduce salivation.
   A. Anticholinergic therapy with glycopyrrolate 0.01 mg/kg SC PRN or atropine 0.02 to 0.04 mg/kg SC PRN or 0.04 mg/kg PO TID to QID
   B. Ligation of parotid salivary duct

Monitoring of Animal

I. Monitoring requirements depend on the underlying abnormality (see Causes) and treatment needed.

II. Excessive salivation may result in dehydration, acidosis, or hypokalemia, so monitor hydration status, electrolytes, and acid-base balance.

Sialadenitis

Definition

I. Inflammation of the salivary gland
   A. May be a primary or secondary (extension from surrounding tissues) process
   B. May be infectious or noninfectious in origin

II. Sometimes referred to as, or grouped with, *necrotizing sialometaplasia, salivary gland necrosis*, and *salivary gland infarction*, because of similarities in clinical signs and histopathologic findings

Causes

I. Primary inflammation
   A. Inflammation associated with salivary mucocele
   B. Salivary gland trauma or foreign body penetration
   C. Idiopathic forms

II. Secondary inflammation from surrounding tissues
   A. If no salivary mucocele is present, inflammation is most likely associated with generalized inflammation of the surrounding connective tissues (Spangler and Culbertson, 1991).
   B. Examples include the following:
      1. Abscesses of the head and neck
      2. Viral diseases: canine distemper, rabies, paramyxovirus (Brown, 1989)
      3. Trauma: bite wounds, foreign body penetration
      4. Carnassial tooth root infection
      5. Infarction of local tissue structures

Pathophysiology

I. Typically, lymphoplasmacytic inflammation is present; however, with infectious causes, suppurative or pyogranulomatous inflammation is possible.

II. Inflammation often results in pain and swelling of the involved salivary gland.

Clinical Signs

I. Painful, swollen, warm salivary glands
   A. Mandibular salivary glands are most commonly affected (Spangler and Culbertson, 1991).
   B. Parotid, sublingual or zygomatic glands are affected less often (Spangler and Culbertson, 1991).

C. Early reports suggest the zygomatic rather than mandibular salivary gland is most commonly involved when inflammation is unilateral (Brown, 1989).

II. Mandibular, parotid, or sublingual involvement
  A. Possible dysphagia, anorexia
  B. Ptyalism
  C. Possible fever
  D. Vomiting, nausea, gagging, or retching
  E. Possible fistula formation

III. Zygomatic involvement
  A. Unilateral exophthalmos (see Chapter 103)
  B. Pain upon opening the mouth

Diagnosis

I. Definitive diagnosis often requires histopathologic examination of affected salivary gland or surrounding secondary structures.
II. Clinical signs, history, and cytology of fine-needle aspirates may be suggestive of inflammation.
III. Ultrasonography may identify salivary gland involvement, abnormalities in surrounding tissues, or the presence of foreign material.

Differential Diagnosis

I. Salivary mucocele or fistula
II. Neoplasia
III. Necrotizing sialometaplasia, salivary gland necrosis, sialadenosis

Treatment

I. Surgically remove the affected salivary gland if a mucocele or fistula is present.
II. Start appropriate antibiotic therapy for bacterial infections.
  A. Ideally, choose antibiotics based on culture and sensitivity results.
  B. Choose a broad-spectrum antibiotic if sensitivity results are not available.
    1. Amoxicillin/clavulanate 13.75 mg/kg PO BID
    2. Cephalexin 30 mg/kg PO BID
    3. Clindamycin 5 to 11 mg/kg PO BID
  C. Continue for 1 week past clinical resolution.
III. Treat any primary problem in the surrounding tissues.
  A. Removal of foreign body
  B. Carnassial tooth extraction
IV. Some viral diseases may be self limiting.
V. Prednisone may be helpful.
  A. To reduce inflammation from noninfectious processes (0.5 to 1 mg/kg PO SID to BID)
  B. To treat suspected immune-mediated disease based on histopathology (1.1 to 2.2 mg/kg PO SID to BID)

Monitoring of Animal

I. Monitor until clinical signs resolve and to ensure complications do not develop (e.g., fistula formation).
II. If clinical resolution is not observed, further diagnostic tests, such as histopathologic evaluation and/or surgical removal of the salivary gland, may be required.

Necrotizing Sialometaplasia

Definition

I. Ischemic necrosis of salivary lobules, with metaplastic proliferation of salivary ducts
II. Sometimes referred to as *salivary necrosis*
III. May be an extension or a stage of sialoadenitis

Causes

I. Unknown
II. Numerous theories suggested
  A. Vascular injury, trauma, or infection (dogs) (Schroeder and Berry, 1998)
  B. Immune-mediated (two dogs) (Schroeder and Berry, 1998; Mawby et al., 1991)
  C. Secondary to esophageal or gastric disease (Schroeder and Berry, 1998)
  D. Possible association with limbic seizures (Breitshwerdt et al., 1979; Brooks et al., 1995)
  E. Idiopathic

Pathophysiology

I. Mandibular salivary glands are involved in most cases.
II. Infarction of salivary lobules occurs with subsequent inflammation and metaplasia of salivary ducts.
III. Small terrier breeds may be predisposed.

Clinical Signs

I. Enlarged, painful salivary glands
II. Usually bilateral mandibular salivary gland involvement
III. Nausea, vomiting, inappetence
IV. Dysphagia, retching, gagging, lip smacking
V. Ptyalism

Diagnosis

I. Physical examination: bilateral salivary swelling, pain
II. Laboratory data
  A. CBC is often normal, but, rarely, leukocytosis is seen (Schroeder and Berry, 1998).
  B. Biochemistry profile is typically normal.
III. Additional diagnostic tests
  A. Thoracic radiography to identify underlying diseases
    1. Megaesophagus
    2. Esophageal diverticulum
    3. Mediastinal mass
  B. Endoscopy of esophagus and stomach
    1. Esophageal diverticulum
    2. Gastric infections: *Helicobacter* spp., *Giardia* spp.
    3. *Spirocerca lupi* granuloma and associated neoplasms
    4. Esophagitis or gastritis
  C. Antinuclear antibody assay: positive in some cases
  D. Fine-needle aspirate and cytology: evidence of inflammation
  E. Biopsy of salivary gland
    1. Required for definitive histopathologic diagnosis
    2. Infarction of salivary lobules, with inflammation and metaplasia of salivary ducts

F. Electroencephalography (EEG): abnormal in some dogs and supports a neurological cause

Differential Diagnosis

I. Sialoadenitis
II. Salivary gland infarction
III. Sialadenosis
IV. Neoplasia: usually unilateral
V. Mucocele: usually unilateral

Treatment

I. Institute treatment of any underlying diseases.
   A. Antimicrobials or antiparasiticals as appropriate for *Helicobacter* spp., *Giardia* spp., or *Spirocerca lupi*
   B. Prednisone (1.1 to 2.2 mg/kg PO SID to BID) when immune-mediated disease is suspected
   C. Antiemetics for nausea
II. Surgical removal of the affected salivary gland has not resulted in resolution of dysphagia, retching, and gagging, which suggests that the disease results from neurological or other systemic influences rather than a primary salivary gland abnormality (see Sialadenosis).
III. Phenobarbital (2 mg/kg PO BID) has resulted in improvement in a number of cases, even when a possible underlying etiology was identified (Schroeder and Berry, 1998).

Monitoring of Animal

I. Animals are monitored weekly for resolution of ptyalism, gagging, reduction of salivary gland size, or changes in other clinical signs.
II. In phenobarbital-responsive cases, affected salivary glands may return to their normal size.
   A. Some animals may be weaned off anticonvulsant therapy, whereas others need continuous therapy to prevent recurrences.
   B. Periodically measure liver enzymes, phenobarbital serum levels, and CBCs when using phenobarbital (see Chapter 22).

Sialolithiasis

Definition and Causes

I. Calculus formation within the salivary gland, duct, or mucocele
II. Underlying etiology unknown, but may occur secondary to inflammation
III. Extremely rare

Pathophysiology

I. Precipitation of fibrin and mucin may form soft stones that become mineralized within mucoceles.
II. Sialoliths in the ducts obstruct salivary flow and cause ductal dilation and possible rupture.
III. Salivary gland inflammation may be detected.
IV. Most are composed of calcium carbonate, calcium phosphate, or magnesium carbonate.
V. Over time, glandular atrophy may occur secondary to ductal obstruction.

Clinical Signs

I. Salivary gland swelling and pain are the most common signs initially.
II. Dysphagia and ptyalism may also be observed.
III. The duct may rupture and form a fistula.

Diagnosis

I. Palpation of firm mass in the area of a salivary gland warrants further investigation.
II. Radiography or ultrasonography may identify mineralization.
III. Computed tomography or sialography may be used to locate site of obstruction and identify the sialolith (Trumpatori et al., 2007).
IV. Surgical removal and stone analysis may be needed for definitive diagnosis.

Differential Diagnosis

I. Mucocele with fibrin and mucin precipitates
II. Foreign body
III. Neoplasia
IV. Sialoadenitis
V. Calcinosis circumscripta of the salivary gland (Movassaghi, 1999)

Treatment and Monitoring

I. Surgical removal of sialolith may be attempted if the duct is intact.
   A. Anastomosis of the duct can be difficult.
   B. It is most worthwhile early in the course, before glandular fibrosis and atrophy develop.
II. Presence of a fistula often requires surgical resection of the duct and salivary gland.
III. During the weeks following surgery, monitor for appropriate healing and complications, such as infection or fistula formation.

IDIOPATHIC DISORDERS

Sialadenosis

Definition and Causes

I. Sialadenosis is noninflammatory enlargement of one or more salivary glands.
II. Cause is unknown.
III. Nervous system disorders may play a role.
   A. Limbic epilepsy
   B. Increased parasympathetic tone
   C. Changes in sympathetic innervation to salivary glands

Pathophysiology

I. Mandibular salivary glands are involved in most cases, and the disease is usually bilateral.
II. Alterations in neurological input may result in salivary gland stimulation, with increased salivary size, ptyalism, and clinical signs of retching and vomiting.

Clinical Signs

I. Enlarged salivary glands
   A. Typically, both mandibular salivary glands are involved.

B. Glands are often nonpainful, but possible gulping or retching may occur with palpation.
II. Nausea, vomiting, inappetence
III. Dysphagia, retching, gagging, lip smacking
IV. Ptyalism
V. Exophthalmus with zygomatic gland involvement

Diagnosis

I. Laboratory tests, cytology, and histopathology of salivary glands are usually normal.
II. Abnormal EEG may be detected in some cases and supports a neurological cause.
III. Positive response to anticonvulsant therapy with phenobarbital is suggestive of the diagnosis.

Differential Diagnosis

I. Sialoadenitis
II. Necrotizing sialometaplasia
III. Salivary gland infarction
IV. Neoplasia: usually unilateral
V. Mucocele: usually unilateral

Treatment and Monitoring

I. Phenobarbital (2 mg/kg PO BID) is the primary treatment and is successful in many dogs.
II. Monitor the animal weekly for resolution of ptyalism, gagging, reduction of salivary gland size, or changes in other clinical signs.
III. In phenobarbital-responsive cases, salivary gland size may return to normal.
IV. Some animals may be successfully weaned off phenobarbital once all clinical signs of disease have resolved, whereas others require continuous therapy to prevent recurrences.
V. Monitor phenobarbital serum levels, liver enzymes, and CBC periodically while the animal is on phenobarbital (see Chapter 22).

IMMUNE-MEDIATED DISORDERS

Sjögren Syndrome

Definition and Cause

I. Sjögren syndrome, or Sjögren-like syndrome, is a rare autoimmune disease characterized by keratoconjunctivitis sicca (KCS), xerostomia, and lymphoplasmacytic lacrimal and salivary adenitis.
II. It may be more common in the English bulldog, West Highland white terrier, miniature schnauzer, and Maltese terrier.
III. The exact etiology is unknown.

Pathophysiology

I. Autoantibodies against glandular tissues result in inflammation and destruction of secretory components.
II. It is often associated with other immune-mediated or autoimmune diseases (e.g., thrombocytopenia, glomerulonephritis).
III. A genetic predisposition may be present in certain breeds.
IV. Females are overrepresented.

Clinical Signs

I. Signs related to KCS are commonly reported (see Chapter 97).
II. Gingivitis, stomatitis, dental caries, lack of salivary secretions, anorexia, and dysphagia may be seen.
III. Other signs reflect other immune diseases present (see Chapters 48 and 67).

Diagnosis

I. Physical examination shows evidence of KCS, xerostomia, and additional supporting signs.
A. Schirmer tear <5 mm/min
B. Confirmation of reduced salivary flow following application of topical atropine to the mouth
C. Petechia, ecchymoses, lethargy
II. Laboratory tests
A. CBC, biochemistry profile, and urinalysis are typically normal, unless other body systems are involved.
B. Antinuclear antibody and rheumatoid factor assays, as well as lupus erythematosus cell tests may be positive.
III. Additional diagnostic tests
A. Histopathologic evidence of lymphoplasmacytic salivary gland inflammation is supportive.
B. Indirect fluorescent antibody test for autoantibodies may be positive in glandular tissues.

Differential Diagnosis

I. Other causes of KCS: drug toxicities, trauma, canine distemper, other immune-mediated diseases, dysautonomia
II. Other causes of dental caries, stomatitis
III. Other causes of thrombocytopenia and glomerulonephritis

Treatment

I. Direct treatment at alleviating clinical signs and complications of KCS (see Chapter 97) and xerostomia.
A. Flushing of the mouth with water may be helpful.
B. Provide readily available water source and feed moist diets or diets with water added.
II. Immunosuppressive therapy may be necessary to treat other systemic immune-mediated processes (see Chapters 48 and 67).

Monitoring of Animal

I. Prognosis may be guarded, particularly when other immune-mediated processes are present.
II. Failure to adequately treat KSC may result in severe corneal ulcers that may require enucleation.
III. Clinical signs are difficult to treat and require lifelong therapy.

VASCULAR DISORDERS

Salivary Gland Infarction

Definition and Causes

I. Infarction of the blood supply to the salivary gland leads to tissue necrosis.

II. The cause of primary salivary gland infarction is often idiopathic.
III. In addition to primary infarction, infarction may occur secondary to salivary neoplasia, inflammation, as a component of necrotizing sialometaplasia, or as a result of an underlying systemic disease (e.g., hyperadrenocorticism, disseminated intravascular coagulopathy, sepsis).
IV. It may be confused with necrotizing sialometaplasia.

Pathophysiology

I. Following an ischemic event of unknown etiology, necrosis, regenerative hyperplasia of ductal epithelium, and capsular fibrosis of one or more salivary glands may be observed.
II. Few cases have been reported in dogs and cats, but most have involved the mandibular or sublingual salivary gland (Spangler and Culberston, 1991; Kelly et al., 1979).

Clinical Signs

I. An acute, painful, firm swelling of the salivary gland is the most common clinical sign.
II. Fever, leukocytosis, and anorexia have also been reported.

Diagnosis

I. Clinical signs are often similar to sialadenitis.
II. Histopathologic confirmation of infarction is necessary for a definitive diagnosis.

Differential Diagnosis

I. Sialadenitis
II. Necrotizing sialometaplasia
III. Salivary gland neoplasia
IV. Sialolithiasis with ductal obstruction

Treatment and Monitoring

I. Most signs resolve in 7 to 10 days regardless of treatment (Spangler and Culbertson, 1991).
II. If improvement is not observed, reevaluate the animal for an underlying disease or another etiology.

NEOPLASIA

Definition and Causes

I. Salivary gland tumors are rare in dogs and cats.
II. Overall incidence of salivary neoplasia in dogs and cats is 0.17% (Carberry et al., 1987).
III. Most tumors are malignant, with adenocarcinomas being the most common type.
IV. Other tumor types include squamous cell carcinoma, acinic cell tumor, mixed carcinomas, and other carcinomas.
V. Nonepithelial tumors include the mast cell tumor, melanoma, fibrosarcoma, osteosarcoma, and lymphoma.
VI. Parotid or mandibular glands are most frequently affected.

Pathophysiology

I. Metastasis to regional lymph nodes is common.
II. Distant metastasis may occur, but is slow to develop.

Clinical Signs

I. Spaniel dogs may be at higher risk.
II. Typically a unilateral, firm, painless swelling is detected in the area of the salivary gland.
III. Mass may be in the upper neck (mandibular and sublingual glands), at the base of the ear (parotid gland), in the retrobulbar space or masseter area (zygomatic gland), or within the mucous membranes of the lips (accessory or minor salivary gland tissue).
IV. Signs of exophthalmos, swelling, or pain may occur.
V. A mucocele may also develop.

Diagnosis

I. Cytological examination of a fine-needle aspirate is often diagnostic for neoplasia.
II. Incisional or excisional biopsy provides a definitive diagnosis and tissue of origin.
III. Lymph node aspirate of regional nodes and thoracic radiography are recommended for tumor staging.

Differential Diagnosis

I. Mandibular lymph node neoplasia: lymphoma, metastasis of a nonsalivary tumor
II. Other unilateral salivary diseases: mucocele, abscess
III. Sialoadenitis: often bilateral
IV. Myxoma or myxosarcoma of the head and neck

Treatment

I. Aggressive resection with the associated lymph nodes is recommended.
   A. Because these tumors are typically invasive and are in close proximity to surrounding structures, wide surgical margins are often unobtainable and complete excision is uncommon.
   B. Recurrence is common owing to incomplete resection.
II. Adjunctive radiation therapy may be effective for local control in dogs (Hammer et al., 2001).
III. The use of adjunctive chemotherapy is largely unstudied and is an unproven modality.

Monitoring of Animal

I. Local recurrence is monitored with repeated examinations.
II. Regular evaluation of local lymph nodes via palpation and possibly fine-needle aspiration is done to detect local metastasis.
III. Thoracic radiographs are repeated every few months to monitor for distant metastasis.
IV. Long-term prognosis is typically poor.
V. Reported median survival time of dogs with salivary gland tumors is 550 days and is 516 days in cats (Hammer et al., 2001).

TRAUMA

Salivary Mucocele

Definition

I. It is a swelling in the cervical, oral, sublingual, or pharyngeal region characterized by an accumulation of saliva.

II. It arises as a single or multiloculated cavity that lacks an epithelial lining and is adjacent to a salivary duct or gland.
III. An inflammatory response may occur in surrounding tissues.
IV. It is also referred to as *sialocele*.
V. If the mucocele is sublingual, it is referred to as a *ranula*.

Causes

I. Mucoceles usually result from rupture of a salivary duct.
II. Trauma or foreign body penetration is considered the most likely cause.
III. It may develop secondary to duct occlusion from a sialolith or tumor.
IV. It is rarely a developmental abnormality.
V. Idiopathic forms may also occur.

Pathophysiology

I. A collection of saliva occurs in the subcutaneous tissues of the cervical or intermandibular areas (cervical mucocele), sublingual tissues (ranula), pharyngeal wall (pharyngeal mucocele), or retrobulbar region following damage to the salivary gland or duct.
II. After salivary gland or duct damage, saliva gravitates ventrally and collects in a pocket that is lined by vascularized connective tissue.
III. The sublingual gland is most often involved (especially in cats), followed by the mandibular and zygomatic glands.
IV. Poodles and German shepherd dogs may be predisposed.
V. It is more commonly seen in dogs <3 years of age.

Clinical Signs

I. A nonpainful swelling slowly develops in the ventral or ventrolateral neck region with mandibular gland mucoceles.
II. With ranulas, a sublingual swelling occurs and may result in lingual elevation and dysphagia.
III. Pharyngeal swelling may occur and result in dysphagia, ptyalism, and dyspnea.
IV. Nonpainful, unilateral exophthalmus or cystic periocular swellings may be observed with zygomatic gland involvement.

Diagnosis

I. History, signalment, and physical findings may be suggestive.
II. Fine-needle aspiration of the swelling yields fluid.
   A. A thick, honey-colored fluid may contain small, white, calcified deposits or may be blood tinged.
   B. Cytological examination reveals mucus and red blood cells.
III. Radiography, ultrasonography, and advanced imaging techniques often are not needed for a diagnosis, except for zygomatic gland mucoceles.
   A. May identify presence of salivary calculus (sialolith)
   B. Sialography difficult to perform
   C. Ultrasonography to differentiate fluid-filled structure from solid mass
IV. Histopathologic examination demonstrates a vascularized connective tissue lining.

Differential Diagnosis

I. Cervical abscesses
   A. Usually painful and warm to the touch
   B. Often develop more quickly
II. Other tumors or cysts of the head and neck
   A. Salivary neoplasia, lymphoma, cystadenoma
   B. Branchial cyst (rare)
   C. Thyroglossal duct cysts (rare)
III. Traumatic hematoma or seroma

Treatment

I. Definitive treatment is sialoadenectomy of the involved salivary glands and duct.
   A. Sialoceles are usually unilateral.
   B. For cervical mucoceles when the involved side is not obvious, place the animal in dorsal recumbency and push on the fluid-filled mass; a protrusion near the mandible usually occurs on the affected side.
II. If the sublingual salivary gland is involved, the mandibular salivary gland is also removed because of the intimate relationship of these glands.
III. Drainage of the mucocele is performed in conjunction with sialoadenectomy.
IV. Temporary drainage may occasionally be performed via aspiration to resolve dyspnea associated with pharyngeal swellings or in cases where general anesthesia is considered high risk.

Monitoring of Animal

I. Postoperative monitoring involves the following:
   A. If drains are placed, monitor discharge and remove the drain when discharge subsides.
   B. Monitor the surgical site for infection and seroma formation.
II. Recurrence is rare with complete excision of the correct salivary gland.

Salivary Gland Fistula

Definition and Causes

I. It is a nonhealing wound or tract that continuously drains saliva.
II. It is most commonly associated with penetrating trauma to salivary tissue or ducts.
III. It occasionally results from tissue trauma during ear resection surgery or lancing of a mandibular swelling.
IV. A fistula also may result from infection or necrosis associated with salivary neoplasia, or from extension of disease in surrounding tissues.

Pathophysiology

I. After trauma, saliva leaks through the skin and continuous saliva flow prevents healing of the wound.
II. Necrosis of involved tissues also predisposes to secondary bacterial infections.

Clinical Signs

I. Swelling is observed most commonly in the neck region, or, rarely, on the lateral aspect of the face below the eye.

II. An open, draining lesion is present.
   A. Drainage may increase during eating.
   B. The discharge may be malodorous when secondary infection is present.

Diagnosis

I. History of trauma is supportive.
II. Cytology of fluid may show red blood cells, white blood cells, and mucin consistent with saliva.
III. Oral pilocarpine administration may increase secretions from the fistula.
IV. Sialography, fistulography, or surgical exploration of the tract helps confirm the salivary gland origin.
V. Culture and sensitivity confirms secondary bacterial infection and guides appropriate antibiotic therapy.

Differential Diagnosis

I. Neoplasia with necrosis
II. Soft-tissue foreign bodies
III. Chronic fistulating infection at previous site of ear surgery

Treatment

I. Definitive treatment involves surgical removal of the salivary gland, with wide surgical margins that include the entire fistulous tract.
II. A less desirable option is salivary duct ligation proximal to the fistula, which ceases the flow of saliva through the opening.
III. When secondary infection is present, antibiotic therapy is also indicated.
   A. Broad-spectrum antibiotics may be chosen empirically.
      1. Amoxicillin/clavulanate 13.75 mg/kg PO BID
      2. Cephalexin 30 mg/kg PO BID
      3. Clindamycin 5 to 11 mg/kg PO BID
   B. Therapy based on culture and sensitivity testing is preferred.

Monitoring of Animal

I. Recurrence is possible if the salivary gland, duct, and fistula are not removed in their entirety.
II. If salivary duct ligation is performed, transient salivary gland swelling may occur until secondary atrophy ensues.

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CHAPTER 30

Esophageal Diseases

Nolie K. Parnell

MOTILITY DISORDERS

Megaesophagus

Definition

I. Megaesophagus is a diffusely dilated esophagus from decreased or absent motility.
II. It can be either congenital or acquired (adult onset).
III. Adult-onset forms can arise from an underlying primary condition or be idiopathic, with most acquired cases being idiopathic.

Causes

I. Congenital megaesophagus is inherited in the wirehaired fox terrier and miniature schnauzer (Cox et al., 1980; Osborne et al., 1967).
   A. Simple, autosomal recessive trait in wirehaired fox terriers
   B. Simple, autosomal dominant (60% penetrance) or autosomal-recessive trait in miniature schnauzers
II. Congenital megaesophagus has been diagnosed in a litter of Chinese shar-peis (Knowles et al., 1990).
III. Other breeds, such as the German shepherd dog, golden retriever, Irish setter, and possibly the Labrador retriever and Newfoundland are predisposed (Gaynor et al., 1997).
IV. Cats can develop megaesophagus, but it is not as common as in dogs.
V. Siamese cats and Siamese-related breeds are predisposed (Mears and Jenkins, 1997).
VI. Etiopathogenesis of idiopathic, adult-onset megaesophagus is unknown.
VII. Secondary acquired megaesophagus is associated with numerous disorders (Box 30-1).
VIII. Myasthenia gravis (MG) is the most common cause of secondary acquired megaesophagus (Gaynor et al., 1997).

Pathophysiology

I. Congenital megaesophagus probably involves abnormal vagal afferent innervation of the esophagus (Holland et al., 2002).
   A. Vagal efferent innervation is normal, and a primary myopathy is unlikely (Holland et al., 1996).
   B. The exact cause of the abnormal vagal afferent innervation is unknown, but it may be a delay in maturation because some dogs may have improved function with age.
II. Adult-onset, secondary megaesophagus can be caused by any disease that disrupts the central, afferent, or efferent neural pathways.
III. Adult-onset secondary megaesophagus can also be caused by diseases that disrupt esophageal musculature.
IV. Idiopathic adult-onset megaesophagus probably involves an abnormal vagal afferent innervation similar to congenital megaesophagus (Mears and Jenkins, 1997).
V. Absent or severely compromised esophageal motility creates esophageal dysfunction, dilatation, and accumulation of ingesta in the esophagus.

Clinical Signs

I. Regurgitation of food and water is the most common clinical sign.

Box 30-1

Diseases Associated with Megaesophagus

Neuromuscular disorders

- Congenital megaesophagus
- Idiopathic megaesophagus (hereditary?)
- Myasthenia gravis
- Systemic lupus erythematosus
- Polymyositis/polymyopathy
- Tetanus
- Canine distemper
- Dysautonomia

Toxicoses

- Botulism
- Lead
- Organophosphates

Miscellaneous conditions

- Hypoadrenocorticism
- Possible hypothyroidism
- Hiatal hernia
- Gastric dilatation or volvulus
- Esophagitis

Adapted from Washaban RJ: Diseases of the esophagus. p. 1142. In Ettinger SJ, Feldman ED (eds): Textbook of Veterinary Internal Medicine, 5th Ed. Saunders, Philadelphia, 2000.

A. Both frequency of regurgitation and timing with respect to eating varies.
B. Careful historical assessment is needed to distinguish regurgitation from vomiting.
C. Ingesta are generally not bile-stained.

II. Halitosis
III. Weight loss, poor body condition from malnutrition
IV. Ptyalism
V. Respiratory signs from secondary aspiration pneumonia: moist cough, crackles, dyspnea

Diagnosis

I. Physical examination may reveal evidence of causes or complications from megaesophagus.
   A. Neurological deficits, muscle pain, weakness
   B. Fever, crackles, and tachypnea from aspiration pneumonia
   C. Cervical neck swelling secondary to esophageal distension
II. Survey thoracic radiography may reveal a dilated, air-filled esophagus.
   A. Air bronchograms suggest aspiration pneumonia.
   B. Barium esophagram also can be done but is generally not necessary if survey radiography reveals an air-filled esophagus.
   C. If a dilated esophagus is not apparent on plain radiographs, fluoroscopy is performed in conjunction with an esophagram to evaluate esophageal motility, but a risk of aspiration pneumonia exists with the procedure.
III. Laboratory testing is indicated to search for an underlying cause and to assess secondary changes (e.g., infection from aspiration pneumonia).
   A. Complete blood count (CBC), serum biochemical profile, urinalysis
   B. Creatine kinase to evaluate for myopathies
   C. Thyroid function tests to detect hypothyroidism
   D. Adrenocorticotropic hormone (ACTH) stimulation testing to test for hypoadrenocorticism
   E. Acetylcholine receptor antibody titer to diagnose MG
   F. Others: blood lead level, antinuclear antibody assay
IV. Miscellaneous tests to consider include the following:
   A. Esophageal manometry: dynamic measurement of esophageal pressure, transit time, and lower esophageal sphincter pressures
   B. Esophageal scintigraphy: quantitatively evaluates esophageal motility
   C. Advanced neurodiagnostic tests in suspected cases of neuromuscular disease
      1. Electromyography (EMG), nerve conduction velocities (NCV), muscle or nerve biopsy
      2. Imaging of the central nervous system (CNS)
      3. Cerebrospinal fluid (CSF) tap and analysis
   D. Endoscopy
      1. Used to search for underlying etiologies that cause secondary adult-onset megaesophagus
      2. Not a sensitive tool to evaluate esophageal diameter and function

Differential Diagnosis

I. Other causes of regurgitation must be ruled out.
II. Other causes of esophageal dysmotility in young animals include vascular ring anomalies and esophageal foreign bodies and strictures.
III. Other causes of adult-onset dysmotility include esophageal neoplasia, severe esophagitis, esophageal strictures, and foreign bodies.

Treatment

I. If an etiology is identified for the megaesophagus, treatment is aimed at that specific disorder.
II. Resolution of the primary disorder does not guarantee that the megaesophagus will resolve or that normal esophageal function will return.
III. Symptomatic care for megaesophagus includes the following:
   A. Elevated feedings
   B. Frequent, small meals of calorie-dense food
   C. Tailoring of the type of diet to each animal
      1. Variability exists as to the affected animal's ability to swallow different types of foods.
      2. Various consistencies (e.g., gruel, meatballs) should be tried.
      3. Solid boluses of food are more likely to stimulate peristaltic activity.
IV. In severely malnourished animals or if oral feeding is unsuccessful, gastrostomy tube placement may be done.
V. Treatment of aspiration pneumonia includes broad-spectrum antibiotics.
VI. Prokinetic drugs are controversial and are not recommended for animals with idiopathic megaesophagus.

Monitoring of Animal

I. Monitoring is variable based on the severity of the disease.
II. Repeated thoracic radiographs and CBCs are used to monitor response to treatment for aspiration pneumonia.
III. Prognosis is variable.
   A. Congenital megaesophagus recovery rates vary from 20% to 46% (Mears and DeNovo, 2000).
      1. Early recognition carries a better prognosis.
      2. Miniature schnauzers are an exception, as most cases tend to resolve by 12 months of age.
   B. Prognosis is poor for animals with adult-onset idiopathic megaesophagus owing to progression of disease, poor nutrition, or recurrent bouts of aspiration pneumonia.
   C. Prognosis for megaesophagus secondary to MG is reasonably optimistic, because 50% of affected dogs respond to therapy (Shelton et al., 1990).

INFLAMMATORY DISORDERS

Esophagitis

Definition

I. Esophagitis involves inflammation of the esophageal mucosa, although in severe cases transmural involvement can occur.

II. Prevalence of esophagitis is probably underestimated because of variable clinical signs and difficulty in diagnosing the disease with minimally invasive techniques.
III. Both acute and chronic esophagitis occur.

Causes

I. The most common cause is gastroesophageal reflux (GER).
   A. Common causes of iatrogenic GER include the duration of preoperative fasting, preanesthetic and anesthetic agents used, and intraabdominal procedures performed.
   B. Poorly positioned nasoesophageal or esophagostomy tubes that cross the lower esophageal sphincter can also cause GER.
II. Ingestion of caustic agents (e.g., sodium hydroxide, benzalkonium chloride) may cause esophagitis.
   A. The esophagus is more susceptible to alkaline than acidic corrosives (Strombeck and Guilford, 1996).
   B. Drugs may be caustic, especially doxycycline in cats (Melendez et al., 2000).
III. Other causes include acute or persistent vomiting, thermal burns, trauma from esophageal foreign bodies, structural abnormalities (e.g., hiatal hernia), and infectious agents (e.g., pythiosis).

Pathophysiology

I. GER is a normal event in dogs and may also be normal in cats.
II. Esophagitis occurs secondarily to GER by the following:
   A. Refluxed gastric contents contain hydrochloric acid, pepsin, trypsin, bile acids, and lysolecithin that are injurious to the esophageal mucosa.
   B. Hydrochloric acid is the most important component.
   C. The most severe injury occurs when hydrochloric acid is combined with pepsin or bile acids.
   D. Inflammation impairs esophageal motility, which allows subsequent refluxed gastric contents to remain in the esophagus longer, thereby worsening the inflammation.
   E. Esophagitis compromises lower esophageal sphincter tone, allowing refluxed contents to enter the esophagus.
   F. A vicious cycle occurs that perpetuates the problem.
III. Esophagitis secondary to drugs or chemicals is affected by several factors.
   A. Tablets and capsules pass easier when given with water than when given alone (dry) (Westfall et al., 2001).
   B. Retention of drugs causes changes in mucosal pH and hyperosmolarity.
   C. Esophageal damage is usually localized (focal lesion), whereas GER causes more generalized inflammation.
IV. Several factors determine the severity of injury.
   A. Length of time refluxed material remains in the esophagus
   B. Amount of bicarbonate available (via saliva) to buffer refluxed contents
   C. Reduced swallowing and secretion of saliva during sleep and anesthesia
   D. Ability of saliva and submucosal esophageal glands to create a barrier mucus layer
V. Mild esophagitis may heal without fibrosis.
VI. Severe esophageal injury that extends into the muscularis layer can cause stricture formation.

Clinical Signs

I. Historical findings are important because of variable clinical signs.
   A. Differentiate between vomiting and regurgitation.
   B. Note any recent drug administration or anesthetic event.
II. Animals with mild esophagitis may exhibit no clinical signs.
III. Moderate to severe esophagitis may induce one or more of the following:
   A. Regurgitation
   B. Dysphagia, ptyalism
   C. Repeated attempts at swallowing
   D. Refusal to eat despite an interest in food
   E. Anorexia, weight loss

Diagnosis

I. Physical examination is often normal but may show pain on palpation of the neck in severe cases.
II. Minimum laboratory database is usually normal or reveals nonspecific changes.
III. Survey radiographs are usually unremarkable.
   A. Radiography is helpful to rule out other causes of regurgitation (e.g., megaesophagus).
   B. Contrast radiography is preferred (see Chapter 4).
      1. An irregular esophageal mucosa with possible retention of barium is suggestive of esophagitis.
      2. Either liquid barium or barium mixed with food can identify esophageal strictures.
      3. Ideally, fluoroscopy is used to evaluate esophageal motility and potentially identify GER.
IV. Endoscopy is the most sensitive and specific tool to diagnose clinically significant esophagitis.
   A. Normal esophagus is smooth and pale with longitudinal folds that flatten with distension.
   B. The distal third of the feline esophagus is smooth muscle, which creates an appearance of mucosal striations and submucosal vascularity.
   C. Esophageal changes associated with inflammation include hyperemia, increased vascularity, roughened mucosal surface, erosions, and ulcerations.
   D. Distal or multiple abnormalities are suggestive of GER, and focal lesions in the proximal third of the esophagus are suggestive of damage from foreign bodies or caustic agents.
   E. Endoscopy also may be able to document the presence of GER.
V. It is difficult to obtain adequate esophageal biopsy samples with standard endoscopic biopsy instruments.
   A. Biopsy is limited to cases not responding to therapy or if the gross appearance is not typical for benign esophagitis.

B. Abnormalities include squamous hyperplasia or dysplasia, erosions, and ulcers.
C. Acute changes include infiltrates of lymphocytes, plasma cells and neutrophils (Han, 2003).

VI. Manometry of the lower esophageal sphincter and continuous monitoring of esophageal pH can be done in a research setting but is difficult in clinical patients.

Differential Diagnosis

I. Megaesophagus
II. Esophageal stricture
III. Vascular ring anomaly
IV. Hiatal hernia
V. Esophageal foreign body
VI. Esophageal neoplasia

Treatment

I. Immediate treatment of caustic or thermal insults is indicated, and specific recommendations can be obtained from the ASPCA Animal Poison Control Center (888-426-4435).
II. Eliminate predisposing factors, such as a hiatal hernia, foreign body, or administration of a dry or caustic drug.
III. Reduce gastric acid secretion.
A. The volume of acid that is refluxed into the esophagus is subsequently decreased.
B. Histamine $(H)_2$-receptor antagonists inhibit hydrochloric acid secretion.
1. Useful in mild esophagitis, but not as effective in moderate to severe esophagitis (Willard and Weyrauch, 2000)
2. Cimetidine 10 mg/kg PO TID to QID (dogs) and 5 mg/kg PO TID (cats)
3. Ranitidine 1 to 2 mg/kg PO BID; also has some prokinetic activity
4. Famotidine 0.5 mg/kg PO SID to BID
C. Proton-pump inhibitors, such as omeprazole 0.7 mg/kg PO SID, are used in severe cases of esophagitis.
IV. Prokinetic drugs promote gastric emptying, which reduces the amount of gastric fluid that is refluxed, and increase lower esophageal sphincter tone, which decreases the amount and frequency of refluxed fluid.
A. Metoclopramide 0.5 mg/kg PO TID to QID (dogs) and 0.2 mg/kg PO TID (cats)
B. Cisapride 0.5 mg/kg PO BID (dogs) and 2.5 to 5 mg PO BID to TID (cats)
1. Superior to metoclopramide in promoting gastric emptying and increasing lower esophageal sphincter tone
2. Superior to metoclopramide in treating esophagitis (Klinkenberg-Knol et al., 1995)
3. Only available through compounding pharmacies
V. Other drugs that have been tried include the following:
A. Sucralfate 0.5 to 1 g PO TID (dogs) and 250 to 500 mg PO BID to TID (cats)
1. Cytoprotective and used to promote healing of gastric ulcers
2. Needs an acidic environment to work (stomach) and must be carried back into the esophagus as refluxate
3. Little evidence of its efficacy in the treatment of esophagitis (Klinkenberg-Knol et al., 1995)
B. Corticosteroid to prevent stricture formation
1. Questionable efficacy at best
2. Increases risk of infection
VI. Withhold food for 24 to 48 hours in cases of acute esophagitis, especially those secondary to caustic or thermal burns
A. Low-fat diets promote gastric emptying, which reduces the amount of GER.
B. Consider a gastrostomy tube to provide nutritional support in animals with severe esophagitis or those that are debilitated from chronic esophagitis.

Monitoring of Animal

I. Duration of drug therapy is based on the severity of the esophagitis.
A. Mild esophagitis is treated a minimum of 7 days.
B. Severe esophagitis is treated a minimum of 4 weeks.
II. Repeat endoscopy to determine whether esophagitis has resolved before discontinuing drug therapy.
III. If reexamination with endoscopy is not possible, use clinical signs as a guide to determine when to discontinue drug therapy.
IV. Return to a normal, maintenance diet after all medications have been discontinued and no signs have recurred.
V. If clinical signs worsen despite therapy, consider the possibility of esophageal stricture formation.
VI. Prognosis is variable, but generally good.

OBSTRUCTIVE DISORDERS

Esophageal Foreign Body

Definition

I. Foreign material or objects do not move through the esophagus into the stomach.
II. Esophageal foreign bodies are potentially life-threatening and are considered emergencies.
III. Young to middle-aged, small-breed dogs, especially terriers, may be more susceptible (Spielman et al., 1992).

Causes

I. Common esophageal foreign bodies in dogs include bones, fishhooks, sticks, and dental chew products.
II. Common esophageal foreign bodies in cats include needles, bones, fishhooks, and trichobezoars.

Pathophysiology

I. Many esophageal foreign bodies lodge in areas of normal narrowing and less distensibility (Bebchuk, 2002).
A. Pharyngeal esophagus
B. Base of the heart
C. Diaphragmatic hiatal region

II. Depending on the size and shape of the foreign body, the obstruction can be partial or complete.
III. Obstruction creates mural pressure, mucosal ischemia, and eventual necrosis.
IV. Pressure necrosis can lead to mediastinitis and esophageal perforation.
V. Sharp esophageal foreign bodies can also cause lacerations and esophageal perforation.
VI. Pain (often severe) occurs with all types of foreign bodies.

Clinical Signs

I. The duration of clinical signs is shorter in dogs with a foreign body and no perforation compared to dogs with a foreign body and esophageal perforation (Parker et al., 1989).
II. Signs are variable depending on the size of foreign body and its duration in the esophagus.
   A. Lethargy, anorexia
   B. Ptyalism, retching, gagging
   C. Exaggerated swallowing movements
   D. Regurgitation
   E. Evidence of pain: restlessness, distress, tachycardia, tachypnea
III. Signs may also develop from secondary complications, such as respiratory distress from aspiration pneumonia.

Diagnosis

I. Early diagnosis is important to decrease the likelihood of esophageal perforation.
II. History may not be helpful if the owner does not recognize that common chew toys and objects are potential esophageal foreign bodies.
III. Physical examination may be normal in acute cases.
   A. Pain may be detected with cervical esophageal palpation.
   B. In chronic cases, fever and abnormal lung sounds may be present.
IV. Laboratory tests are often normal in acute cases.
   A. Hematology can reveal leukocytosis (from inflammation) and hemoconcentration in chronic cases or in cases with esophageal perforation.
   B. Biochemical parameters are usually normal.
V. It is important to radiograph the entire esophagus.
   A. Survey radiographs are diagnostic if the foreign body is radiopaque.
      1. Identification can be challenging if the foreign body is not radiopaque.
      2. Air or fluid may be visualized proximal to the foreign body.
      3. Segmental esophageal dilatation may occur proximal to the foreign body.
      4. Pneumomediastinum, pneumothorax, or evidence of mediastinitis is suggestive.
      5. A pulmonary alveolar pattern is seen with pneumonia.
   B. Contrast radiography may be helpful.
      1. It is used to diagnose radiolucent foreign bodies.
      2. If esophageal perforation is suspected, barium is contraindicated, and either aqueous iodine or iohexol are used instead (see Chapter 4).
VI. Esophagoscopy allows direct visualization of the foreign body.
   A. It allows identification of perforations and mucosal abnormalities (erythema to severe ulcerations).
   B. If perforation is not suspected, it may allow endoscopic removal of the foreign body.

Differential Diagnosis

I. Other causes of esophageal obstruction: vascular ring anomalies, periesophageal masses
II. Esophagitis from GER, caustic or thermal burns

Treatment

I. An esophageal foreign body is considered an emergency.
II. Endoscopic retrieval is the preferred route of removal.
   A. Flexible or rigid endoscopy can be performed.
   B. Various instruments may be used to move the foreign body.
      1. Long, blunt-ended grasping forceps
      2. Flexible alligator forceps
      3. Foley urethral catheters
   C. Objects that are not sharp and are lodged in the distal esophagus can be pushed into the stomach.
      1. Attempt this only when removal through the mouth is unsuccessful.
      2. Attempt this only when further injury to the mucosa is unlikely.
   D. After removal, evaluate the mucosa for lacerations or perforations.
III. Surgery (lateral thoracotomy) is indicated when endoscopic retrieval is unsuccessful.
   A. Surgery is also indicated if an esophageal perforation is present.
   B. Surgery may be combined with endoscopy to remove fish hooks (Michels et al., 1995).
IV. Following retrieval of the foreign body, medically manage the associated esophagitis (see Esophagitis).
V. Consider insertion of a gastrostomy tube for nutritional support if severe mucosal ulceration or perforation is present.

Monitoring of Animal

I. If no complications occur, postretrieval monitoring is minimal.
II. Complications occur in about 30% of cases (Strombeck and Guilford, 1996).
   A. Esophageal perforation
      1. False-negatives may occur with contrast radiography when a foreign body is still present.
      2. Esophageal perforations up to 12 mm in diameter can be treated conservatively without surgical repair (Killen and Pridgen, 1961).
   B. Esophageal stricture
   C. Esophageal fistulation into the respiratory tract

D. Pneumomediastinum, pneumothorax, pleuritis
E. Pneumonia
F. Segmental dysmotility of the esophagus

III. If signs of esophageal disease begin 7 to 14 days after removal, evaluate for esophageal stricture formation.

Esophageal Stricture

Definition

I. It is a circular band of scar tissue that compromises the esophageal lumen.
II. Esophageal strictures can be singular or multiple and can occur anywhere in the esophagus.

Causes

I. Most esophageal strictures occur secondary to severe esophagitis.
   A. GER that occurs during anesthesia is the most common cause (Sellon and Willard, 2003).
   B. Other causes include chronic vomiting, esophageal surgery, and certain medications (e.g., doxycycline in cats).
II. Esophageal foreign bodies that create mechanical and chemical injury are also common causes.
III. Esophageal neoplasia uncommonly causes strictures.

Pathophysiology

I. An esophageal injury initially causes inflammation of the mucosa, submucosa, and muscularis (Weyrauch and Willard, 1998).
II. Secondary formation of fibrous, connective tissue narrows the esophageal lumen.
III. Time from mucosal damage to stricture formation is usually 1 to 2 weeks.

Clinical Signs

I. Dependent on location and severity of esophageal narrowing
II. Dysphagia, regurgitation
III. Refusal to eat despite interest in food
IV. Able to retain liquids better than solids
V. Weight loss
VI. Respiratory distress with proximal strictures

Diagnosis

I. History of recent anesthetic event, esophageal foreign body, vomiting, or oral medication administration
II. Diagnostic imaging
   A. Survey thoracic radiographs are usually unremarkable.
   B. Esophagogram with barium alone or mixed with canned food usually shows esophageal narrowing.
      1. Demonstrates both the number and the location of the stricture(s)
      2. May also demonstrate GER
III. Endoscopy
   A. Direct visualization is the most sensitive diagnostic test.
   B. It allows for both diagnosis and treatment.
      1. If a malignant cause of the stricture is suspected, mucosal biopsy can be performed.
      2. Treatment with balloon catheter dilatation may be undertaken.
   C. Areas at the heart base and near major vessels can be misinterpreted as partial strictures.
   D. Esophagoscopy does not allow identification of extraluminal causes of esophageal narrowing (e.g., vascular ring anomaly, periesophageal masses).

Differential Diagnosis

I. Extraluminal etiologies of esophageal narrowing: lymphadenopathy, granuloma, adhesions from previous trauma or inflammation
II. Vascular ring anomalies in young animals

Treatment

I. Benign strictures are treated with balloon catheter dilatation, esophageal bougienage, intraluminal esophageal stent placement, or surgical resection.
II. Limited experience exists with intraluminal esophageal stents in dogs and cats.
   A. High complication rate
      1. Pressure necrosis at the stent site
      2. Migration of the stent
      3. Tracheoesophageal or bronchoesophageal fistulization
   B. Expensive
   C. Only recommended when medical management fails
III. Surgical resection usually requires thoracic surgery to access the esophagus.
   A. It has a lower success rate than balloon catheter dilatation (Burk et al., 1987).
   B. Iatrogenic stricture formation at the surgery site is common.
   C. It is recommended only when other methods fail.
IV. Esophageal bougienage is the passage of rigid or semirigid dilators of incrementally larger sizes through the stricture.
   A. Greater shear forces are generated than radial forces.
   B. Shear forces increase the likelihood of esophageal perforation.
V. Balloon catheter dilation is the treatment of choice for benign esophageal strictures.
   A. Only radial forces are created because the balloons are stationary within the stricture during dilation.
   B. The balloon catheter is positioned within the stricture using endoscopic guidance and is then inflated to mechanically dilate the strictured site.
   C. Multiple balloon dilation procedures are usually necessary (mean, 2; range, 1 to 5 (Leib et al., 2001).
   D. Intralesional corticosteroids to prevent reformation of fibrous tissue may be indicated for strictures that do not respond to repeated balloon dilation.
   E. Complications include hemorrhage, mucosal tears, and esophageal perforation.
VI. Concurrent medical management is indicated with balloon catheter dilation.
   A. Nutritional support is indicated with severe esophageal strictures or for animals with poor nutritional status.

B. Aggressive treatment of esophagitis is done for at least 14 to 21 days (see Esophagitis).
C. Long-term management of GER may also be indicated.

VII. Malignant esophageal strictures are treated surgically, with adjunctive radiation therapy and chemotherapy.

Monitoring of Animal

I. Prognosis for benign esophageal strictures is good.
   A. *Successful outcome* is defined as diminished or resolved clinical signs and the ability to maintain adequate nutritional status.
   B. A success rate of 88% has been reported with balloon dilation (Leib et al., 2001).
   C. Successful outcome is not defined as a return of normal intraluminal esophageal diameter.

II. Prognosis for malignant causes of esophageal strictures is poor.

MISCELLANEOUS DISORDERS

Hiatal Hernia

Definition

I. It is a protrusion of abdominal contents through the esophageal hiatus of the diaphragm into the thoracic cavity (Callan et al., 1993).
II. Although uncommon, it occurs in both cats and dogs.
III. Two types of hiatal hernias exist.
   A. Sliding hiatal hernia
      1. Cranial displacement of the abdominal esophagus and parts of the stomach through the esophageal hiatus
      2. Most common form in dogs and cats
   B. Paraesophageal hiatal hernia
      1. Abdominal esophagus and lower esophageal sphincter remain in a fixed position.
      2. A portion of the stomach herniates into the mediastinum adjacent to the thoracic esophagus.
IV. Both congenital and acquired forms exist.
   A. Congenital form is the most common.
   B. The congenital form is reported in the Chinese sharpei, English bulldog, and chow chow (Washabau and Hall, 1997).

Causes

I. The cause is not completely understood.
II. Congenital hiatal hernias may occur secondary to incomplete closure of the diaphragmatic hiatus during embryologic development.
III. Acquired hiatal hernia has been associated with chronic vomiting (increased intraabdominal pressure), trauma (via damage to the diaphragmatic nerves), and respiratory distress from airway obstruction (increased negative intrathoracic pressure) (Jergens, 2000).

Pathophysiology

I. Possible loss of contraction of the right crus of the diaphragm around the esophagus occurs during inspiration (Sivacolundhu et al., 2002).
II. Displacement of the gastroesophageal junction leads to increased pressure against the lower esophageal sphincter.
III. Progressive compromise of the lower esophageal sphincter occurs.
IV. Failure of the lower esophageal sphincter allows for GER and secondary esophagitis.
V. Esophageal hypomotility may also contribute to the clinical presentation.

Clinical Signs

I. Some animals are asymptomatic.
II. Signs can be intermittent with sliding hiatal hernia.
III. Regurgitation, hypersalivation, inappetence, and anorexia may be noted.
IV. Respiratory signs can occur secondary to aspiration pneumonia.

Diagnosis

I. Physical examination findings
   A. ± Normal examination or low body condition score
   B. Abnormal lung sounds with pneumonia
II. Laboratory evaluation
   A. Most likely normal
   B. Evidence of inflammation with pneumonia
III. Survey radiography
   A. Caudal, dorsal, gas-filled, intrathoracic, soft-tissue opacity associated with the esophagus
   B. Occasionally megaesophagus
   C. ± Alveolar infiltrates compatible with pneumonia (occasionally)
IV. Contrast radiography
   A. It confirms the presence of a hiatal hernia.
   B. When combined with fluoroscopy, GER and esophageal dysmotility can be documented.
V. Esophagoscopy
   A. It may be helpful if radiography fails to document an intermittent, sliding hiatal hernia.
   B. Changes consistent with esophagitis may be visualized.
   C. An abnormal gastroesophageal junction may be detected.

Differential Diagnosis

I. Congenital megaesophagus
II. Other causes of esophagitis
III. Esophageal foreign body
IV. Esophageal stricture
V. Vascular ring anomaly

Treatment

I. None indicated in asymptomatic animals
II. Medical management
   A. Treat esophagitis secondary to GER for a minimum of 30 days.
   B. Feeding small, frequent meals of a low-fat, softened, or liquefied food may be successful in controlling signs (Lorinson and Bright, 1998).
   C. Antibiotics are indicated if pneumonia is present.
III. Surgical management

A. Indicated for paraesophageal hiatal hernias or if medical therapy of a sliding hiatal hernia fails
B. Many techniques possible
   1. Esophagopexy resolves clinical signs in most animals (Lorinson and Bright, 1998).
   2. Esophagopexy may be combined with hiatal plication and gastropexy.
   3. Fundoplication is not indicated, given the high complication rate and failure to resolve clinical signs (Lorinson and Bright, 1998).

Monitoring of Animal

I. Continue medical therapy for a minimum of 30 days.
II. Prognosis is guarded in animals with concurrent esophageal dysmotility.
III. Prognosis is good in animals that respond to either medical or surgical therapy.

Fistula

Definition

I. A fistula is an abnormal communication between the esophagus and the respiratory tract.
II. Several types of fistula can occur.
   A. Bronchoesophageal: most common
   B. Tracheoesophageal
   C. Pulmonary-esophageal
III. Although uncommon, both congenital and acquired fistulas occur and arise most often in toy and small-breed, terrier-type dogs.

Causes

I. Congenital fistulas may arise from incomplete separation of the esophagus and airways during embryonic development.
II. Cairn terriers may be predisposed to congenital fistulas (Basher et al., 1991).
III. Acquired fistulas arise as complications of esophageal perforations from foreign bodies and neoplasia.

Pathophysiology

I. An intraluminal foreign body (most commonly bones) creates local mucosal ischemia and necrosis.
II. The right caudal lung lobe is frequently affected (van Ee et al., 1986).
III. A fibrous communication with the respiratory tract forms during subsequent healing.
IV. Leakage of esophageal contents causes contamination of the respiratory tract.

Clinical Signs

I. Chronic coughing: frequently associated with drinking and eating
II. Regurgitation, dysphagia
III. Anorexia
IV. Pyrexia and abnormal lung sounds with pneumonia

Diagnosis

I. Crackles may be auscultated over affected lung lobes.
II. Hematology reflects inflammation secondary to pneumonia.
III. On survey radiography a radiopaque esophageal foreign body may be visible.
   A. An alveolar pattern consistent with pneumonia may be seen, especially in areas adjacent to any foreign bodies.
   B. Esophageal diverticula may also be present.
IV. Contrast radiography definitively identifies the communication between esophagus and respiratory tract, but use of hyperosmolar contrast agents should be avoided.
V. Esophagoscopy and bronchoscopy are of limited value.

Differential Diagnosis

I. Aspiration pneumonia
II. Pulmonary abscess
III. Pulmonary granuloma

Treatment

I. Antibiotics are indicated for pneumonia.
II. Lung lobectomy is usually necessary owing to the long-standing pulmonary pathology.
   A. Simple ligation of the fistula is avoided.
   B. Submit excised tissues for culture and histopathology.
III. Nutritional support is indicated for chronic, debilitated animals.

Monitoring of Animal

I. Intensive monitoring is required in the immediate post-operative period.
   A. Frequent monitoring of vital signs
   B. Repeated blood counts and thoracic radiographs
II. Complications include dehiscence, pneumothorax, and pulmonary abcessation.
III. Prognosis is good if the animal successfully recovers from surgery.

Diverticula

Definition

I. A diverticulum is a pouchlike dilatation of the esophageal wall.
II. Diverticula, although rare, may be either congenital or acquired.
III. Acquired forms occur more frequently and are either traction or pulsion in origin.
IV. Diverticula most commonly occur in three areas, namely the pharyngoesophageal, midthoracic, or caudal thoracic (Nawrocki et al., 2003).
V. Cairn terriers and miniature poodles are over-represented (Nawrocki et al., 2003).

Causes

I. Congenital esophageal diverticula result from anomalous separation of the respiratory tract from the foregut (Pearson et al., 1978).

II. Acquired esophageal diverticula arise as follows:
  A. Pulsion diverticula develop from increased intraluminal pressure associated with esophageal strictures, vascular ring anomalies, and esophageal foreign bodies.
  B. Traction diverticula develop secondary to inflammation and periesophageal fibrous tissue, and are most commonly associated with perforating esophageal foreign bodies.

Pathophysiology

I. Pulsion diverticula
  A. Increased esophageal intraluminal pressure compromises a focal area of the esophageal wall.
  B. Mucosal herniation develops.
  C. Accumulation of food in the diverticula leads to inflammation.
  D. Large diverticula compromise motility, cause mechanical obstruction, and induce esophagitis.
  E. With large diverticula, nutritional intake is affected.
II. Traction diverticula
  A. Local inflammation causes fibrous adhesions between the serosal surface of the esophagus and surrounding structures (trachea, lungs, pulmonary hilus).
  B. Adhesions cause chronic esophageal dysmotility, which leads to focal dilatation.

Clinical Signs

I. Small diverticula may be asymptomatic.
II. Regurgitation is common.
III. Halitosis occurs from food accumulation within the diverticulum.
IV. Inappetence, and distress or gasping shortly after eating (odynophagia) may be noted.

Diagnosis

I. Diverticula in the cervical esophagus may be palpated if they contain impacted food.
II. Abnormal lung sounds are auscultated if pneumonia is present.
III. Hematology reflects inflammation if severe, ulcerative esophagitis or aspiration pneumonia is present.
IV. Survey radiography may reveal the following:
  A. Air- or fluid-filled opacity in the area of the esophagus
  B. Alveolar pattern consistent with pneumonia
V. A barium esophagogram shows pooling of contrast medium in the diverticulum.
VI. Esophagoscopy confirms the diagnosis and allows assessment of the severity of food impaction and esophagitis.

Differential Diagnosis

I. Normal esophageal redundancy that is occasionally seen at the thoracic inlet (Strombeck and Guilford, 1996)
II. Esophageal foreign body
III. Periesophageal diseases: abscess, hilar lymphadenopathy, neoplasia
IV. Other causes of esophageal hypomotility: megaesophagus

Treatment

I. Correct the underlying cause of pulsion diverticula.
II. Conservative medical management may be attempted for small diverticula.
  A. Feed in an upright position.
  B. Feed frequent, small meals of a canned, semiliquid, or liquid diet to minimize food impaction.
III. Surgical correction is indicated for large diverticula.
  A. Diverticulectomy is the preferred procedure.
  B. The complication rate is high because of the unique characteristics of the esophagus (Shamir et al., 1999).
    1. Absence of serosal layer and omentum
    2. Inability to rest the esophagus because of continual movement from swallowing and diaphragmatic movement
    3. Poor tolerance to longitudinal stretching and tension
IV. Gastrostomy tube is inserted to provide nutritional support in animals with large diverticula.

Monitoring of Animal

I. Prognosis is guarded owing to the high complication rate associated with surgery.
II. If signs recur 7 to 10 days postoperatively, an esophageal stricture must be considered.
III. Dysmotility may persist following diverticulectomy.

NEOPLASIA

Definition

I. Primary tumors of the esophagus are rare in the dog and cat (<0.5% of all neoplasia) (Rolfe et al., 1994).
II. Metastatic lesions occur more frequently than primary tumors.
III. Both benign and malignant tumors have been identified.
IV. Most tumors occur in middle-aged to older animals.

Causes

I. Leiomyomas are the most common primary benign tumor, and occur most frequently at the lower esophageal sphincter.
II. Fibrosarcoma and osteosarcoma are the most common primary malignant tumors in the dog.
III. Esophageal sarcoma in dogs is associated with *Spirocerca lupi* infection.
IV. Squamous cell carcinoma is the most common primary malignant tumor in the cat.
V. Metastatic tumors or secondary tumors include the following:
  A. Thyroid carcinoma: most common (Ridgway and Suter, 1979)
  B. Other carcinomas: bronchogenic, mammary, gastric
  C. Lymphosarcoma

Pathophysiology

I. Tumors cause obstruction by decreasing intraluminal space.
II. Esophageal hypomotility may arise secondary to infiltration of the tumor into the esophageal wall.

III. Esophagitis may also occur from the tumor or secondary GER.
IV. The exact mechanism for the development of sarcomas associated with *S. lupi* is unknown.
  A. Migrating larvae incite local inflammation, hemorrhage, necrosis, and occasionally, abscesses (Johnson, 1992).
  B. The intense inflammatory reaction may cause an uncontrolled proliferation of fibroblasts (Ranen et al., 2004).
  C. Pathogenesis may be similar to vaccine-associated sarcomas.

Clinical Signs

I. Usually slowly progressive
II. Associated with altered function of the esophagus
  A. Dysphagia, regurgitation, ptyalism
  B. Inappetence, weight loss
III. Hematemesis (rare)
IV. Respiratory signs secondary to aspiration pneumonia

Diagnosis

I. History of middle-aged to older animals with progressive esophageal signs
II. Physical examination findings
  A. Can be normal
  B. May reflect poor nutritional status (low body condition score)
  C. Palpable cervical mass in some cases
  D. Abnormal pulmonary auscultation, if pneumonia present
III. Laboratory evaluation
  A. Normal in most cases
  B. Sarcomas associated with *S. lupi*
    1. Hematology reflecting inflammation (leukocytosis)
    2. Microcytic, hypochromic anemia (Ranen et al., 2004)
IV. Survey radiography
  A. Air may be visualized proximal to the mass.
  B. Segmental esophageal dilatation may be detected proximal to the mass.
  C. Tracheal displacement may be seen.
  D. An intraluminal esophageal soft-tissue structure may be identified.
  E. Pulmonary infiltrates may be present with metastatic disease or aspiration pneumonia.
  F. Hypertrophic osteopathy is reported in dogs with *S. lupi*-associated fibrosarcoma (Ranen et al., 2004).
V. Contrast radiography
  A. It is useful in detecting mucosal irregularities and luminal narrowing.
  B. When used with fluoroscopy, contrast radiography can identify dysmotility.
VI. Computed tomography
  A. Determines extent of disease
  B. May identify metastasis in local lymph nodes
  C. Discriminates between benign esophageal stricture and neoplasia
VII. Esophagoscopy
  A. It allows for direct visualization and biopsy of the mass.
  B. Leiomyomas at the lower esophageal sphincter may be difficult to differentiate from variations in normal mucosa.
  C. Esophageal mucosa can be difficult to biopsy.
  D. Endoscopic biopsies provide small samples that may be inadequate for definitive diagnosis.
VIII. Histopathology
  A. Necessary for definitive diagnosis
  B. May require surgical biopsy if endoscopic samples are inadequate

Differential Diagnosis

I. Esophageal foreign body
II. Esophageal granuloma
III. Esophagitis
IV. Hiatal hernia
V. Compression of esophagus from mediastinal masses

Treatment

I. Dependent on tumor type
II. Leiomyoma: surgical resection usually curative
III. Primary malignant tumors
  A. Most cases have advanced disease at the time of diagnosis.
  B. Partial esophagectomy is indicated but has a significant complication rate.
  C. Adjunctive chemotherapy may be started after recovery from surgery.
IV. Metastatic neoplasia
  A. Surgical resection may be used to relieve any obstruction but is not curative.
  B. Chemotherapy may be attempted.
  C. Most therapy is palliative.
V. Palliative balloon dilatation of the intraluminal obstruction may be considered, but it carries the risk of esophageal perforation.
VI. Nutritional support via a gastrostomy tube may be helpful.

Monitoring of Animal

I. Prognosis for benign tumors is good if the tumor is surgically resectable.
II. Prognosis for malignant and metastatic neoplasia is poor.
III. Palliative measures provide temporary relief from disease, but most animals are euthanized owing to quality of life issues.

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CHAPTER 31

Diseases of the Stomach

Lisa E. Moore

CONGENITAL/DEVELOPMENTAL DISORDERS

Pyloric Stenosis

Definition

I. It is a congenital disease of boxers and Boston terriers.
II. Stenosis of the pyloric canal occurs from hypertrophy of the pyloric circular muscle.

Causes

I. The cause is unknown, but an oversecretion of gastrin has been postulated.
II. A functional abnormality has also been proposed, as some animals with pyloric outflow obstruction do not have muscular thickening.

Pathophysiology

I. Stenosis of the pyloric canal causes gastric outflow obstruction.
II. Elevated levels of gastrin can lead to thickening of the pyloric smooth muscle from its trophic effects.
III. Gastrin can also lead to hypertrophy of the mucosa, which can worsen the outflow obstruction.

Clinical Signs

I. Clinical signs are related to delayed gastric emptying.
II. Generally, animals vomit food >12 hours after eating.
  A. The vomiting may be explosive.
  B. The food in the vomitus is usually digested, but may appear undigested.
III. Abdominal distention may be noted.
IV. Weight loss may occur from inability to retain food.
V. Anorexia is uncommon.

Diagnosis

I. Pyloric outflow obstruction is suspected based on the pattern of vomiting.
II. Laboratory findings may show hypokalemia, hypochloremia, and metabolic alkalosis.
III. Plain radiography often shows a stomach distended with gas and fluid.
IV. Contrast radiography may show delayed gastric emptying and a narrowing of the pyloric canal that is referred to as the *beak sign.*
V. Nuclear scintigraphy may also be used to identify delayed gastric emptying.
VI. Abdominal ultrasonography can be used to detect thickening of the pylorus.
VII. Endoscopy may be normal if the mucosa is not thickened.
VIII. At surgery, the pylorus is palpably thickened, and gastrotomy reveals a thickening of the muscular layer.

Differential Diagnosis

I. Other causes of mechanical pyloric outflow obstruction: mucosal hypertrophy, intraluminal masses (e.g., polyps, neoplasia, foreign bodies)
II. Causes of a functional delay in emptying: electrolyte disorders, pain, peritonitis, acute pancreatitis, dysautonomia, gastric ulceration

Treatment and Monitoring

I. After the animal has been stabilized with appropriate fluid and electrolyte therapy, the definitive treatment is surgery.
II. Surgical procedures include pyloromyotomy or various pyloroplasty techniques.
III. Prognosis following adequate surgical correction is good.

INFECTIOUS DISORDERS

Parasitic Gastritis

Definition and Causes

I. Parasites affecting the stomach of cats include *Ollulanus tricuspis* and *Physaloptera* spp. (less common).
II. Gastric parasites of dogs include *Physaloptera* spp.
III. Parasites attach to the gastric mucosa, causing inflammation and gastritis.

Clinical Signs

I. Infections in both dogs and cats may be inapparent.
II. Intermittent vomiting is the most common clinical sign.
III. Variable anorexia may also occur.

Diagnosis

I. *Ollulanus* spp. can be difficult to diagnose.
  A. The parasites and eggs are usually missed on routine parasitologic (usually not passed in the feces) and endoscopic (very small in size) examinations.

B. The best method of diagnosis is microscopic examination of the vomitus.
C. Organisms may also be seen on histopathology.
D. Chronic hypertrophic fibrosing gastritis may also be seen on histopathology.

II. Diagnosis of *Physaloptera* spp. is a little easier.
A. Eggs may be found on fecal flotation, but may not be routinely isolated.
B. The parasites can be seen with endoscopy and appear as 1- to 4-cm–long, white worms attached to the stomach.

Differential Diagnosis

I. Other causes of acute gastritis (see below)
II. Causes of chronic and secondary gastritis

Treatment and Monitoring

I. *Ollulanus* spp.: fenbendazole 10 mg/kg PO SID for 3 days
II. *Physaloptera* spp.: pyrantel pamoate 5 mg/kg PO for two doses, 3 weeks apart
III. Prognosis is excellent for recovery after treatment.

Helicobacter Gastritis

Definition

I. *Helicobacter* gastritis is inflammation of the stomach caused by various species of the genus *Helicobacter*.
II. Many cats and dogs that have colonization of the stomach with these spiral organisms do not have concurrent inflammation.

Causes

I. The organisms are spiral-shaped, gram-negative, motile bacteria.
II. Various species have been isolated from the stomachs of cats, dogs, ferrets, cheetahs, and others.
III. *Helicobacter heilmannii* and *Helicobacter felis* are the most common species that naturally occur in dogs and cats.
IV. *Helicobacter pylori* has been found in laboratory cats, but not in dogs.
V. These bacteria may be normal inhabitants of the stomach.

Pathophysiology

I. The pathophysiology of this disease is unclear.
II. The organisms produce urease (urea $\rightarrow NH_3 + HCO_3$) that buffers acid and allows colonization of the superficial mucus and gastric glands of the stomach.
III. The bacteria have been observed intracellularly.
IV. In infected animals, degeneration of gastric glands, as well as vacuolation and necrosis of parietal cells, has been seen.
A. The inflammation is generally mononuclear (lymphocytes, plasma cells) and can vary in the degree of severity.
B. Lymphoid follicle hyperplasia can be seen.
V. Infected animals may have up-regulation of various cytokines.

Clinical Signs

I. Chronic vomiting is the most common sign.
II. Diarrhea, anorexia, pica, and polyphagia have also been reported.
III. Uncommonly, fever and/or bloody diarrhea may be seen.

Diagnosis

I. Laboratory tests are usually normal, but may show nonspecific changes (e.g., stress leukogram).
II. Abdominal radiography and ultrasonography are usually normal.
III. The best method of diagnosis currently is endoscopic biopsy.
A. Organisms can be visualized on the epithelium or in the mucus layer.
B. Warthin-Starry silver stains enhance visualization of the organisms.
C. Multiple biopsy samples are taken as the colonization can be patchy.
D. Endoscopy also allows evaluation of the mucosa for the type and severity of inflammation and for other changes.
IV. The rapid urease test may be performed and is based on the production of urease by almost all *Helicobacter* spp.
A. The test is also known as the *Campylobacter*-like organism (CLO) test.
B. Gastric tissue is incubated in broth with a pH indicator (phenol red) so that a color change indicates production of ammonia via urease.
C. The degree of color change is proportional to the density of organisms.
D. Results are available in 1 to 24 hours.
E. This test has a sensitivity of 70% to 90% (Happonen et al., 1996).
V. Brush cytology of gastric mucus is a relatively sensitive method of detecting organisms but does not allow determination of whether inflammation is present.
VI. Culture is not usually performed because the organisms are hard to grow in the laboratory.
VII. The C13 urea breath test also has been used in dogs and cats; however, it is not widely available.
VIII. Polymerase chain reaction (PCR) assays of gastric tissue allows diagnosis as well as identification of the species present; however, it is not widely available.
IX. Serological testing is widely used as a screening test in humans, but tests designed for humans should not be used in dogs and cats because the primary organism affecting humans (*H. pylori*) is not generally found in dogs or cats.
X. Serological testing is also difficult in animals because multiple species of *Helicobacter* may occur.

Differential Diagnosis

I. Other causes of chronic vomiting: chronic gastritis, pyloric outflow obstruction
II. Vomiting caused by nongastrointestinal diseases

Treatment

I. The best therapy has yet to be identified in the dog and cat.
II. "Triple therapy" is recommended in symptomatic humans and involves administration of an acid-inhibiting drug, bismuth compounds, and an antibiotic (e.g., clarithromycin, amoxicillin).
III. Most of the therapies tried in dogs and cats have not been 100% successful; many animals, although initially cleared of the organism, become reinfected.
IV. Combinations that have been tried include the following:
   A. Metronidazole, amoxicillin, and famotidine
   B. Azithromycin, tinidazole, bismuth, and ranitidine
   C. Clarithromycin, metronidazole, bismuth, and ranitidine
   D. Amoxicillin, metronidazole, and omeprazole
   E. Amoxicillin, metronidazole, and clarithromycin
V. Therapy is usually given for 2 to 3 weeks.

Monitoring of Animal

I. Monitoring is generally via physical examination and clinical signs.
II. To definitively determine if the organisms have been cleared, invasive testing may need to be repeated, but this is usually not done if the clinical signs resolve.

Gastric Pythiosis

Definition and Cause

I. Gastric pythiosis in dogs is caused by the aquatic oomycete *Pythium insidiosum*.
II. It has been documented only as a cutaneous and subcutaneous infection in cats; however, unpublished information indicates it can occur rarely as a gastrointestinal (GI) infection in cats.
III. The organism may dwell in water or soil.
IV. In the United States, the infection occurs most commonly in the Gulf Coast states, but it has been recognized as far north as New Jersey and Illinois, and as far west as Oklahoma, Missouri, and Kansas.

Pathophysiology

I. Pythiosis occurs most commonly in young, male, large-breed dogs—especially outdoor, working dogs.
   A. Affected dogs are usually exposed to areas of warm, fresh water.
   B. The animals are usually immunocompetent.
II. The infective form is likely the zoospore and may cause infection by encysting in damaged GI mucosa.
III. Infection is characterized by severe transmural thickening of the stomach, and the gastric outflow tract is one of the most common sites of infection.
IV. Inflammation is usually in the submucosa, with variable mucosal ulceration.
V. The disease may extend through to the serosal surface, and associated lymph nodes may be enlarged.

Clinical Signs

I. Severe weight loss and vomiting are common.
II. Lethargy is not usually seen unless obstruction has occurred.
III. Diarrhea and hematochezia may be seen when other parts of the GI tract are involved.

Diagnosis

I. Laboratory abnormalities may include eosinophilia, anemia, hyperglobulinemia, and hypoalbuminemia.
II. Abdominal radiography and ultrasonography reveal thickening of the gastric (usually pyloric) wall.
III. Associated lymphadenopathy also is usually seen on ultrasonography.
IV. Definitive diagnosis requires identification of the organism.
V. Cytology of aspirates of enlarged lymph nodes or thickened stomach wall shows pyogranulomatous, suppurative, or eosinophilic inflammation, but the organism is seen only occasionally.
VI. A presumptive diagnosis can be made based on histopathology.
   A. Findings include granulomatous, eosinophilic to pyogranulomatous inflammation with fibrosis.
   B. Organisms are usually found in the center of granulomas or in areas of necrosis.
   C. The organisms are easier to visualize with Gomori's methamine silver (GMS) staining.
   D. Immunohistochemistry techniques may also be used.
VII. Culture of the organism is difficult unless special sample handling and culture techniques are used.
VIII. A serological enzyme-linked immunosorbent assay (ELISA) has been developed for the detection of antibodies and is highly sensitive and specific in dogs and cats.
IX. Western immunoblot analysis also can be used.

Differential Diagnosis

I. Gastric neoplasia
II. Hypertrophic gastritis
III. Other systemic fungal infections.

Treatment

I. Aggressive surgical resection (3- to 4-cm margins) of the infected area is the treatment of choice.
   A. The organisms may not be present in enlarged lymph nodes, so they are not routinely resected.
   B. Medical therapy for 2 to 3 months (as follows) is recommended following resection because of the possibility of recurrence.
II. If resection is not possible, antifungal therapy can be tried.
   A. Response is often poor, but up to 15% of dogs may respond (Grooters, 2003).
   B. Itraconazole 10 mg/kg PO SID and terbinafine 5 to 10 mg/kg PO are recommended for 6 to 9 months.
   C. Alternatively, amphotericin B lipid complex is given at 2 to 3 mg/kg IV QOD up to a cumulative dose of 24 to 27 mg/kg.

INFLAMMATORY DISORDERS

Acute Gastritis

Definition

I. It is inflammation of the stomach that has an acute onset.
II. It implies that the cause and the inflammation can be eliminated, so that the stomach returns to normal health, with no residual inflammation or fibrosis.

Causes and Pathophysiology

I. Ingestion of pathogenic bacteria rarely cause gastritis because they are usually unable to colonize the stomach.
II. The main exception is the spiral bacteria (*Helicobacter* spp., see *Helicobacter* gastritis).
III. Viruses (e.g., parvovirus, distemper virus, coronavirus) may cause gastritis as part of a more widespread condition.
IV. Bacterial toxins produced by *Clostridium* spp., *Escherichia coli*, and *Klebsiella* spp. have been suggested.
V. Physical damage from foreign bodies and thermal injury can result in gastritis.
VI. Chemicals, such as cleaning agents, floor finishes, and various plant toxins, are also potential causes.
VII. Certain drugs (aspirin) may be directly cytotoxic to the stomach, whereas others exert their toxic effects by indirect mechanisms.
VIII. Garbage ingestion is a common cause of acute gastritis in dogs.
IX. Many metabolic diseases cause gastritis (e.g., renal and hepatic failure, hypoadrenocorticism).

Clinical Signs

I. Acute vomiting is the most common clinical sign, especially after eating or drinking.
II. Blood is occasionally present in vomitus.
III. Varying degrees of anorexia, depression, and abdominal pain may also be noted.

Diagnosis

I. Tentative diagnosis is based on the history and clinical signs.
II. Definitive diagnosis is not commonly made, because animals usually recover rapidly.
III. Laboratory tests are usually unremarkable.
IV. Abdominal radiographs are usually unremarkable, unless an opaque foreign body is present.

Differential Diagnosis

I. Causes of chronic or secondary gastritis: gastrinoma, mast cell tumor, renal failure, hepatic failure
II. Nongastric diseases that cause vomiting: pancreatitis, hypoadrenocorticism

Treatment

I. Administer fluid therapy if needed.
  A. A balanced electrolyte solution is adequate.
  B. Give fluids SC or IV, depending on the severity of the clinical signs.
II. Stop all oral intake (nothing by mouth [NPO]) for 12 to 36 hours.
III. Reintroduce bland food as small, frequent meals.
  A. The food should contain an easily and highly digestible starch, be low in protein, and contain moderate to low fat.
  B. Several commercial canine and feline formulations are on the market and most are labeled as "intestinal formulas."
  C. Homemade diets for dogs include boiled hamburger and rice, low-fat cottage cheese and rice, chicken and rice, cooked egg whites and rice, or tofu and rice, all in ratios of 1:2 or 1:4.
  D. Homemade diets for cats include chicken or turkey, possibly combined with baby rice cereal in a 1:1 ratio.
IV. Antiemetics are used when necessary; they are only symptomatic therapies, so are not to be used in place of adequate diagnostic and specific therapies.
  A. They are reserved for intractable vomiting when the cause of the vomiting is known.
  B. They vary in their site(s) of action.
    1. Alpha$_2$-adrenergic antagonists (phenothiazines)
      a. The sites of action are the chemoreceptor trigger zone (CRTZ) and the vomiting center.
      b. These are potent antiemetics and are effective for most causes of vomiting.
      c. Side effects include sedation and hypotension.
      d. Examples for both dogs and cats include prochlorperazine *(Compazine)* 0.5 mg/kg IM, SC TID and chlorpromazine *(Thorazine)* 0.2 to 0.4 mg/kg SC TID.
    2. Histaminergic (H_1) antagonists (antihistamines)
      a. Sites of action are the CRTZ and the vestibular apparatus.
      b. Side effects include sedation.
      c. These are usually given only for motion sickness.
      d. Examples in the dog include diphenhydramine *(Benadryl)* 2 to 4 mg/kg PO, IM TID and dimenhydrinate *(Dramamine)* 4 to 8 g/kg PO TID.
    3. Dopaminergic ($D_{2)}$ antagonists
      a. Sites of action include the CRTZ and GI smooth muscle.
      b. They are used for vomiting secondary to uremia, delayed gastric emptying, etc.
      c. Side effects include extrapyramidal signs (from metoclopramide) and sedation (from haloperidol).
      d. Examples include metoclopramide *(Reglan)* 0.2 to 0.4 mg/kg PO, SC, IM TID to QID, or 1 to 2 mg/kg/day IV as a constant rate infusion (dog, cat) and haloperidol *(Haldol)* 0.02 mg/kg PO BID (dog).
    4. Serotonergic 5HT$_3$ antagonists
      a. Sites of action are the CRTZ and vagal afferent neurons.
      b. They are used primarily during chemotherapy.
      c. Side effects include sedation.
      d. An example in the dog is ondansetron *(Zofran)* 0.5 to 1.0 mg/kg PO SID to BID or 30 minutes before chemotherapy.

5. Serotonergic $5HT_4$ agonists
   a. Sites of action are the myenteric neurons.
   b. They are used primarily for delayed gastric emptying, rather than as an antiemetic.
   c. An example is cisapride *(Propulsid)* 0.1 to 0.5 mg/kg PO BID to TID (dog, cat).
6. Motilin agonists
   a. Site of action is the GI smooth muscle (motilin receptors).
   b. They are used for delayed gastric emptying, rather than as an antiemetic.
   c. Side effects include vomiting.
   d. An example in the dog is erythromycin 0.5 to 1 mg/kg PO, IV TID.

V. Inhibition of gastric acid secretion is usually not needed; however, H_2 blockers may be used if gastric bleeding is noted (see next section).
VI. Antibiotics are not indicated unless a specific bacterial pathogen is suspected or documented, or disruption of the gastric mucosal barrier is significant.
VII. Locally acting protectants (sucralfate, bismuth subsalicylate) are usually not needed, but may be used safely if desired (see next section).

Gastric Ulceration and Erosion

Definition and Causes

I. Ulceration may be acute and caused by chemicals, gastric dilatation-volvulus, drugs, disseminated intravascular coagulation (DIC), shock, or foreign bodies.
II. Ulcers may arise with chronic disorders, such as inflammatory bowel disease (IBD), neoplasia, renal failure (acute or chronic), and hepatic failure.
III. The most common causes include nonsteroidal anti-inflammatory drugs (NSAIDs), neoplasia, shock, renal and hepatic failure, and hypoadrenocorticism.

Pathophysiology

I. NSAIDs inhibit prostaglandin production, which results in loss of an important part of the gastric mucosal barrier.
   A. Certain drugs (aspirin) can be directly cytotoxic to the epithelial cells.
   B. Risk factors for ulcer formation include higher doses, long-term administration, and concurrent administration with another NSAID or a corticosteroid.
II. Certain neoplasms commonly cause gastric ulceration.
   A. Mast cell tumors release histamine, which causes an increase in H^+ production.
   B. Gastrinomas release gastrin, which also results in increased H^+ production.
III. Shock results in disruption of blood flow to the stomach, leading to ischemia and ulceration.
IV. Renal and hepatic failure causes abnormal metabolism of gastrin (among other substances), with increased production of H^+.
V. In the preceeding situations, reparative mechanisms of the mucosa are overwhelmed and superficial damage (erosions) occurs, or severe lesions that penetrate to the muscularis or deeper (ulcers) develop.

Clinical Signs

I. Clinical signs are variable, with vomiting being the most common.
II. The vomitus may contain fresh or digested blood ("coffee grounds").
III. Anorexia may be noted.
IV. Abdominal pain can occur that may be ameliorated by food (from buffering action of food).
V. Animals may develop acute abdominal pain from gastric perforation and peritonitis, with few or no prior clinical signs.

Diagnosis

I. Laboratory findings may be normal.
II. The cause of ulceration may be detected by laboratory findings (e.g., azotemia, hepatic failure).
III. Acute or chronic microcytic, hypochromic anemia may be seen.
IV. Abdominal ultrasonography reveals changes in the gastric wall consistent with ulceration and focal or diffuse accumulation of peritoneal fluid if a perforation is present.
V. Any free abdominal fluid may be sampled with ultrasound guidance.
VI. Definitive diagnosis requires visualization of the ulceration/erosion via endoscopy.

Differential Diagnosis

I. Other causes of vomiting
II. Other causes of GI bleeding and melena, including thrombocytopenia and other clotting disorders

Treatment

I. Treat any underlying conditions and stabilize the animal with appropriate fluid therapy, electrolyte replacement, and transfusion therapy as necessary.
II. If the animal is receiving a drug that may cause an ulceration, discontinue the drug.
III. Institute specific treatment with antacids.
   A. Acid neutralizers
      1. These agents neutralize acid that has already been produced by the stomach.
      2. They can be very effective, but must be given at least six times per day.
      3. Examples include magnesium hydroxide *(Milk of Magnesia),* aluminum hydroxide *(Amphojel),* and calcium carbonate *(Tums).*
      4. Aluminum-containing antacids decrease absorption of phosphorus and may stimulate mucosal defense mechanisms.
      5. Calcium-containing antacids may cause constipation.
   B. H_2-receptor antagonists
      1. These agents selectively and reversibly bind to H_2 receptors on the oxyntic cell, thus inhibiting the acid secretagogue effect of histamine.

2. Although these drugs only partially inhibit acid secretion, they often allow healing to occur.
3. Cimetidine (5 to 10 mg/kg PO, SC TID to QID in dogs and cats) reversibly inhibits the hepatic microenzyme system (cytochrome P-450), and can interfere with clearance of drugs metabolized by this route.
4. Ranitidine may be six to ten times more potent than cimetidine.
   a. Ranitidine inhibits microsomal enzymes less than cimetidine.
   b. Ranitidine may have gastric prokinetic properties.
   c. Dose is 1 to 4 mg/kg PO, SC, IV BID to TID (dogs and cats).
5. Famotidine has potency similar to ranitidine in dogs, with a longer elimination half-life.
   a. Dose in dogs is 0.5 mg/kg PO, SC, IV SID to BID
   b. Dose is not established for cats.

C. Proton pump antagonist
1. These drugs irreversibly inhibit the hydrogen-potassium-ATPase pump at the apical border of the oxyntic cells.
2. A single daily dose results in virtual antacidity.
3. They also inhibit hepatic microsomal enzymes similar to cimetidine.
4. They are superior to H_2 blockers for treatment of severe reflux esophagitis and indolent gastroduodenal ulceration in dogs.
5. Dose of omeprazole is 0.7 to 2 mg/kg PO SID in dogs; very little experience exists in cats.

IV. Gastric protectants are also useful.
A. Misoprostol is a synthetic prostaglandin E1 analog that inhibits gastric acid secretion and stimulates gastric mucosal defense mechanisms in dogs.
1. Its primary therapeutic use is prophylaxis against gastric mucosal injury caused by NSAIDS.
2. Its main adverse effect is diarrhea.
3. Do *not* use it in pregnant animals, and do *not* allow pregnant women to handle it (can cause abortion).
4. Dose in dogs is 1 to 5 µg/kg PO BID to TID.

B. Sucralfate is a complex salt of sucrose sulfate and aluminum hydroxide.
1. In an acidic environment, sucralfate binds to exposed submucosa and polymerizes.
2. Its primary action is to stimulate mucosal defense and reparative mechanisms, as well as inhibit pepsin activity.
3. Sucralfate stimulates bicarbonate and mucus secretion, increases the viscosity of gastric mucus, and stimulates the release of prostaglandins (facilitates mucosal blood flow and repair).
4. It is not absorbed from the GI tract, but may inhibit absorption of other drugs.
5. It may cause constipation.
6. Dose is 0.25 to 1 g PO BID to QID in dogs and 0.125 to 0.25 g PO BID to TID in cats.

C. Bismuth subsalicylate *(Pepto-Bismol)* has cytoprotective properties by complexing with glycoproteins to retard hydrogen ion diffusion through the mucosa and by decreasing pepsin output.
1. It also has antibacterial activity.
2. Dose in dogs is 0.5 to 1 mL/kg PO every 4 to 8 hours.
3. It must be used with caution in cats because of the salicylate component (0.25 mL/kg PO BID).

V. Antiemetics are used as needed (see Acute Gastritis).
VI. Prokinetic agents enhance GI motility, specifically gastric emptying.
A. Metoclopramide has antiemetic and prokinetic properties.
1. It increases gastroesophageal sphincter (GES) pressure and hastens gastric emptying.
2. Dose in both dogs and cats is 0.2 to 0.4 mg/kg PO, SC, IM TID to QID or 2 mg/kg/day IV as a constant rate infusion.

B. Cisapride has prokinetic and antiemetic effects, but is used primarily as a prokinetic agent.
1. It increases GES pressure, accelerates gastric emptying, enhances colonic propulsive motility, and probably enhances motility of the small intestine.
2. Dose in both dogs and cats is 0.1 to 0.5 mg/kg PO BID to TID.
3. Cisapride is available through a few compounding pharmacies.

C. Erythromycin has an action similar to endogenous motilin, as well as an antiemetic action.
1. It accelerates gastric emptying and has intestinal promotility affects.
2. Dose is 0.5 to 1 mg/kg PO, IV TID in dogs.

D. Ranitidine and nizatidine may stimulate gastric, intestinal, and colonic motility, but their clinical efficacy is unknown.

VII. Uncommonly, gastric ulcers may bleed profusely or may be so deep that perforation is imminent, making partial gastrectomy and resection of the affected area necessary.

Monitoring of Animal

I. Laboratory tests are repeated to ensure that electrolytes have normalized and anemia (if present) is stable or improving.
II. Endoscopy can be repeated to determine definitively if the ulceration has healed, but is not usually done unless clinical signs persist.

Chronic Idiopathic Gastritis

Definition and Causes

I. It is defined as chronic inflammation of the stomach where no cause can be found.
II. The condition may be immune-mediated, and is considered a form of IBD that is localized to the stomach.
III. Postulated causes include food allergy, loss of tolerance to bacterial (normal flora) antigens, genetic susceptibility, or an abnormal immune response (host hypersensitivity).

Pathophysiology

I. The pathophysiology of IBD is complex and poorly understood.
II. Chronic gastritis is a diagnosis of exclusion.
III. Histopathologic findings include occasional microerosions of the epithelium, infiltration of the interstitium with lymphocytes, plasma cells or eosinophils.
  A. Fibrosis of gastric tissue is seen after prolonged, untreated inflammation.
  B. Lesions can be patchy or diffuse.
IV. In cats, eosinophilic gastritis may be seen as part of a more generalized disease (hypereosinophilic syndrome).

Clinical Signs

I. Vomiting is the most common clinical sign.
II. Mild weight loss is seen less commonly.
III. Variable anorexia and depression may occur.

Diagnosis

I. Laboratory tests are usually normal or show nonspecific changes (e.g., stress leukogram, eosinophilia).
II. Abdominal radiographs are usually normal.
III. Abdominal ultrasonography may show a thickened stomach wall and/or enlargement of gastric lymph nodes.
IV. Known causes of gastritis must be excluded.
  A. Negative fecal examination and no response to deworming
  B. No history of NSAID use
V. Gastric biopsy is necessary for definitive diagnosis.
  A. Endoscopic biopsies are often adequate.
  B. Biopsies also may be obtained via exploratory laparotomy.
VI. At endoscopy, the mucosa may appear grossly normal, granular, friable, hyperemic, edematous, or eroded.

Differential Diagnosis

I. Other causes of primary gastritis: food intolerance, parasites, foreign body
II. Other causes of secondary gastritis: renal or hepatic failure, hypoadrenocorticism

Treatment

I. Treatment often involves a combination of dietary changes and/or drug therapy.
II. Feed small, frequent meals of a low-fiber, low-to-moderate–fat diet to hasten gastric emptying.
III. Diets can be of three types.
  A. An easily and highly digestible commercial diet or a home-cooked diet can be prepared.
  B. A novel protein diet can be tried.
  C. A hypoallergenic diet consisting of hydrolyzed protein sources can be tried.
  D. The dietary change may be effective alone, or may be used in combination with drug therapy.
IV. Antiinflammatory or immunosuppressive drugs are indicated if nutritional management alone does not control the clinical signs.
  A. Give prednisone at 2 mg/kg PO SID for dogs and 2 to 4 mg/kg PO SID for cats for 2 to 4 weeks, then gradually tapered over 3 to 6 months.
  B. Some animals may be weaned completely off corticosteroids, whereas others must remain on chronic low doses (usually 0.5 to 1 mg/kg PO QOD).
V. If the animal is refractory to steroid therapy, relapses, or has unacceptable side effects, alternative drugs may be needed.
  A. Metronidazole may be helpful.
  B. Other options include azathioprine or cyclosporine in dogs and chlorambucil or cyclosporine in cats.
VI. Mucosal protectants are used as needed if erosions are present.
VII. Inhibition of gastric acid secretion with H_2 blockers or a proton pump inhibitor may be beneficial.
VIII. Prokinetic agents may be of value if delayed gastric emptying is a concurrent problem.

Monitoring of Animal

I. Repeat laboratory tests to ensure that the animal is stable.
  A. Some animals with severe idiopathic gastritis may have gastric bleeding, so the monitor the packed cell volume (PCV).
  B. Some animals may develop side effects (e.g., diabetes mellitus) secondary to corticosteroid use, so monitor blood glucose as well.
II. Repeat endoscopy and biopsy to definitively determine if the inflammation is under control; however, they are not usually done unless clinical signs persist.

Atrophic Gastritis

Definition and Causes

I. It is a very uncommon condition.
II. The etiology is unknown, but it may be immune-mediated or the terminal stage of idiopathic gastritis.

Pathophysiology

I. The pathophysiology is unknown.
II. Histopathology shows a reduced gastric mucosal parenchyma (loss of glands and cells), some inflammatory cells (lymphocytes and plasma cells), flattened epithelium, shortened gastric pits, metaplastic cells, and fibrosis.
III. Achlorhydria (loss of ability to produce H^+) often results and leads to small intestinal bacterial overgrowth, which in turn may lead to malabsorption.

Clinical Signs

I. Intermittent vomiting is the most common clinical sign.
II. Mild weight loss may be seen, and anorexia and depression may occur.

Diagnosis

I. Laboratory tests are usually normal, but may show nonspecific changes (e.g., stress leukogram).
II. Abdominal radiographs and ultrasonography are usually normal.

III. Endoscopy with biopsy is the method of choice for diagnosis.
IV. The mucosa may appear grossly normal or discolored and thin (more common), with submucosal blood vessels visible under the mucosa.

Differential Diagnosis

I. Other GI causes of vomiting: food intolerance, parasites, foreign body
II. Non-GI causes of vomiting: renal or hepatic failure, hypoadrenocorticism

Treatment

I. Change the diet to small, frequent meals of an easily digested diet, or try a novel protein diet.
II. Use mucosal protectants if erosions are present.
III. Inhibition of gastric acid secretion may make clinical signs worse if achlorhydria is present.
IV. Prokinetic agents are of value if delayed gastric emptying is a problem.
V. Antiinflammatory drugs are indicated if nutritional management alone does not control the clinical signs.
   A. Prednisone is given at 1 to 2 mg/kg PO SID for 2 to 3 weeks then gradually tapered over 3 to 6 months.
   B. Additional antiinflammatory agents are uncommonly needed.

Monitoring of Animal

I. Laboratory monitoring is done for side effects secondary to corticosteroid use (e.g., blood glucose, alkaline phosphatase).
II. Endoscopy and biopsy can be repeated to determine definitively if the inflammation is under control, but are not usually done unless clinical signs persist.

Hypertrophic Gastritis

Definition

I. Hypertrophic gastritis is characterized by focal or diffuse mucosal proliferation along with inflammation.
II. In the focal form, polypoid lesions may occur.
III. Widespread mucosal thickening is less common.

Causes

I. The etiology of this uncommon condition is unknown.
II. Genetics may play a role because it is more common in small-breed dogs (e.g., Lhasa apso, shih tzu, Maltese, basenji).
III. An immune-mediated cause has also been postulated.
IV. Male dogs are predisposed.

Pathophysiology

I. The pathophysiology is unknown, but hypergastrinemia may be involved, as gastrin is trophic to the gastric mucosa.
II. Histopathology shows hypertrophy and hyperplasia of the mucosa, metaplasia of glandular epithelium, and variable amounts of fibrous tissue and inflammatory cells (lymphocytes, plasma cells).

Clinical Signs

I. Intermittent vomiting is the most common clinical sign.
II. Mild weight loss may be seen with variable anorexia and depression.

Diagnosis

I. Laboratory tests and abdominal radiographs are usually normal or show nonspecific changes (e.g., stress leukogram).
II. On endoscopy the mucosa is diffusely or focally thickened, usually in the area of the antrum, and biopsy confirms the diagnosis.
III. Measurement of serum gastrin concentration is done to rule out a gastrin-secreting tumor.

Differential Diagnosis

I. Other GI causes of vomiting: food intolerance, parasites, foreign body.
II. Non-GI causes of vomiting: renal or hepatic failure, hypoadrenocorticism.

Treatment

I. Change the diet to small, frequent meals of an easily digested diet, or try a novel protein diet.
II. Mucosal protectants may be beneficial if erosions are present.
III. Inhibition of gastric acid secretion with H_2 blockers or a proton pump inhibitor may be helpful.
IV. Prokinetic agents are of value if delayed gastric emptying from a motility problem is present, but they are indicated if hypertrophied mucosa causes a physical obstruction.
V. Prednisone may be tried (1 to 2 mg/kg PO SID for 2 to 3 weeks, then gradually tapered over 3 to 6 months) if inflammation is present and nutritional management does not control the signs.
VI. Surgical resection of focal areas of hypertrophy is performed, especially when bleeding polypoid lesions or gastric outflow obstruction are present.

Monitoring of Animal

I. Laboratory monitoring is done for side effects secondary to corticosteroid use (e.g., blood glucose, alkaline phosphatase).
II. Endoscopy and biopsy can be repeated to determine definitively if the inflammation is under control, but they are not usually done unless clinical signs persist.

MISCELLANEOUS DISORDERS

Delayed Gastric Emptying

Definition

I. Food is retained in the stomach for an abnormally long time.
II. The stomach is usually completely empty within 10 to 12 hours after a normal meal.

Causes

I. Various primary intestinal diseases can result in delayed gastric emptying.
   A. Mechanical obstruction from gastric mucosal hypertrophy, pyloric muscular stenosis, foreign bodies, polyps, neoplasia, pythiosis
   B. Functional obstruction or motility disorders from acute or chronic gastritis, acute pancreatitis, gastric ulceration, gastric neoplasia
II. Delayed gastric emptying may also be secondary to non-GI disease.
   A. Metabolic acidosis, electrolyte disorders (hyper- or hypocalcemia, hypokalemia)
   B. Diabetes mellitus, pain, peritonitis, trauma, abdominal surgery
   C. Drugs (narcotics), dysautonomia, hypoadrenocorticism, hepatic failure, uremia

Pathophysiology

I. Pathophysiology depends on the underlying cause.
II. Mechanical obstruction is a physical impedance to outflow of contents from the stomach.
III. Functional obstruction arises from an alteration in normal gastric motility causing defective gastric propulsion, and may be related to an abnormality of neuronal or smooth muscle function or coordination.

Clinical Signs

I. Acute or chronic vomiting is the most common clinical sign.
   A. Whether the vomiting is acute or chronic depends on the underlying condition.
   B. The vomiting often occurs long after ingestion of the meal at a time when the stomach would normally be empty (>10 to 12 hours after eating).
   C. The vomiting may be explosive or projectile.
II. Abdominal discomfort is sometimes noted.
III. Anorexia and depression are uncommon.
IV. Weight loss may be seen with chronic disease.
V. Various other clinical signs are seen depending on the underlying cause, such as polyuria and polydipsia with diabetes mellitus and renal failure.

Diagnosis

I. Regardless of the cause, laboratory tests often shows hypochloremic metabolic alkalosis secondary to loss or pooling of HCl in the stomach.
II. Other laboratory changes depend on the underlying cause (e.g., hyperglycemia with diabetes mellitus, azotemia with renal failure).
III. Contrast radiography is one of the best methods to identify a mechanical outflow obstruction.
IV. Fluoroscopy is also helpful when a functional disorder is suspected.
V. Endoscopy can be used to help determine the cause of a mechanical obstruction, but it is not very helpful if a functional problem is present.

Differential Diagnosis

I. Other causes of acute and chronic vomiting
II. Motility problems of the intestines

Treatment and Monitoring

I. Certain foreign bodies can be removed via endoscopy, while others require surgical removal.
II. Surgery is the treatment of choice for antral pyloric muscular hypertrophy, certain cases of mucosal hypertrophy, pythiosis, and other causes of mechanical obstruction.
III. The underlying cause must be treated in cases of functional obstruction.
   A. Insulin therapy and electrolyte replacement for diabetes mellitus
   B. Antiinflammatory medications for chronic gastritis
IV. Prokinetic agents often are very helpful for functional disorders (see Treatment under Gastric Ulceration and Erosion).
V. Endoscopy and biopsy, ultrasound, or fluoroscopy with contrast media can be repeated to definitively determine if the disease is under control, but these tests are not usually performed unless clinical signs persist.

Bilious Vomiting Syndrome

Definition and Causes

I. Bilious vomiting syndrome is an idiopathic disorder associated with duodenogastric reflux of bile.
II. Duodenogastric reflux stimulates the vomiting reflex.

Clinical Signs

I. Dogs tend to vomit small amounts of bile first thing in the morning on an empty stomach.
II. The physical examination is usually normal.

Diagnosis and Differential Diagnosis

I. Diagnosis is suggested based on the pattern of vomiting and lack of other clinical signs.
II. Laboratory tests are normal.
III. Definitive diagnosis is by exclusion of other causes of chronic vomiting.

Treatment and Monitoring

I. A small meal given just before bed often helps.
II. A prokinetic drug at bedtime may be added if needed.
III. Prognosis is good to excellent for control of the condition.

NEOPLASIA

Definition and Causes

I. Adenocarcinoma is the most common gastric neoplasm of the dog, and lymphoma is the most common tumor of the cat.
II. Other tumors affecting the stomach include the fibrosarcoma, leiomyoma, leiomyosarcoma, and plasmacytoma.

Pathophysiology

I. Neoplastic cells infiltrate the stomach in either a focal (adenocarcinoma) or diffuse (lymphoma) pattern, and may be mucosal or transmural.
II. Mucosal ulceration is common.
III. Lymphoma in cats has been described as large or small cell in type.

Clinical Signs

I. Chronic vomiting, weight loss, and inappetence are the most common clinical signs.
II. Vomitus may include old blood (coffee grounds appearance), and melena may be seen in some cases.

Diagnosis

I. Laboratory tests may be normal or show nonspecific changes (e.g., stress leukogram).
   A. Anemia may be seen with bleeding tumors.
   B. The anemia may be acute and nonregenerative, or chronic (microcytic, hypochromic).
II. Survey abdominal radiographs may reveal a mass effect or gastric wall thickening.
   A. Positive contrast techniques or pneumogastrography may be helpful (see Chapter 4).
   B. Both techniques are performed *after* abdominal ultrasonography, because they interfere with visualization of the stomach and other organs.
III. Abdominal ultrasonography may reveal a gastric mass, enlarged lymph nodes, or evidence of metastasis (liver).
IV. Definitive diagnosis requires biopsy and histopathology.
V. Endoscopy may be performed to obtain a biopsy diagnosis, but does not determine whether metastasis is present.
VI. Surgery can be performed for diagnostic purposes, as well as for therapy.

Differential Diagnosis

I. Other causes of chronic vomiting: GI and non-GI in origin
II. Other neoplasia of the GI track and abdomen

Treatment and Monitoring

I. Treatment depends on the tumor type.
II. The recommended therapy for lymphoma is multi-drug chemotherapy (see Chapter 69).
   A. Remission times are much shorter for dogs than cats.
   B. Small-cell lymphoma in cats is usually treated with prednisone (or prednisolone) and chlorambucil.
      1. Prednisone is started at 5 mg PO BID and chlorambucil at 15 mg/m^2 PO SID for 4 days and repeated every 3 weeks.
      2. An alternative regimen is to give chlorambucil at 6 mg/m^2 PO QOD.
      3. Long-term remissions may be achieved in these cats.
III. Recommended therapy for other types of gastric neoplasia is surgical resection.
   A. The primary mass is resected and >2- to 3-cm margins are included if possible.
   B. With adenocarcinomas, large margins are difficult and metastases are often present at the time of diagnosis.
   C. Prognosis may be better for leiomyosarcoma if the mass is resectable.
   D. Adjunctive chemotherapy has not been shown be beneficial for most gastric tumors, although carboplatin and doxorubicin may be alternated every 3 weeks for three treatments each.
   E. Median survival times are often short (approximately 4 months).

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CHAPTER 32

Gastric Dilatation-Volvulus

Emily Soiderer

Definition

I. Gastric dilatation-volvulus (GDV) is an acute, life-threatening condition in dogs characterized by rapid accumulation of gas in the stomach, malposition of the stomach, increased intragastric pressure, and circulatory shock.
II. Gastric dilatation is an acute overdistension of the stomach with gas, fluid, or ingesta.
III. Gastric volvulus is rotation of the stomach around its long axis in a clockwise direction (when viewed from the ventrodorsal perspective), which obstructs outflow of the duodenum and esophagus and compromises the blood supply to the stomach.

Causes

I. The true cause of GDV is unknown and overall prevalence in the general dog population is low.
II. Middle-aged to older, large- and giant-breed, deep-chested dogs are at greatest risk; however, GDV has also been reported in small breeds (e.g., dachshund, basset hound, pug) and the cat (rare).
III. A combination of environmental, anatomical, physiological, and pathologic risk factors include the following (Rasmussen, 2003; Glickman et al., 2000b):
   A. Increased risk in large- and giant-breed dogs, especially Great Danes
   B. Dogs with a first-degree relative with a history of GDV
   C. Large, thoracic, depth-to-width ratio (deep-chested)
   D. Lean body condition
   E. Age
   F. Behaviors that promote aerophagia
   G. Eating from a raised food bowl
   H. Stress and nervous temperament
   I. Feeding a large volume of food per meal (Raghavan et al., 2004)
   J. Feeding of dry foods containing a fat or oil in the first four listed ingredients (Raghavan et al., 2006)
   K. Pyloric outflow obstruction

Pathophysiology

I. Pyloric outflow is compromised (cause usually unknown) and normal methods of removing air are hindered (eructation, vomiting, pyloric emptying), which leads to accumulation of gas, fluid, and/or ingesta.
   A. The source of gas is likely from aerophagia; however, bacterial fermentation may produce some gas.
   B. Fluid accumulates from normal gastric secretion, ingesta, and translocation from venous obstruction, contributing to dilatation.
   C. Progressive dilatation leads to decreased blood flow to the stomach wall, compression of the caudal vena cava, obstruction of venous return to the heart, portal hypertension, and shock.
II. Progressive dilatation of the stomach secondary to gastroesophageal sphincter and pyloric dysfunction is followed by gastric volvulus; alternatively, gastric volvulus occurs first, which leads to gastric dilatation and/or GDV (Brockman et al., 2000).
III. Whether dilatation occurs before or after volvulus is unknown.
IV. Gastric volvulus most commonly occurs in a clockwise direction around the long axis of the esophagus, with the animal in dorsal recumbency and viewed from the caudoventral perspective (Rasmussen, 2003).
   A. The pylorus and duodenum move cranioventrally and to the left.
   B. Gastric distention increases as the pylorus and the gastric body move clockwise.
   C. The pylorus lies along the left body wall, with the fundus on the right.
   D. The degree of volvulus can be from 90 to 360 degrees.
V. The large, overdistended stomach compresses the caudal vena cava and obstructs blood flow from the caudal half of the body returning to the heart.
   A. Decreased cardiac output
      1. From decreased venous return to the heart
      2. Aggravated by endotoxemia
      3. Myocardial ischemia secondary to decreased coronary artery blood flow
      4. Release of cardiodepressant factors
      5. Arrhythmias common
   B. Decreased portal blood flow
      1. Compression of the portal system by the overdistended stomach
      2. Portal hypertension
      3. Interstitial edema and increased tissue hydrostatic pressure within gastrointestinal (GI) tract
      4. Decreased clearance of endotoxins and bacteria
   C. Splanchnic hypoperfusion
      1. From decreased cardiac output
      2. Caudal vena caval and portal hypertension

3. From gastric distention
4. Myocardial ischemia-induced arrhythmias
5. Reperfusion injury

VI. Hypovolemic shock may arise from sequestration of blood volume and from decreases in venous return to the heart, cardiac output, arterial pressure, and coronary artery blood flow, which lead to inadequate delivery of oxygen to the tissues.

VII. Septic shock from gastric perforation, septic peritonitis, or bacterial translocation from compromise of the gastric mucosal barrier can also lead to inadequate delivery and uptake of oxygen by the tissues.

VIII. Gastric dilatation impairs gastric blood flow as small capillaries in the gastric wall are occluded secondary to increased intragastric pressure.
- A. Venous congestion occurs secondary to dilatation and volvulus.
- B. Increased tissue hydrostatic pressure develops.
- C. The short gastric vessels may twist and become thrombosed or avulse, contributing to hemoabdomen.
- D. Thrombosis of the gastric microvasculature may occur.
- E. Fluid and protein shift from the intravascular space into the gastric lumen and become sequestered.
- F. Gastritis, gastric ulceration, necrosis, and perforation may occur as the gastric mucosa is further compromised.

IX. Thoracic and diaphragmatic movements are restricted by the large distended stomach, which results in hypoventilation, decreased tidal volume, ventilation-perfusion mismatch, and hypoxemia.

X. Intestinal ileus and inadequate perfusion of abdominal organs may develop.
- A. Pancreatic edema and congestion predisposing to pancreatitis
- B. Splenic congestion
- C. Renal failure
- D. Liver congestion and necrosis
- E. Intestinal edema, hemorrhage, and mucosal injury

XI. Reperfusion injury occurs when blood flow is returned to tissues that have been deprived and may lead to tissue damage.
- A. Normal waste products and abnormal toxins accumulate when there is inadequate perfusion.
- B. Inflammatory mediators and oxygen free radicals cause local tissue damage as it is reperfused.
- C. Reperfusion injury may lead to multiorgan failure.
- D. Disseminated intravascular coagulation occurs secondary to the intense inflammatory reaction.

Clinical Signs

I. Restlessness
II. Ptyalism, retching
III. Abdominal distention, pain
IV. Weakness, collapse
V. Tachypnea, dyspnea

Diagnosis

I. A presumptive diagnosis of gastric dilatation can be made based on signalment, history, and physical examination.

II. Physical examination findings may include some or all the following:
- A. Distended, painful, tympanic abdomen
- B. Distention not always seen in giant-breed dogs from dilated stomach surrounded by the rib cage (Brockman and Holt, 2000)
- C. Tachycardia, poor peripheral pulse quality
- D. Pale, tacky mucous membranes, prolonged capillary refill time
- E. Tachypnea

III. Radiography of the abdomen is used to assess gastric position and to confirm gastric dilatation and volvulus.
- A. Radiography should be performed *only* after fluid therapy and gastric decompression have been started.
- B. Right lateral abdominal view is the radiographic view of choice and findings may include:
  1. Large, gas-distended stomach
  2. Gas-filled intestines caudally displaced by the stomach
  3. Soft tissue compartmentalization, with a fold of the stomach crossing the dilated stomach, indicating presence of a gastric volvulus
  4. Splenomegaly
  5. Loss of abdominal detail
  6. Free gas from gastric necrosis and rupture or an iatrogenic source (abdominocentesis)
  7. Small caudal vena cava

IV. Hematological and coagulation assays may show the following:
- A. Hemoconcentration
- B. A stress or inflammatory leukogram and possible left shift
- C. Leukopenia suggestive of overwhelming inflammation or endotoxic shock
- D. Thrombocytopenia indicating a hypercoagulable state or blood loss
- E. Prolonged activated clotting time (ACT), prothrombin time (PT), and activated partial thromboplastin time (APTT)

V. Serum chemistry abnormalities may include the following:
- A. Electrolyte abnormalities: most commonly hypokalemia
- B. Hypoalbuminemia
- C. Azotemia
- D. Hepatocellular injury: elevated alanine transferase
- E. Biliary stasis: elevated alkaline phosphatase, bilirubinemia
- F. Pancreatic enzyme elevation
- G. Increased plasma lactate
  1. It is used as a predictor of gastric necrosis and eventual outcome.
  2. If lactate concentration is <6 mmol/L, the dog (99%) is likely to survive.
  3. Median plasma lactate concentration in dogs with gastric necrosis was significantly higher than those without necrosis (de Papp et al., 1999).

VI. Acid–base disorders are common.
- A. Metabolic acidosis occurs secondary to decreased tissue perfusion and a shift by the tissues to anaerobic metabolism resulting in lactic acidosis.

B. Metabolic alkalosis can occur from sequestration of hydrogen ions in the gastric lumen.

Differential Diagnosis

I. Gastric dilatation alone
II. Splenic torsion
III. Mesenteric volvulus
IV. Peritonitis

Medical Treatment

I. Initial emergency treatment is aimed at stabilizing the cardiovascular and respiratory systems; treatment is not delayed by diagnostic tests.
II. Packed cell volume (PCV), total solids (TS), and blood glucose (BG) can be quickly obtained at presentation and are useful for guiding fluid therapy.
III. Aggressive fluid therapy is initiated followed by gastric decompression.
   A. Intravenous access is obtained with two large-bore catheters via the cephalic veins or a jugular catheter.
   B. The saphenous veins are avoided, because venous return to the heart from the caudal half of the body is obstructed by the dilated stomach.
   C. Crystalloids are administered at rates for shock (60 to 90 mL/kg/hr IV).
   D. Colloids are beneficial in raising arterial blood pressure and maintaining plasma oncotic pressure.
      1. Hetastarch is given at 5 to 10 mL/kg IV bolus or at a maintenance rate of 20 mL/kg/day IV.
      2. Colloids can be combined with crystalloids (10 to 40 mL/kg IV).
   E. Hypertonic (7%) saline combined with dextran-70 (6%) has also been used for rapid expansion of intravascular volume (Allen et al., 1991; Schertel et al., 1997).
      1. Dose: 5 mL/kg IV over 5 to 15 minutes
      2. Usually reserved for rapidly deteriorating, hypovolemic animals
IV. Monitor electrocardiography (ECG) and blood pressure during the stabilization period to judge effectiveness of therapy.
   A. Heart rate and blood pressure are improved.
   B. Mucous membrane color, capillary refill time, and pulse quality improve.
   C. Positive inotropes are considered if appropriate fluid therapy does not maintain mean arterial pressures >80 mm Hg.
      1. Dobutamine 5 to 15 μg/kg/min IV (Plumb, 2005)
      2. Dopamine 1 to 3 μg/kg/min IV (Plumb, 2005)
V. Gastric decompression is undertaken immediately.
   A. Orogastric tube decompression
      1. The tube is measured from the tip of the nose to the xiphoid and a piece of tape is placed on the tube at that mark.
      2. A mouth gag is inserted (a roll of 2-inch tape works well) and held by an assistant grasping the dog's muzzle.
      3. Sedation and analgesia are helpful to decrease stress of the dog and ease passage of the tube.
         a. Hydromorphone 0.05 to 0.1 mg/kg IV or buprenorphine 0.005 to 0.01 mg/kg IV combined with diazepam or midazolam 0.2 mg/kg IV
         b. Minimal cardiovascular effects
      4. The orogastric tube is lubricated and inserted into the esophagus.
      5. If resistance is met, the tube can be gently rotated and/or the dog repositioned.
      6. The tube is *never* forced caudally because of the risk of perforating the esophagus.
      7. Once the tube has reached the stomach, gas and fluid should escape.
      8. Water (7 to 10 mL/kg) can be used to lavage the stomach and help remove more solid matter (Rasmussen, 2003).
      9. If water is not recovered, discontinue lavaging, as perforation may be present.
   B. Trocarization
      1. Trocarization is often used when decompression with an orogastric tube fails.
      2. A tympanic area on the dorsolateral abdomen is clipped and aseptically prepared.
      3. A large-bore, over-the-needle IV catheter is inserted through the skin and into the stomach.
         a. The stylet is removed and the catheter hub is checked for an acrid odor and/or bubbling of fluid.
         b. A large-gauge needle can also be used instead of the IV catheter.
      4. Ballottement of the abdomen helps mobilize and release gas after the catheter has been inserted.
   C. Temporary gastrostomy
      1. This technique is reserved for those animals that are too unstable for surgery.
      2. The technique is used if gastric dilatation is severe, and if attempts to decompress via orogastric tube and trocarization have failed.
   D. Adequate decompression essential before surgery
      1. After decompression, the stomach may return to its normal position.
      2. Surgery is still required in these cases to assess gastric viability and prevent recurrence.
VI. Ventricular arrhythmias are common and can occur up to 24 hours later, so continuous ECG monitoring is warranted.
   A. Treatment of arrhythmias is first aimed at normalizing fluid deficits, acid-base and electrolyte abnormalities, and providing adequate analgesia.
   B. For dogs with pulse deficits, multifocal ventricular premature contractions, and a ventricular rate >160 beats per minute, consider antiarrhythmic drugs.
   C. Lidocaine can be given at 2 mg/kg IV bolus and repeated up to a total dose of 8 mg/kg IV (Plumb, 2005).
   D. Lidocaine constant rate infusion (CRI) can be started at 25 to 50 μg/kg/min IV.

E. Other drug choices include procainamide 6 to 8 mg/kg IV bolus over 5 minutes, possibly followed by a CRI of 25 to 50 μg/kg/min IV, and magnesium sulfate 50 mg/kg IV bolus over 5 minutes, possibly followed by CRI of 100 μg/kg/min IV for 6 hours (Rasmussen, 2003).

Surgical Treatment

I. General principles
   A. After adequate cardiovascular stabilization, surgical treatment is pursued.
      1. Surgery must not be delayed, owing to risk of perforation of a necrotic stomach and recurrence of gastric dilation.
      2. Recurrence rates of GDV with medical management alone are 75% to 80% (Meyer-Lindenberg et al., 1993).
   B. The goals of surgery are as follows:
      1. Anatomic repositioning of the stomach
      2. Assessment of gastric and splenic viability
      3. Partial gastrectomy and/or splenectomy, if indicated
      4. Permanent gastropexy to prevent recurrence

II. Anesthesia
   A. Preanesthetics
      1. Hydromorphone 0.05 to 0.1 mg/kg IM, IV (Plumb, 2005)
      2. Diazepam 0.2 to 0.3 mg/kg IV (Plumb, 2005)
   B. Induction agents
      1. Those that do not cause significant cardiovascular disturbances are preferred.
      2. Lower doses than those listed below may be sufficient; give only to effect.
      3. Ketamine 6.6 mg/kg IV is combined with diazepam 0.5 mg/kg IV.
      4. Etomidate is given at 1 mg/kg IV to effect and can be combined with diazepam 0.25 mg/kg IV.
      5. Propofol is titrated to effect.
         a. It is only used in well-hydrated, hemodynamically stable animals.
         b. Similar precautions apply to thiopental (Dodam, 2003).
      6. Mask induction with inhalation agents can be done, but lack of rapid airway access (intubation) is a disadvantage.
   C. Maintenance
      1. Isoflurane or sevoflurane
      2. Combination of inhalation agent and opioid (fentanyl 5 to 15 μg/kg/hr IV CRI (Dodam, 2003)
   D. Assisted ventilation often necessary
   E. Monitoring
      1. Heart rate
      2. Respiratory rate
      3. Arterial blood pressure
      4. Mucous membrane color and capillary refill time
      5. Peripheral pulse quality
      6. End-tidal CO_2
      7. Pulse oximetry
      8. ECG
      9. Blood gases

III. Celiotomy
   A. Make a ventral midline incision beginning at the xiphoid and extending just cranial to the pubis.
   B. Take care when incising the linea alba to avoid puncturing the distended stomach.
   C. Once the abdomen is exposed, identify the distended stomach with the greater omentum stretched over its surface.
   D. Further gastric decompression is performed; either by passage of an orogastric tube by an assistant, or trocarization by the surgeon.
   E. Once the stomach is decompressed, it is returned to its normal position.
      1. With the surgeon standing on the dog's right side, the pylorus is found in the left dorsal abdomen and is gently grasped with the right hand.
      2. The left hand rests on the body of the stomach on the dog's right side.
      3. The pylorus is drawn ventrally and toward the right while at the same time the body of the stomach is pushed dorsally and toward the left.
   F. Once the stomach is in its normal position, an initial assessment of its viability is made.
   G. An abdominal exploratory surgery is then performed.
      1. It allows assessment of the spleen and its vasculature, identification of underlying pathology, and gives the stomach time to reperfuse.
      2. If the splenic vessels are thrombosed, a splenectomy may be indicated.
   H. The stomach is carefully evaluated for areas of necrosis and perforation.
      1. Color and texture are currently the most useful indicators of viability; other characteristics such as tone and peristalsis are also assessed.
      2. Abnormal areas consistent with necrosis are often gray to green, black, or blue-black in color.
      3. Thinning of the abnormal gastric wall can be appreciated upon palpation.
      4. Incising questionable areas in the seromuscular layer may reveal poor perfusion.
      5. Fluorescein dye testing is unreliable (Wheaton et al., 1986).
      6. Assessing capillary blood flow in the stomach wall using laser Doppler flowmetry may be useful (Monnet et al., 2006).
   I. If necrosis is present, determine the extent (usually involves fundus along the greater curvature) and perform a partial gastrectomy.

IV. Gastropexy techniques
   A. The purpose of the gastropexy is to form a permanent adhesion between the stomach and the right body wall to prevent the stomach from becoming malpositioned.
      1. The serosa of the stomach and the peritoneum of the body wall must be disrupted to obtain an adhesion.

2. Multiple gastropexy techniques have been developed, including laparoscopic and laparoscopic-assisted techniques.

B. With an incisional gastropexy, the stomach is drawn to the right body wall to a site that allows the stomach to lie in a normal position once the abdomen is closed and a normal posture is resumed.
   1. This area is usually caudal to the last rib and approximately one third the distance from ventral midline dorsally.
   2. An incision is made through the seromuscular layer of the stomach parallel to its long axis, at the level of the pyloric antrum, midway between the lesser and greater curvatures.
   3. An incision of corresponding length is made in the right abdominal wall just caudal to the last rib through the peritoneum and into the transverse abdominal muscle.
   4. The stomach is brought up to the right abdominal wall and the dorsal incisions are sutured together with monofilament delayed-absorbable (e.g., polydioxanone) or monofilament nonabsorbable (e.g., polypropylene) suture in a simple continuous pattern.
   5. The ventral incisions are then apposed in a similar fashion.
   6. This is a quick and simple gastropexy technique that forms a strong adhesion and has a low recurrence rate (MacCoy et al., 1982).

C. With a belt-loop gastropexy, two parallel incisions (approximately 2 cm apart) are made through the peritoneum and transverse abdominal muscle behind the last rib on the right lateral body wall.
   1. A tunnel is created with blunt dissection between the incisions.
   2. A U-shaped incision is then made through the seromuscular layer of the stomach in the pyloric antrum, including an epiploic branch of the gastroepiploic artery and vein at the base of the flap.
   3. The flap is elevated and then brought through the muscular tunnel created in the abdominal wall and sutured back into place on the stomach.
   4. This technique forms a slightly stronger adhesion than incisional or tube gastropexy; however, it is technically challenging and takes longer to perform (Whitney et al., 1989).

D. A circumcostal gastropexy is very similar to the belt-loop method.
   1. A tunnel is formed under the 11th or 12th ribs at the level of the costochondral junction; the flap is passed under the rib, and sutured back to its original area on the stomach.
   2. This is the strongest of the gastropexies; however, it is technically challenging and potential complications include pneumothorax (if the diaphragm is penetrated) and rib fracture (Woolfson and Kostolich, 1986).

E. A tube gastropexy requires a stab incision through the right abdominal wall, caudal to the last rib, and approximately one third of the way up from the ventral midline.
   1. The stomach should rest at this site without excessive tension or displacement.
   2. The mushroom tip end of a Pezzer tube is brought through the incision in the abdominal wall and into the abdomen.
   3. A purse-string suture is placed in the pyloric antrum halfway between the lesser and greater curvatures in an area where the mushroom tip of the Pezzer tube will not block pyloric outflow.
   4. A stab incision is then made into the stomach in the center of the purse-string, the mushroom tip of the tube is inserted into the stomach, and the purse-string is tied snugly.
   5. Sutures (4 to 5) are preplaced between the pyloric antrum and the body wall surrounding the tube where it exits.
   6. The stomach is brought up to the body wall and the sutures are tied securely and omentum is wrapped around the site.
   7. The tube is secured to the skin using the Chinese finger trap method or with friction sutures, and a bandage is applied to the abdomen.
   8. This is the weakest of the gastropexies and it requires entering the lumen of the stomach.
   9. Advantages include ease of placement, ability to decompress the stomach postoperatively, and provision of an enteral route for nutritional support of anorectic animals (Flanders et al., 1984).

F. Laparoscopic and laparoscopic-assisted gastropexies have been investigated for prophylaxis and may become common as laparoscopy becomes more widely available (Wilson et al., 1996; Rawlings et al., 2002).

V. Perioperative antibiotics
   A. Cefazolin 22 mg/kg IV is given at induction and may be continued postoperatively if the gastric and intestinal mucosal barrier has been damaged.
   B. If sepsis or perforation has occurred, broad-spectrum antibiotics are administered.

Monitoring of Animal

I. IV fluid therapy is continued, and electrolytes and acid–base balance are monitored.
   A. Postoperative hypokalemia may occur and is supplemented appropriately.
   B. IV fluid therapy requirements vary, but are continued until oral fluid intake is adequate to maintain hydration.

II. Food is usually offered 12 to 24 hours postoperatively.

III. Hypoalbuminemia/hypoproteinemia may occur from losses through damaged GI mucosa, and colloidal support may be necessary.

IV. Also monitor for anemia.
   A. For PCVs <20%, consider transfusion of packed red blood cells or whole blood.
   B. For total solids <4.0 gm/dL, initiate colloidal support.

V. Hemodynamic status is monitored through intermittent or continuous measurement of the following:
   A. Blood pressure
   B. Urine output
   C. ECG (see Medical Treatment)
   D. Central venous pressure

VI. Monitor for sepsis via repeated physical examination, complete blood counts, and serum biochemistry abnormalities.
   A. Abdominocentesis or diagnostic peritoneal lavage can identify intracellular bacteria indicating septic peritonitis.
   B. Emergency surgery is indicated if septic peritonitis is confirmed.
   C. Perform blood and urine cultures if septicemia is suspected from bacterial translocation.

VII. Disseminated intravascular coagulation is a potential complication and is suspected with the following:
   A. Petechial and ecchymotic hemorrhages
   B. Unexplained blood loss
   C. Worsening hemodynamic parameters or organ function
   D. Prolonged PT and APTT, decreased fibrinogen, increased fibrinogen degradation products (D-dimers), and thrombocytopenia

VIII. Gastritis secondary to mucosal ischemia is a common postoperative complication and may cause vomiting.
   A. If severe or persistent vomiting occurs, a centrally acting antiemetic is useful.
   B. Secondary gastric ulcers may occur, and H_2-receptor blockers help to reduce acidity.
      1. Famotidine 0.5 mg/kg IV, SC, PO BID
      2. Ranitidine 0.5 mg/kg IV, PO BID
      3. Cimetidine 5 mg/kg IV, IM, PO TID to QID

IX. High mortality rates have been associated with GDV in the past.
   A. More recently, mortality rates of 15% (Brockman et al., 1995), 18% (Brourman et al., 1996), and 24.3% (Glickman et al., 1998) have been reported with surgical intervention.
   B. Dogs with gastric necrosis and perforation had lower survival rates (de Papp et al., 1999).
   C. Recurrence rates of GDV after gastropexy is <10% (Glickman et al., 1998).

X. Prevention involves the following:
   A. Feeding multiple, small meals per day that are low in fat and oil
   B. Feeding from nonraised food bowls
   C. Minimizing stress

XI. Prophylactic gastropexies are recommended in dogs at risk for GDV and can be easily performed at the time of ovariohysterectomy or castration via laparotomy or laparoscopy.

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CHAPTER 33

Diseases of the Small Intestines

Debra L. Zoran

CONGENITAL/DEVELOPMENTAL DISORDERS

See Table 33-1.

INFECTIOUS DISEASES

Viral Infections

Definition and Causes

I. A number of viruses are implicated as enteric pathogens in dogs and cats, especially in puppies and kittens <6 months of age.
II. Primary intestinal viruses in dogs include canine parvoviruses (CPV-1, CPV-2), canine coronavirus (CCV), distemper virus, and rotavirus.
   A. Astrovirus, enterovirus, herpesvirus, and parainfluenza viruses have been identified in feces, but their pathogenicity is unknown (Greene, 2006).
   B. Both CPV-2a and CPV-2b are responsible for most illness, with CPV-2b as the most common isolate in the United States and Japan, and CPV-2a as the most common isolate in the Far East (Greene, 2006).
III. The primary intestinal viruses in cats include parvovirus (panleukopenia), coronavirus (enteric or feline infectious peritonitis [FIP] virus), rotavirus, and astrovirus.
   A. Feline immunodeficiency virus (FIV) and feline leukemia virus (FeLV) may cause enteric signs as part of the overall infection.
   B. Other viruses have been identified in feline feces, including torovirus-like particles, reovirus, calicivirus, and picornavirus-like particles, but their significance is unknown (Greene, 2006).

Pathophysiology

I. Viral infections cause disease by invading the enterocytes lining the intestinal villi or crypts, in most instances from oronasal exposure to contaminated feces.
II. CPV-2 is highly contagious, because the organism is extremely resistant in the environment.
   A. It may persist on the dog's hair coat, caretaker clothing, or floors for >5 months; it is resistant to normal disinfectants.
   B. Only sodium hypochlorite (common household bleach) is known to be consistently effective.
III. The severity of clinical signs is highly variable.
   A. Villous cell damage (e.g., coronavirus or rotavirus infection) is well tolerated (less severe clinical signs), because affected enterocytes are soon replaced.
   B. Viral infections causing crypt cell damage or destruction (e.g., CPV-2 infection) result in severe clinical signs.
      1. Normal enterocyte proliferation is completely disrupted from destruction of crypt cells.
      2. Massive loss of villous absorptive and barrier functions occur, predisposing to ascending infections, endotoxemia, and severe fluid and electrolyte losses.

Clinical Signs

I. Canine parvovirus (CPV-2b)
   A. Infection can cause inapparent or subclinical infection or may result in acute, fatal disease.
   B. Lethargy , anorexia, depression, dehydration, vomiting, and diarrhea are the most common signs.
      1. The most severe clinical signs are seen in dogs <4 months of age because of their lack of protective immunity and increased number of rapidly dividing cells.
      2. The clinical course ranges from 4 to 7 days.
   C. Diarrhea is often profuse and hemorrhagic, and vomiting may be intractable.
   D. Fever and leucopenia are common initially, but hypothermia, disseminated intravascular coagulation (DIC), and endotoxic shock occur terminally with septicemia, which may develop within 48 hours in a fulminant infection.
   E. Certain breeds have increased susceptibility, including the rottweiler, Doberman pinscher, American pit bull terrier, German shepherd dog, Labrador retriever, and Alaskan sled dog breeds.
   F. Most adult dogs infected with parvovirus have subclinical disease.
   G. Puppies infected in utero or perinatally (<8 weeks) can develop myocarditis that may progress to cardiomyopathy and sudden death.
   H. Other complications include thrombosis (from DIC), erythema multiforme, hypoglycemia, and septicemia.
II. Canine coronavirus
   A. Infection is via the fecal-oral route, signs are uncommon in adult dogs, and they are generally mild and self-limiting in weanling puppies.

TABLE 33-1

Congenital and Developmental Disorders

DISORDER	DEFINITION AND CAUSE	CLINICAL SIGNS	DIAGNOSIS	TREATMENT
Intestinal atresia	Congenital agenesis of a segment of intestine Occurs in the small intestine in dogs and in the large intestine in cats Three types of atresia have been reported (Guilford et al., 1996): *Membrane atresia:* normal intestine with a luminal membrane that prevents normal flow of ingesta *Cord atresia*: two segments of intestine connected by tissue *Blind end atresia*: two segments of intestine not connected together	High neonatal mortality from inability to digest or process milk or other ingesta Failure to thrive, poor growth, and death are most common in puppies Kittens may develop enlarged abdomens and vomiting owing to colonic obstruction	Clinical signs and signalment are suggestive Definitive diagnosis is by documentation of the anomaly (from imaging studies, at surgery or postmortem)	Treatment is removal of the affected segment of bowel by intestinal resection and anastomosis In kittens, a subtotal colectomy may be required if a significant segment of the large intestine is involved
Intestinal diverticulum	Rare condition in both dogs and cats Most commonly seen in the jejunum in dogs	Many cases are subclinical Clinical signs are nonspecific, including vomiting, diarrhea, weight loss, or inappetence and occur from diverticulitis or diverticular perforation or obstruction	Imaging studies, such as contrast radiographs or ultrasonography, may identify the abnormal structure Definitive diagnosis is made by visualizing the defect (at surgery)	Resection and anastomosis of the affected segment of the intestine are curative In animals not exhibiting any clinical signs, the best approach is often benign neglect
Selective cobalamin malabsorption	Selective inability in the giant schnauzer, border collie, and shar-pei to absorb cobalamin (vitamin B_{12}) (Fyfe et al., 1989; Guilford et al., 1996) Inherited in giant schnauzers as an autosomal recessive trait Results in a defect in the ileal receptor for the cobalamin and intrinsic factor complex, called *cubulin* (Fyfe et al., 1989)	Inappetence and failure to thrive (poor weight gain and lethargy) Clinical signs occur after weaning, at 6-12 weeks of age in giant schnauzers, and often later in border collies and shar-peis	Signalment and history are suggestive Definitive diagnosis is made by finding an extremely low serum cobalamin concentration (normal is 6.7-17.4 µg/L) Dyserythropoiesis is evident by 8-16 weeks of age, with development of a nonregenerative, normochromic normocytic anemia (PCV 27%-31%) by 20-22 weeks of age Abnormal granulopoiesis and low neutrophil numbers may also be seen	Parenteral cyanocobalamin (0.25-1.0 mg SC, IM weekly for 4 weeks, then every 3-6 mo indefinitely) Response is rapid Appetite returns in 24-48 hours, reticulocytosis occurs in 3-4 days, and methylmalonic aciduria stops within 1 week Reevaluate cobalamin levels every 3-6 months Neuter affected dogs

PCV, Packed cell volume.

TABLE 33-1

Congenital and Developmental Disorders—*cont'd*

DISORDER	DEFINITION AND CAUSE	CLINICAL SIGNS	DIAGNOSIS	TREATMENT
	Defect is not defined in either the border collie or shar-pei		Cobalamin deficiency leads to reduced activity of two enzymes important in energy (succinyl CoA) and amino acid synthesis (methionine), which results in the development of methylmalonic aciduria (Fyfe et al., 1989)	
Short bowel syndrome	Rare condition in both dogs and cats Lack of development of a major segment of the small intestine (Guilford et al., 1996; Simpson and Hall, 2000) Acquired short bowel syndrome is more common and is from surgical removal of a large segment of bowel Dogs are able to compensate if 30-40 cm of small intestine are present; cats require 18-20 cm of small bowel for adequate function	Appropriate historical and clinical signs in a young puppy or kitten are suggestive of a congenital defect Clinical signs include a failure to gain weight or weight loss; poor body or coat condition; and chronic, small bowel diarrhea with characteristics of severe malabsorption (steatorrhea, abnormal color, etc.)	Definitive diagnosis is made from imaging studies (e.g., contrast radiographs) showing the abnormally short bowel	There is no specific therapy for short bowel syndrome Compensation can occur if enough of the bowel remains; these animals have soft or semi-formed feces and are able to maintain body weight Feed highly digestible diets to maximize digestion of food and minimize the amount of feces produced
Gluten enteropathy of Irish setter	Autosomal recessive disorder linked to the MHC genes *MQA* and *DQB* in affected dogs (Garden et al., 2000) Disease causes a progressive loss of villous height and increased numbers of goblet cells and intraepithelial lymphocytes Wheat gluten may also have direct toxic effects on the intestinal mucosa of affected dogs	Inappetence, poor growth (stunted or small stature), and chronic diarrhea are the most common signs Diarrhea usually starts in puppies immediately postweaning (4-6 weeks of age) Signs may include semiformed feces or severe, liquid and explosive small bowel diarrhea	Typical history and clinical signs in a young Irish setter are suggestive Affected dogs may have abnormal sugar permeability tests, decreased serum folate (normal serum cobalamin), and negative duodenal juice culture (e.g., no evidence of bacterial overgrowth) Intestinal biopsy reveals vilous atrophy and increased numbers of intraepithelial lymphocytes (distinguish from IBD) A presumptive diagnosis is based on the resolution of clinical signs after the withdrawal of dietary gluten	Only diets that contain no wheat products are fed to Irish setters with this problem Affected dogs will be normal within 4-6 weeks of the diet change Neuter affected dogs

CoA, Coenzyme A; *MHC,* major histocompatibility complex; *IBD*, inflammatory bowel disease.

Continued

TABLE 33-1

Congenital and Developmental Disorders—*cont'd*

DISORDER	DEFINITION AND CAUSE	CLINICAL SIGNS	DIAGNOSIS	TREATMENT
			A definitive diagnosis is confirmed when the clinical signs return on challenge with gluten	
Enteropathy of soft-coated wheaten terriers	Immunological defect that results in a protein-losing enteropathy and nephropathy of unknown cause or inheritance (Vaden et al., 2000) The pathogenic cause of the protein-losing enteropathy is unknown, but wheat gluten does not appear to be the trigger	Typical signs include vomiting, diarrhea, and weight loss (which may be severe) Affected dogs are young, and the most severely affected may die before the age of 5 years In severely hypoproteinemic dogs, ascites and peripheral edema may be observed Dogs that survive the initial insults often develop renal insufficiency secondary to the chronic protein-losing glomerulopathy	This enteropathy is characterized by the presence of IBD with varying morphological characteristics, but lymphocytes and plasma cells often predominate Intestinal protein loss occurs from IBD, lymphangiectasia, or both, and may be detected by measuring fecal α_1-protease inhibitor levels Protein-losing nephropathy occurs secondary to the chronic inflammatory disease in the intestines Intestinal biopsy is necessary to confirm the presence of IBD and lymphangiectasia There is no definitive test for this specific enteropathy other than finding the concurrent GI and renal protein loss in this breed	Treatment of affected dogs is symptomatic, using immunosuppressive doses of prednisolone (2-4 mg/kg/day PO) as for IBD; antibiotics as needed for control of small intestinal bacterial overgrowth; and a low-fat, highly digestible diet to minimize malabsorption and diarrhea Neuter affected dogs
Immunoproliferative small intestinal disease of basenjis	Disease results in the development of chronic diarrhea, gastropathy, and hypergammaglobulinemia in young basenjis (Breitschwerdt et al., 1984) Mode of inheritance is still undetermined	Chronic, intractable diarrhea and emaciation are the most common signs Some dogs will have concurrent vomiting from hypergastrinemia and mucosal hyperplasia Young basenjis may have severe fulminating disease, while adult dogs often have chronic, intermittent diarrhea with acute exacerbations	Confirmation of the diagnosis is by finding lymphoplasmacytic IBD, hypertrophic gastropathy, and concurrent protein-losing enteropathy (hypoalbuminemia, elevated fecal α_1-protease inhibitor levels) in a young basenji	Treatment of basenjis with severe immunoproliferative enteropathy is generally unsuccessful In less severely affected dogs, aggressive treatment of IBD is helpful Novel antigen diets may also be helpful Neuter affected dogs

GI, Gastrointestinal.

B. Neonatal puppies have the most severe clinical signs (vomiting, diarrhea, anorexia), and are often concurrently infected with other viruses, intestinal parasites, or bacteria (e.g., salmonellosis, campylobacteriosis), and are housed in crowded, stressful living conditions, with poor hygiene and nutrition.
C. Fever and bloody diarrhea are very uncommon in puppies with coronavirus enteritis alone, and death from diarrheal disease is very uncommon, except in situations where dehydration or acidosis is untreated.
D. The virus is not as stable in the environment as parvoviruses nor as resistant to disinfectants, so appropriate kennel hygiene is highly beneficial.

III. Canine distemper virus
A. Explosive diarrhea with vomiting, dehydration, and depression may occur before onset of central nervous system signs.
B. The most common clinical signs are lethargy, anorexia, fever, and upper respiratory tract infection, which may be followed by mild gastrointestinal (GI) signs.

IV. Canine rotavirus
A. Rotavirus infections are common enteric pathogens in dogs that are transmitted by the fecal-oral route, but rarely cause more than mild, mucoid to watery diarrhea.
B. Very young puppies (<2 weeks) may develop a fever or more severe signs.

V. Feline panleukopenia virus
A. Fever, anorexia, severe diarrhea, and intractable vomiting are common in young, unvaccinated kittens, with the highest morbidity and mortality occurring between 3 and 5 months of age.
B. In adult cats or in kittens from a well-vaccinated queen, anorexia, lethargy, and mild GI signs may occur, but usually the infection is self-limiting and subclinical.
C. Clinical disease is rare in vaccinated cats and in kittens born to vaccinated queens.
D. Unvaccinated kittens with peracute infection have a high morbidity and mortality rate from severe leukopenia and anemia, and may be found dehydrated, hypothermic, and comatose within 12 hours of onset.

VI. Feline enteric coronavirus (FEC) and FIP virus
A. Infections with enteric coronavirus are most often subclinical, especially in adult cats, but may cause mild, self-limiting diarrhea and fever in young or immunocompromised cats.
B. Clinically apparent FEC infections are most common in kittens 4 to 12 weeks of age.
C. FEC is nearly ubiquitous, especially in colonies, and inapparent infection is common.
D. Clinical signs in cats infected with FIP virus are variable (see Chapter 112).
1. FIP granulomas of the GI tract are known to occur in 10% to 20% of cases and cause chronic, intermittent to persistent small or large bowel diarrhea (Harvey et al., 1996).
2. The lesions may be large enough to be palpable (mass effect), but in many cases are only detected by ultrasonography or exploratory surgery.

VII. Feline leukemia virus
A. In cats that develop alimentary lymphosarcoma, signs of bowel obstruction (anorexia, vomiting, diarrhea, weight loss) or malabsorption (diarrhea, weight loss) may be observed.
B. A panleukopenia-like syndrome (small bowel diarrhea, weight loss) is also occasionally observed.

VIII. Feline immunodeficiency virus
A. The most common GI signs are anorexia, emaciation, and chronic diarrhea, which are secondary to villous atrophy and granulomatous inflammation in the intestinal tract.
B. In some cats, diarrhea may be chronic and intermittent, and not result in weight loss; however, in immunocompromised cats, diarrhea may be very severe and associated with high mortality.

Diagnosis

I. Hematological changes in viral infections
A. Parvoviruses of dogs and cats cause severe leukopenia (primarily neutropenia), and remaining neutrophils may have toxic changes.
1. Cats are also usually anemic (mild, nonregenerative) and thrombocytopenic.
2. Both dogs and cats exhibit a neutrophilia during the recovery phase.
B. Distemper virus in dogs causes leukopenia from lymphopenia.
1. Blood smears may show reactive lymphocytes and occasionally viral inclusion bodies in red blood cells (RBCs) or neutrophils.
2. Thrombocytopenia may also occur, but varies in intensity.
C. CCV, FEC, rotavirus, and other enteric viruses do not usually cause significant changes in the hemogram.
D. FIP is usually associated with a nonregenerative anemia, leukopenia or leukocytosis (with a left shift), and increased serum globulins.

II. Diagnostic tests for viral infection
A. Immunological assays (e.g., commercial enzyme-linked immunosorbent assay [ELISA] for antigen or antibody) are available for detection of parvovirus (antigen), CCV (antibody), FeLV (antigen), rotavirus (antigen, outside of the United States), and FIV (antibody).
1. The tests have a high degree of sensitivity (low false negatives) and specificity (low false positives).
2. Following vaccination with a modified live vaccine for parvovirus, some fecal shedding of virus occurs up to a week and is detected on fecal ELISA assay.
3. The most common reason for a false-negative parvovirus ELISA is testing before active shedding has started or after the brief period of shedding has stopped (10 to 12 days postinfection).
B. Serology for viral infections is useful if the antigen is available for detection (e.g., present in the tissue assayed), and often requires acute and convalescent serum samples.

1. The sensitivity and specificity of serological assays are low or moderate.
2. The presence of large amounts of immunoglobulin M suggests a recent or active infection.
3. A positive hemaglutination titer (HA) present in dog or cat after ≥3 days of clinical illness is diagnostic of CPV-2b or feline panleukopenia infection.
4. FEC can only be confirmed with immunohistochemical or immunofluorescent staining of gut biopsies (Giordano et al., 2005).
5. Definitive diagnosis of FIP requires histopathology, with clinical diagnosis primarily one of exclusion.

C. Viral isolation is rarely used because sample quality is extremely important, and both susceptible cell culture systems and antiserum against the virus must be available.
D. CCV and FEC do not grow well in tissue or cell culture systems.
E. Electron microscopic detection of viral particles in feces rapidly confirms the presence of virus, but requires specialized equipment and a high concentration of virus.
F. Applied molecular diagnostics are increasingly important in the detection of viral infections.
1. The two most common methods are immunoblotting (Western blot) and polymerase chain reaction (PCR) testing.
2. The sensitivity and specificity of these methods are very high and allow detection of preclinical disease.
3. They require only a small quantity of sample for detection of the virus.
4. They require specialized equipment and time and are not yet used for routine diagnosis except in cases where ELISA or virus isolation is not available or diagnostic (e.g., FIP).
5. Detection of FIP messenger ribonucleic acid (mRNA) via PCR in circulating monocytes or in macrophages in effusions is a highly promising new technique.

G. Tissue biopsy, necropsy, and light microscopy are diagnostic in most cases of canine distemper, feline panleukopenia, canine parvovirus, and FIP.

Differential Diagnosis

I. Nonspecific enteritis, including dietary indiscretion or dietary intolerance
II. Bacterial or parasitic enteropathies
III. Toxin-induced intestinal disease
IV. GI obstruction: foreign bodies, intussusception, masses
V. Acute pancreatitis, hepatitis, or other extra-GI inflammatory disease

Treatment

I. In mild cases, supportive care provided on an outpatient basis is adequate.
A. Withhold food for 24 to 48 hours and provide water in small, frequent quantities or as ice cubes.
1. Oral hydration solutions *(Enterolyte, Rebound)* may be given instead of water.
2. The goal of oral fluid therapy is to provide at least 40 to 60 mL/kg/day.

B. Once vomiting resolves, food is reintroduced as small quantities of a bland, highly digestible diet.
1. Examples for dogs include low-fat chicken or turkey with rice or potato, or commercial diets (e.g., Hill's i/d, Purina Veterinary Diets EN, Royal Canin Low Fat, Eukanuba Low Residue).
2. In cats, low-fat intestinal diets may not be palatable enough, so recovery diets (e.g., Hill's a/d) or canned maintenance foods are also offered.
3. Enteral nutrition is essential for recovery of enterocytes (especially in parvoviral infections) and return of normal gut motility patterns, so is reintroduced as soon as possible.
4. In some cases, feeding a liquid diet through a nasoesophageal tube may be necessary.

C. Do not withhold food for >3 days without further nutritional or fluid support, especially in cats (to prevent the risk of hepatic lipidosis) or young kittens and puppies.
D. Once vomiting or diarrhea resolves, reintroduce the regular diet over a period of 3 to 7 days.

II. Parenteral fluid therapy is required for dogs and cats that are dehydrated, have severe vomiting or diarrhea, or are anorectic for >3 days.
A. Lactated Ringer's solution or Normosol-R is given at a rate of 40 to 60 mL/kg/day IV, SC, with additional fluids to correct dehydration and replacing ongoing losses.
B. Potassium chloride (20 to 40 mEq/L) is added to the fluids if anorexia, vomiting, and diarrhea are severe, or if hypokalemia is present.
C. Replacement of magnesium sulfate may also be required if serum concentrations of magnesium are low.
D. In animals with low serum magnesium and hypokalemia, serum potassium does not return to normal until magnesium levels are corrected.
E. Hypoglycemia is a potential complication of severe enteritis in young animals, and requires addition of dextrose to the fluids after the animal is rehydrated.
F. IV nutrition (premade amino acid solutions with dextrose or parenteral solutions formulated by a nutritionist and compounded by a pharmacist) may be indicated in dogs or cats that are unwilling or unable to eat after 3 to 4 days of illness.
G. Anorectic animals, especially cats, become deficient in B vitamins, so add a multiple B-complex solution (5 to 10 mL/L) to the IV fluids or give SC SID.
H. Acid-base disorders are common, but the type and severity vary.
1. Fluid therapy and resolution of vomiting and diarrhea resolve most of these abnormalities.
2. Specific therapy is recommended only in severe, life-threatening cases when blood gas analysis is performed.

I. Hetastarch or plasma therapy is indicated in dogs with severe hypovolemia, endotoxemia, or severe hypoalbuminemia (<1.5 g/dL).

J. SC fluid therapy may be sufficient in animals with only moderate clinical signs.

III. Isolate affected dogs or cats from other animals to prevent spread of infection.
   A. Meticulous hygiene, both of personnel and the hospital cages and runs, is essential to prevent spread of viral infection.
   B. Instruct owners to properly dispose of all fecal material to reduce environmental contamination.
   C. Parvoviruses and coronaviruses are very hardy and can survive for long periods in the environment, but sodium hypochlorite *(Clorox)* and some newer disinfecting agents will kill these viruses.

IV. Antibiotics are rarely necessary in mild cases of viral enteritis.
   A. In animals with severe or hemorrhagic gastroenteritis, especially with leukopenia, use parenteral antibiotics to prevent septicemia.
      1. Some puppies with parvovirus infection have asymptomatic bacteruria, suggesting antibacterial therapy is essential.
      2. Four-quadrant therapy protects against gram-negative and gram-positive aerobic and anaerobic bacterial septicemia.
      3. Utilize ampicillin 11 to 22 mg/kg IV, IM TID to QID and amikacin 6 to 8 mg/kg IV SID, or enrofloxacin 2.5 to 5 mg/kg IV, IM BID.
   B. In dogs with suspected septicemia or endotoxemia, more aggressive antibiotic therapy may be necessary.
      1. Cefoxitin 15 to 30 mg/kg IV, IM TID to QID
      2. Timentin 40 to 50 mg/kg IV TID to QID
      3. Imipenem 2 to 7 mg/kg IV, IM TID

V. Antiemetic therapy is indicated for severe vomiting.
   A. Prochlorperazine 0.25 to 0.5 mg/kg IM BID to TID in the dog and 0.125 mg/kg IM BID in the cat
   B. Metoclopramide 0.2 to 0.5 mg/kg SC, IM, IV BID to QID or as a constant rate infusion of 0.01 to 0.02 mg/kg/hr IV
   C. Chlorpromazine 0.05 mg/kg IV TID to QID or 1 to 2 mg/kg SC TID to QID in the dog
   D. Dolasetron 0.3 to 0.6 mg/kg SC SID to TID
   E. Ondansetron 0.1 to 0.2 mg/kg SC TID in the dog

VI. Other supportive therapy includes the following:
   A. IV immune globulin can be administered to severely neutropenic dogs with parvovirus infection, but it is expensive and difficult to obtain.
   B. Recombinant granulocyte colony-stimulating factor may be given to increased neutrophil counts; however, it may not affect morbidity or survival (Cohn et al., 1999).
   C. Motility-modifying agents or antidiarrheals are not recommended in acute, infectious gastroenteritis, and are given only to dogs with mild diarrhea.
   D. In cats with FIP, corticosteroids are recommended to maintain appetite and reduce the granulomas associated with the dry form of the disease, but their effectiveness has not been proven.
   E. Antiviral therapy has not been shown to improve survival in FIP or CPV infections and may be associated with significant side effects.
   F. Anecdotally, oseltamixir phosphate *(Tomiflu)* may be beneficial in dogs when given at 2 mg/kg PO BID for 5 days, especially if administered within 24 to 48 hours of onset of signs.

Monitoring of Animal

I. Frequently assess hospitalized animals for hydration status, response to therapy, and complications such as septic shock, DIC, or intussusception.

II. Daily monitoring includes determining body weight, performing a complete physical examination, and monitoring packed cell volume (PCV), total solids, blood glucose, and electrolytes.

III. The prognosis for most dogs and cats with viral enteritis is good if aggressive supportive care is initiated early, neutropenia is not associated with sepsis, and secondary complications are mild.

IV. The prognosis is more guarded for very young animals, animals with concurrent infections, or for cats with FeLV, FIV, or FIP infections.

V. All potentially exposed animals are vaccinated or revaccinated if their vaccine status is questionable.

VI. Disinfection of the premises with bleach reduces the risk of transmitting viruses to other animals.

Bacterial Infections

Definition and Causes

I. *Escherichia coli* is part of the normal bacterial flora of the ileum and colon.
   A. Documentation of pathogenic *E. coli* as the cause of intestinal infection is very difficult because many strains are found in clinically healthy dogs and cats (Greene, 2006; Marks and Kather 2003).
   B. Strains of *E. coli* that may cause diarrhea include enteropathogenic, enterotoxigenic, enterohemorrhagic, necrotoxigenic, enteroaggregative, or enteroinvasive (Greene, 2006).
   C. The best way to distinguish pathogenic *E. coli* from nonpathogens is the use of assays for specific toxin genes or molecular typing (Pass et al., 2000).

II. *Salmonella* spp. are frequently isolated from feces of normal dogs (1% to 36%) and cats (1% to 18%); however, their actual prevalence may be much higher in animals fed raw meat diets (Greene, 2006).
   A. *Salmonella typhimurium* is the most important pathogen in small animals (McDonough and Simpson, 1996; Greene, 2006).
   B. The risk factors for clinical disease include age (puppies and kittens <1 year), immunosuppression or stress from hospitalization, malnutrition, neoplasia, coinfection with FeLV or FIV, diabetes mellitus, and immunosuppressive therapy.
   C. Most cats that develop clinical disease are bacteremic, are systemically ill, and also have GI signs.
   D. Most dogs and cats infected with *Salmonella* spp. have transient or subclinical infections, and <10% became severely ill or die (Greene, 2006).

E. "Song bird fever" is caused by *S. typhimurium;* it is a seasonal illness that occurs in outdoor cats that prey on birds in the northeastern United States, and it manifests an acute, febrile, self-limiting gastroenteritis lasting for 2 to 7 days.

III. *Yersinia enterocolitica* and *Yersinia pseudotuberculosis* may cause a relatively mild enterocolitis, but fecal shedding of the organism may persist for weeks.
   A. *Y. enterocolitica* has been isolated from the feces of clinically normal dogs and cats, so it is probably a commensal that only rarely causes clinical disease.
   B. *Y. pseudotuberculosis* causes enteritis during cold, wet, winter months, because it replicates more effectively in cooler temperatures.

IV. *Clostridium* spp. are involved with several different intestinal diseases.
   A. *Clostridium piriformis* (Tyzzer's disease) is a rare disease that causes a chronic hemorrhagic enterocolitis with hepatic necrosis.
   B. *Clostridium difficile* is isolated in both healthy and diarrheic dogs and cats.
      1. *Clostridium* spp. produce three toxins (A, B, and C).
      2. Toxins A (enterotoxin) and B (cytotoxin) have been associated with diarrhea in dogs (Marks and Kather, 2003), but the association in cats is less well defined.
      3. Infection was thought to occur only rarely, was secondary to antibiotic use, and caused pseudomembranous colitis (Weese et al., 2001); however, outbreaks have been reported in dogs without prior antibiotic use.
   C. *C. perfringens* is part of the normal colonic flora in dogs and cats, but under conditions that allow sporulation (e.g., alkaline environment, antibiotic therapy, dietary changes, immunosuppression), enterotoxin is released, causing a watery or hemorrhagic acute to peracute diarrhea.

V. *Campylobacter jejuni* and *Campylobacter upsaliensis* are motile, microaerophilic bacteria that cause enteritis most commonly in puppies or kittens that are housed in kennel situations, or that are stressed or immunocompromised.

VI. *Helicobacter cinaedi* and *Helicobacter fennelliae* have both been cultured in feces from dogs, but whether they are a primary cause of diarrhea in immunocompetent dogs and cats is unknown.

VII. *Shigella* spp. can cause enteritis in dogs that are exposed to feces from infected hosts (primates, humans).

Pathophysiology

I. Diarrhea caused by toxin-producing bacteria occurs from increased chloride secretion and subsequent water and electrolyte loss.
   A. Enteropathogenic *E. coli* adheres to the mucosal cells of the small intestine, causing loss of microvilli.
   B. Enterotoxigenic *E. coli* produces both heat-stable toxins that increase chloride secretion by deregulating guanylyl cyclase activity or stimulating cyclic nucleotide-independent secretion, and heat-labile toxins that alter adenylate cyclase activity, resulting in inhibition of sodium and chloride absorption, and increased secretion of chloride by crypt epithelial cells.
   C. Enterohemorrhagic *E. coli* produces verotoxins (*Shigella*-like toxins) that cause damage to the vascular endothelium, inhibit protein synthesis, and alter fluid secretion.
   D. Necrotoxigenic *E. coli* produces cytotoxic necrotizing factors that attach to the mucosal cells and cause diarrhea by invasion and destruction of the cells.

II. Invasive organisms cause enteritis by invading the bowel epithelium and causing local inflammation and mucosal disruption.
   A. Examples of organisms that are invasive include *Salmonella* spp., *Yersinia* spp., *Campylobacter* spp., and enteroinvasive *E. coli* strains.
   B. Inflammation disrupts the mucosal barrier, resulting in loss of fluids, electrolytes, and in some cases blood.
   C. Mucosal disruption can result in the development of bacteremia.

III. Inappropriate or excessive antibiotic therapy alters the normal intestinal flora and allows invasion of antibiotic-resistant strains of bacterial pathogens.

Clinical Signs

I. Diarrhea caused by toxin-secreting bacteria is less common than that caused by invasive bacteria.
   A. Toxigenic diarrhea is usually watery, with little evidence of an inflammatory response or systemic disease.
   B. Diarrhea of this type leads rapidly to dehydration and electrolyte imbalances, but there is rarely blood, mucus, or cellular debris in the feces.

II. Invasive diarrheas are often acute, hemorrhagic, or mucoid in nature and may cause other clinical signs of illness (e.g., fever, abdominal discomfort, vomiting, anorexia).
   A. Diarrhea may result in severe gastroenteritis and fluid loss, or may affect primarily the large bowel, with signs of colitis.
   B. Animals that develop septicemia may be collapsed, hypothermic, or febrile; hypovolemic; in endotoxic shock; or have signs of DIC.
   C. Organisms that induce severe systemic clinical disease include *Salmonella* spp., enteroinvasive or enterohemorrhagic *E. coli,* and *C. piriformis.*

III. Some bacteria cause clinical syndromes with features of both invasive and toxigenic species.
   A. *Y. enterocolitica* typically causes a mild, self-limiting enterocolitis in dogs.
   B. *C. jejuni* is associated with a hemorrhagic diarrhea, but may also cause chronic colitis.
   C. Enteroadherent *E. coli* may cause a mild to severe enterocolitis with watery to hemorrhagic diarrhea.

Diagnosis

I. Tentative diagnosis is based on typical signalment, history, and clinical signs, and is only rarely based on fecal culture.

II. Definitive diagnosis requires fecal culture, PCR detection of bacterial toxins or DNA, or demonstration of bacterial toxin in the feces.
   A. A positive fecal culture must be interpreted very cautiously, because most of the bacteria implicated in bacterial enteritis are also normal flora (e.g., *E. coli, Salmonella* spp., *Clostridium* spp., and *Campylobacter* spp.) and are found in clinically healthy animals.
   B. When submitting bacterial cultures of fecal material, submit individual samples in media appropriate for each organism suspected.
      1. Diagnosis of campylobacteriosis is best made by culture of the organism from fresh feces placed into anaerobic transport media.
      2. Diagnosis of salmonellosis is best made by culturing the organism; however, caution is advised, as *Salmonella* spp. are isolated from healthy dogs without diarrhea.
   C. The significance of culture results is based on the signalment, history, other test results for viral and parasitic agents, histopathology (if the diarrhea is chronic), and presence of toxin (if it is a toxin-secreting species).
   D. Definitive diagnosis of *C. perfringens* is difficult because detection of endospores (fecal cytology), toxin formation (by ELISA), or the gene for clostridial enterotoxin production (by PCR) are all associated with false-positive and false-negative results.
      1. Presumptive diagnosis is made by increased numbers of spores or a positive fecal enterotoxin in the presence of diarrhea.
      2. The best way to diagnose clostridial diarrhea is finding clostridial enterotoxin in feces by ELISA or PCR, in a dog with acute diarrhea (Marks and Kather, 2003).
   E. Identification of pathogenic *E. coli* requires either specific typing for known pathogenic strains or demonstration of toxin production.
III. Bacterial enteritis may occur secondary to viral infection (e.g., parvovirus).
IV. Toxin assays are available for identification of the presence of toxin in fecal material from *C. difficile, C. perfringens,* and certain *E. coli*, and are used to determine whether these organisms are responsible for the clinical signs.
V. Fecal cytology helps identify the type of enteritis (presence of inflammatory cells, type of cells, number and type of bacteria), determine its severity (presence or absence of RBCs, epithelial cells, leukocytes), and in some cases identifies the cause (e.g., seagull-shaped bacteria characteristic of *Campylobacter* or *Helicobacter* spp.).
   A. Finding *Clostridium* spp. spores (safety pin-shaped organisms) in large numbers (>5 per high-power field) is not an important consideration in the diagnosis of clostridial enterocolitis.
   B. The mere presence of spores does not indicate they are secreting toxin and causing the diarrhea (Marks and Kather, 2003).
VI. Hematological or biochemical changes may be nonspecific; however, significant leukocytosis or leukopenia is suggestive of bacterial causes.
VII. In dogs or cats with diseases of high mortality (e.g., hemorrhagic colibacillosis, salmonellosis, Tyzzer's disease), diagnosis is often based on postmortem examination.

Differential Diagnosis

I. Viral enteritis: especially in puppies and kittens
II. Severe intestinal parasitism in puppies in and kittens
III. Toxin-induced enteritis
IV. Dietary indiscretion and other nonspecific enteritis
V. Extraintestinal causes of diarrhea

Treatment and Monitoring

I. Supportive care is essential to replace lost fluids and electrolytes, and to correct acid-base disturbances from moderate to severe diarrhea.
   A. In animals that are not vomiting and have only mild signs, oral replacement fluid therapy is usually adequate (see Viral Infections earlier in this chapter).
   B. If vomiting is present, institute appropriate IV fluid therapy.
   C. Do not use motility-modifying agents, because removal of the bacterial toxins and inflammatory mediators is enhanced by the diarrhea.
   D. Intestinal protectants are occasionally beneficial in dogs with mild disease to decrease effects of the toxins and reduce inflammation.
      1. Consider bismuth subsalicylate *(Pepto-Bismol)* at 1 to 2 mL/kg PO TID to QID.
      2. *Pepto-Bismol* is not recommended in cats owing to the risk of salicylate toxicity.
II. Antibiotic therapy is indicated, especially if the pathogen is definitively identified; however, antibacterial therapy is controversial for animals with *Campylobacter* spp. or *Salmonella* spp. infections when there are no systemic signs of disease.
   A. Give ampicillin 10 to 22 mg/kg IM, SC, or IV TID to QID for *Salmonella* spp., or *Clostridium* spp. infections.
   B. Administer amikacin 6 to 8 mg/kg IM, IV SID alone for *Salmonella* spp., *Helicobacter* spp., *Yersinia* spp., and *Campylobacter* spp. infections, or in combination with cephalothin for systemic salmonellosis.
   C. Use trimethoprim-sulfadiazine 15 mg/kg SC, PO BID for elimination of salmonella carrier states and treatment of yersiniosis.
   D. Give erythromycin 20 mg/kg PO BID (dogs) and 10 mg/kg PO TID (cats) for *Campylobacter* spp. and *Helicobacter* spp. infections.
   E. Substitute, if necessary, newer generation macrolides, such as azithromycin (5 mg/kg PO SID) for erythromycin (fewer side effects).
   F. Clindamycin 5 to10 mg/kg PO BID may also be effective against *Clostridium* spp.
   G. Metronidazole at 5 to 15 mg/kg PO BID is used for bacterial overgrowth and clostridial enterocolitis.

H. Consider using enrofloxacin 5 to 10 mg/kg PO SID (dogs) or 2.5 to 4 mg/kg PO, SC SID (cats) for gram-negative bacterial infections (*Campylobacter* spp., *Salmonella* spp., and *E. coli*).
I. Tylosin 11 mg/kg PO BID to TID may be used for unidentified bacterial enteritis or antibiotic responsive enteritis.

III. Prevention of infection is achieved by removal of potential sources, such as wild prey or contaminated food products.
IV. Monitoring of animal is similar to that recommended under Viral Infections.

Intestinal Parasitism

See Table 33-2.

Mycotic and Algal Diseases

Definition

I. Mycotic and algal diseases are uncommon in dogs, except in regions where the organism is endemic (e.g., histoplasmosis, phycomycosis), and are rare in cats.
II. They tend to be opportunistic and occur primarily in dogs that are immunocompromised from malnutrition, infection, neoplasia, or drugs, or in dogs with abnormal gut microflora.

Causes

I. *Histoplasma capsulatum*
   A. Infection occurs primarily in the Missouri, Mississippi, and Ohio river valleys; southeastern Texas; and the Gulf Coast region (Greene, 2006).
   B. Dogs are more likely to develop GI histoplasmosis alone.
   C. Cats with GI signs generally have a systemic infection.
II. Miscellaneous infections
   A. These include *Pythium insidiosum, Lagenidium* spp., other Zygomycetes, and *Prototheca zopfii* (Grooters, 2003).
   B. *P. insidiosum* is a water-borne pathogen belonging to the class Oomycetes that causes cutaneous or GI disease in tropical or subtropical regions.
   C. Pythiosis is more common in dogs than in cats and causes only cutaneous infections in cats.
   D. Lagenidiosis is primarily observed in dogs and is associated with cutaneous disease unless it becomes disseminated and systemic signs develop.
   E. The primary zygomycosis associated with GI disease in dogs or cats is mucormycosis caused by *Mucor* spp., *Rhizopus* spp., or *Absidia* spp.
   F. *Prototheca zopfii* is a blue-green algae capable of causing GI and other organ disease in dogs.
III. *Candida albicans:* opportunistic infection
IV. *Aspergillus* spp.
   A. GI involvement is part of disseminated disease.
   B. It is a rare disease and is more common in dogs (especially German shepherd dogs) than in cats.

Pathophysiology

I. *H. capsulatum* is a dimorphic fungus, having both infective and tissue stages.
   A. The free-living mycelial stages (macroconidia and microconidia) live in the soil and are the source of infection.
   B. Once in the body, microconidia are converted into the yeast form in the tissues, are then engulfed by macrophages, and initiate intracellular replication.
II. Pythiosis is the most clinically important miscellaneous organism.
   A. *Pythium* spp. differ from true fungi in producing motile, flagellate zoospores, and having cell walls that contain cellulose, no chitin, and very little ergosterol.
   B. The infective stage is released into warm water environments and likely causes infection by encysting in the GI mucosa.
   C. Pythiosis causes granulomatous inflammatory lesions that may form masses and obstruct the GI tract, or may cause diffuse infiltrative granulomatous enteritis.
   D. Lesions are most frequently observed in the stomach and duodenum, but may involve any segment of the small intestine, with the ileocolic junction another common location.
III. *Lagenidium* spp. infections typically cause cutaneous or subcutaneous draining nodules in dogs, but the disease may disseminate to other body systems.
IV. *Candida* spp. invade and proliferate in the GI tract following prolonged antibiotic therapy, or when the normal GI flora are altered by disease or dysfunction.
V. Disseminated aspergillosis may infiltrate the small intestine, but only when there is severe immunodeficiency or immunosuppression.

Clinical Signs

I. Histoplasmosis
   A. Chronic weight loss, anorexia, and large bowel diarrhea (tenesmus, hematochezia, mucus, urgency) are the most common clinical signs in dogs with primary GI histoplasmosis.
   B. With small intestinal involvement, the diarrhea is either profuse and watery or bloody.
   C. With systemic involvement, fever, lymphadenopathy, hepatomegaly, splenomegaly, icterus, anemia, ascites, cough, and dyspnea are often observed.
   D. Histoplasmosis is more common in young (<4 years) dogs and cats.
II. Miscellaneous fungal/algal infections
   A. Signs include weight loss, anorexia, vomiting, and diarrhea, which are often associated with a palpable abdominal mass.
   B. Infections are more common in male, large-breed dogs living in tropical or subtropical regions.
   C. Cutaneous forms of pythiosis are less common than GI forms in dogs, but skin disease is more common in cats.
   D. Signs of systemic illness can occur with pythiosis, but only after development of intestinal obstruction or perforation.

TABLE 33-2

Small Intestinal Parasitism

PARASITE	CLINICAL FEATURES	DIAGNOSIS	TREATMENT
Nematodes			
Ascarids Dogs: *Toxocara canis* *Toxascaris leonina* Cats: *Toxocara cati* *Toxascaris leonina*	*T. canis* is the most important nematode of public health significance (visceral larval migrans) Clinical signs from migration: coughing, ill thrift, pneumonitis Clinical signs from mucosal dysfunction: malabsorption, weight loss, retarded growth, diarrhea, poor hair coat, enterocolitis Puppies are infected in utero (transplacental), postpartum (transmammary), and by fecal–oral route Feline ascarids do not cross placenta or mammary gland	Fecal flotation with salt or sugar solutions	Pyrantel pamoate Dogs: 1 mL/10 lb (5 kg) PO Cats: 1 mL/5 lb (2.5 kg) PO Fenbendazole 50 mg/kg PO SID × 3 days Milbemycin Drontal Plus: dogs Drontal: cats Selamectin: cats only Puppies are treated prophylactically every 2-3 wk, until >6 wk old, then as needed Prepatent period is 4-6 wk
Hookworms Dogs: *Ancylostoma caninum* *Ancylostoma braziliense* Cats: *Ancylostoma tubeforme* *Ancylostoma braziliense* *Uncinaria stenocephale*	*A. caninum* is the most important hookworm of public health significance (cutaneous larva migrans) Voracious blood-sucking ability causes severe life-threatening anemia in young puppies Diarrhea is the most common sign; may be blood-tinged Iron deficiency anemia in adults	Fecal flotation with salt or sugar solutions	See Ascarids Prepatent period is 2-3 wk
Strongyloides Dogs: *S. stercoralis* Cats: *S. tumefaciens*	Most common in young dogs from kennel or shelter environments Clinical signs include vomiting or diarrhea, coughing, lethargy, and respiratory distress *Strongyloides* spp. are a public health risk as the larvae are infectious	Baermann exam is best to detect larvae Direct visualization of worms in emesis	Fenbendazole 50 mg/kg PO SID × 3 days Ivermectin 200-300 µg/kg PO
Whipworms Dogs: *Trichuris vulpis*	Whipworm infections are most common in urban environments from persistent fecal contamination and reinfection Enterocolitis (large bowel diarrhea)	Fecal flotation with sugar or zinc sulfate solution is best Eggs are shed intermittently, so multiple fecal examinations may be required	Fenbendazole 50 mg/kg PO SID × 3 days Drontal Plus: dogs Milbemycin Ivermectin 200-300 µg/kg PO Prepatent period is 3 mo
Coccidia			
Cystisospora spp. *Cryptosporidium* spp. *Toxoplasma* spp. Others: *Hammondia* spp., *Sarcocystis* spp., *Besnoitia* spp., *etc.*	*Cystisospora* spp. are not highly pathogenic; inapparent infections common; mucoid, foul-smelling diarrhea in young kittens or puppies Cryptosporidia may cause chronic, severe diarrhea and ill thrift in puppies, kittens, and immunocompromised adults	Fecal flotation is best, using salt or sugar solution *Cryptosporidium* spp. are extremely small (3-4 µm) and require both special stains and high-power microscopy for visualization Fecal ELISA is available for detection of cryptosporidia	Animals with asymptomatic *Cystisospora* spp. infections do not require treatment Sulfadimethoxine 55 mg/kg PO once, then 27.5 mg/kg PO SID × 14 days Sulfamethazine 100 mg/kg PO once, then 50 mg/kg PO BID × 14 days

Continued

TABLE 33-2

Small Intestinal Parasitism—*cont'd*

PARASITE	CLINICAL FEATURES	DIAGNOSIS	TREATMENT
	Cryptosporidia are not host specific like most coccidia, thus are zoonotic, especially to immunocompromised humans *Toxoplasma* spp.: see Chapter 116	*Toxoplasma* spp. oocysts are also extremely small and rarely seen on fecal flotation examinations. Toxoplasmosis is diagnosed by measuring serum IgM and IgG levels	For *Cryptosporidium* spp.: paromomycin 125-165 mg/kg PO BID × 5 days For toxoplasmosis: clindamycin 10-25 mg/kg PO BID × 14 days
Protozoa			
Giardia lamblia *Entamoeba histolytica* *Balantidium coli*	*Giardia* spp. infections are characterized by acute or chronic small bowel diarrhea, weight loss, and protein-losing enteropathy Subclinical infections are common Zoonotic, both by direct contact with feces, but also via fomites, as cysts are highly resistant to disruption *Entamoeba* spp. and *Balantidium* spp. are rare, but cause signs of enterocolitis	Zinc sulfate flotation is the most effective concentration method for detection Testing of three separate fecal samples increases the sensitivity from 65% to 96% Trophozoites may be observed on direct saline smears of feces, but the sensitivity is low Fecal ELISA for detection of *Giardia* spp. antigen has a 93% sensitivity, but the specificity is lower than zinc sulfate flotation	Metronidazole 25-50 mg/kg PO SID × 5 days (dogs); 10 mg/kg PO BID (cats) Fenbendazole 50 mg/kg PO × 7 days Furazolidone (cats) 4 mg/kg PO BID × 7 days Drontal Plus: dogs *Giardia* spp. in cats: give Drontal Plus at 2 small dog tablets PO SID × 5 days
Trichomonads			
Pentatrichomonas hominis	Healthy dogs and cats may be carriers Animals with diarrhea found to have *Pentatrichomonas* spp. may have other intestinal diseases or immunodeficiency	Direct examination of feces Special stains may be needed to differentiate from *Giardia* spp.	No effective treatment has been identified
Tritrichomonas foetus	Healthy cats or young kittens with foul, pasty diarrhea Often associated with anal hyperemia No vomiting or anorexia	Direct examination of feces (least sensitive) Culture of organism PCR for organism	Self-elimiting in some cats after several months Ronidazole 10-30 mg/kg PO BID × 14 days; can be neurotoxic
Cestodes			
Tapeworms Dogs: *Dipylidium caninum* *Taenia pisiformis* Cats: *Dipylidium caninum* *Taenia taeniaeformis*	Rarely associated with clinical abnormalities May observe proglottid segments on perineum Severe infestation may result in unthriftiness	Proglottid segments seen on perineum or in litter box Oocysts may occasionally be seen on fecal flotation	Epsiprantel 5 mg/kg PO once (dog); 2.5 mg/kg PO once (cat) Praziquantel 5-7.5 mg/kg PO once (dog); 5 mg/kg PO once (cat)

ELISA, Enzyme-linked immunosorbent assay; *IgM,* immunoglobulin M; *IgG,* immunoglobulin G; *PCR,* polymerase chain reaction.

E. *Lagenidium* spp. and Zygomycetes infections only cause GI signs when they become disseminated.

III. Candidiasis and aspergillosis
   A. They cause chronic, nonhealing ulcerative lesions of the mucosa that result in diarrhea in dogs.
   B. Systemic involvement is more common with aspergillosis, producing clinical signs of anorexia, weight loss, fever, weakness, vomiting, uveitis, and neurological dysfunction.

Diagnosis

I. Histoplasmosis
   A. Definitive diagnosis is made by cytological or histological identification of organisms in macrophages from infected tissues.
   B. Serology is not recommended because of a high percentage of false-positive and false-negative results.

II. *Pythium* spp., *Lagenidium* spp., and others
   A. Definitive diagnosis is made by identification of the organisms (poorly septate and branching fungal hyphae) on histopathologic examination of affected tissues (endoscopic or surgically obtained biopsies).
   B. An ELISA is available for use in dogs and cats, and it has very high sensitivity and specificity.
      1. It can be used before more invasive diagnostics are undertaken.
      2. It is also useful to guide the duration of therapy and detect recurrences (Grooters, 2003).
   C. No consistent laboratory or imaging abnormalities occur.

III. Aspergillosis and candidiasis
   A. Definitive diagnosis is achieved by identification of organisms in cytological or histological specimens from affected tissues.
   B. Serology for aspergillosis includes an agar gel immunodiffusion (AGID) assay or ELISA; however, false negatives are common, and a positive test does not rule out other concurrent diseases, which are common in dogs with aspergillosis.
   C. Both organisms can be cultured from the affected tissue, but must be done with extreme caution as the organisms can be infective to laboratory personnel.

Differential Diagnosis

I. Inflammatory bowel disease (IBD)
II. Intestinal neoplasia
III. Protein-losing enteropathies (PLE)
IV. Obstructive intestinal diseases: intussusception, foreign body
V. Other diffuse enteropathies causing malabsorption

Treatment

I. Histoplasmosis
   A. The drug of choice is itraconazole administered for ≥4 to 6 months or 1 month beyond resolution of clinical signs (Greene, 2006).
      1. Dose in dogs: 10 mg/kg PO SID or divided BID
      2. Dose in cats: 5 to 10 mg/kg PO SID; liquid form preferred as it is well absorbed
   B. Some animals require treatment for 9 to 12 months, and long-term treatment beyond that is occasionally necessary.
   C. If treatment is stopped prematurely, relapses are common.
   D. Alternatives to itraconazole include amphotericin B or fluconazole (see Chapter 111).
   E. Ketoconazole is less effective against histoplasma organisms and has greater toxicity.
   F. Antibiotics or other supportive care may be required in severe cases.
   G. In cats, anorexia may warrant insertion of a feeding tube.

II. Pythiosis and other miscellaneous fungal or algal infections
   A. Wide and complete surgical excision is the only effective treatment and may be curative if the lesion is focal.
   B. Itraconazole, miconazole, and terbinafine have in vitro susceptibility to the organism, but their effectiveness in vivo is questionable.
      1. These drugs may prevent dissemination or local recurrence following surgical excision.
      2. Itraconazole and terbinafine used together appear to be the most effective combination, but the rate of success is still quite low.
   C. Liposome-encapsulated amphotericin B has not been shown to be effective and has greater toxicity.
   D. A new antifungal drug, caspofungin, may be much more effective against pythiosis and other oomycoses, but is extremely expensive, and dosing and safety data have not been reported in dogs.
   E. Supportive care with correction of electrolyte disturbances and dehydration is essential, especially for cases where surgery is to be performed.

III. Aspergillosis and candidiasis
   A. *Candida* spp. are susceptible to itraconazole, fluconazole, and ketoconazole.
   B. Aspergillosis can be effectively treated with itraconazole or one of the newer azoles (voriconazole) or amphotericin B; however, disseminated disease is often unresponsive because of concurrent immunocompromise.
   C. Treatment must be continued for 1 month past the resolution of signs, and correction of the underlying cause is imperative.

IV. Supportive care is very important and may include fluid therapy, nutritional support, antibiotics, control of vomiting, and good husbandry.

Monitoring of Animal

I. The overall prognosis for fungal diseases is fair to poor, depending on the organism involved, the extent of disease, and the response to treatment.
   A. The prognosis is generally better for dogs or cats with pulmonary disease alone than for those with GI or disseminated disease.

B. Dogs with diffuse GI pythiosis or other oomycoses have a very guarded to poor prognosis.

II. Therapy must be given for a long time (≥4 to 6 months) in animals with GI disease, and early withdrawal results in a relapse of the clinical disease.

III. A number of other adverse effects of drug administration must also be monitored (see Chapter 111).

IV. Response to treatment is monitored by assessment of body weight, return of appetite, and resolution of clinical and biochemical abnormalities.

CANINE HEMORRHAGIC GASTROENTERITIS

Definition and Cause

I. Hemorrhagic gastroenteritis (HGE) is a peracute, hemorrhagic diarrhea of dogs that is accompanied by hemoconcentration and an acute onset of vomiting.

II. The etiology is unknown, but it may be an enterotoxemia from *E. coli* or *Clostridium* spp. (Marks and Kather, 2003).

Pathophysiology

I. A dramatic increase in small intestinal vascular and mucosal permeability may be responsible for the rapid loss of blood, protein, and fluids from the GI tract.

II. The syndrome may represent a hypersensitivity or immunological reaction to bacteria or bacterial toxins.

Clinical Signs

I. Signalment is as follows:
   A. HGE is most frequently seen in small-breed dogs, with the miniature schnauzer, poodle, bichon frisé, dachshund, sheltie, and Cavalier King Charles spaniel overrepresented.
   B. HGE is most common in young dogs (2 to 4 years), and there is classically no known exposure to different foods, garbage, or other inciting causes.

II. The clinical signs are peracute and severe, resulting in rapid development of severe hypovolemia and shock.

III. The typical signs include hematochezia, melena, depression, acute onset of anorexia, vomiting (may have hematemesis), abdominal pain, and occasionally fever.

IV. Endotoxic shock occurs in severely affected dogs, as evidenced by hyperemic mucous membranes, slow capillary refill time, hypothermia, generalized weakness, or collapse.

Diagnosis

I. There is no definitive diagnostic test for this syndrome.

II. Presumptive diagnosis is based on the characteristic signalment, history, and clinical signs in a previously healthy dog.

III. Dogs have marked hemoconcentration (PCV=50% to 80%), but the total protein is often normal or low (despite the severe dehydration).
   A. Other hematological and biochemical parameters are usually normal.
   B. The white blood cell count may show a stress leukogram, neutropenia, or neutrophils with toxic changes; however, in most cases the condition is too peracute for these changes to occur.

IV. Tests for viral and bacterial enteric pathogens and fecal evaluations for parasites are negative.

V. Radiography of the abdomen is often unremarkable with the exception of ileus, which may be marked.

VI. Coagulation tests are normal unless the dog is in severe endotoxic shock, and then evidence of DIC may be present.

Differential Diagnosis

I. Parvoviral enteritis

II. Bacterial enteritis, especially *Salmonella* spp., *Clostridium* spp., or hemorrhagic *E. coli*

III. Intestinal obstruction: intussusception, foreign body, volvulus, neoplasia, fungal granuloma

IV. Other causes of hypovolemic or endotoxic shock resulting in hemorrhagic diarrhea

V. Coagulopathies: warfarin toxicity, DIC

Treatment

I. Aggressive treatment of fluid and electrolyte derangements is the most important aspect of initial treatment.
   A. Start IV fluid therapy with isotonic, polyionic crystalloid solutions (Normosol-R, lactated Ringer's) at 60 to 90 mL/kg in the first hour in severely hypovolemic, shocky dogs.
      1. Once the dog is stabilized, fluids are modified to match the ongoing losses.
      2. In many dogs, the best approach is the placement of a central venous catheter to allow measurement of central venous pressure (CVP) during the replacement and maintenance phases of fluid therapy.
   B. In dogs that are severely hypoproteinemic (total protein [TP] <4.0 mg/dL, albumin <2.0 mg/dL), colloid therapy (hetastarch 10 to 20 mL/kg IV) or plasma is preferred to prevent fluid overload, edema formation, and further deteri-oration of the clinical condition.
   C. Electrolyte losses are often severe.
      1. Potassium supplementation (20 to 40 mEq/L) is usually the most critical.
      2. Magnesium and phosphorus (owing to metabolic acidosis and blood loss) must also be monitored.

II. Antibiotic therapy is very important because bacterial translocation via deranged mucosal permeability and shock are common complications.
   A. Four-quadrant therapy is recommended to provide protection against aerobic, anaerobic, gram-positive, and gram-negative bacteria (see doses in Viral Infections).
      1. Ampicillin and amikacin
      2. Ampicillin and enrofloxacin
      3. Cefoxitin or other second- or third-generation cephalosporins
      4. Imipenem or Timentin
   B. Antibiotic therapy is continued for 3 to 5 days beyond the cessation of clinical signs.

III. The use of corticosteroids in dogs with shock is controversial and not recommended for this condition.

IV. Treatment of vomiting is indicated, with drugs such as metoclopramide, prochlorperazine, ondansetron, or dolasetron.
V. Consider ranitidine, famotidine or omeprazole if the vomiting is severe, or blood is present in the vomitus.
VI. Treatment of diarrhea with antidiarrheal agents (loperamide, diphenoxylate, or *Pepto-Bismol*) is not recommended.
VII. A short-term fast (1 to 3 days) is indicated, at least until the vomiting is controlled.
   A. Do not fast dogs for long periods, because the gut requires food to repair itself.
   B. When ready, offer small amounts of a canned, highly digestible, low-fat, low-fiber food.

Monitoring of Animal

I. Monitor serum electrolytes, PCV, and total solids BID to QID initially, depending on the severity of the abnormalities.
II. In very small or toy breeds, blood glucose is also assessed.
III. The rate of fluid administration is monitored by assessing CVP, urine output, PCV, TP, and body weight.
IV. The prognosis is good if the dog is not severely hypoproteinemic and aggressive supportive care is administered.
   A. In most cases, dogs begin to recover in 2 to 3 days.
   B. In dogs with severe hypoproteinemia or with secondary complications, the prognosis is more guarded.
   C. Dogs that do not respond to therapy in 2 to 3 days must be reevaluated, because it is likely that the diagnosis is incorrect or that other complications have developed (e.g., intussusception, endotoxemia, sepsis, DIC).
V. The mortality rate is very high in dogs that are not treated aggressively.

DISORDERS OF MALABSORPTION

Definition

I. Malabsorption or malassimilation is a disorder that results in a primary failure of absorption (e.g., lymphangiectasia, small intestinal disease affecting mucosal transport), and is distinguished from maldigestion caused by failure of digestive processes (e.g., exocrine pancreatic insufficiency, brush border enzyme deficiency).
II. The distinction between maldigestion and malabsorption is artificial because both are inextricably linked; therefore malabsorption is often used as a general term for either defective digestion or absorption.

Causes and Pathophysiology

I. The causes of malabsorption are separated by the site where the primary abnormality occurs.
   A. Examples are luminal, mucosal, or hemolymphatic (postmucosal) disorders (Simpson and Hall, 2000).
   B. No matter the cause or site, the end result is decreased nutrient absorption from the small intestine.
II. Luminal causes of malabsorption include the following:
   A. Motility disorders: hyperthyroidism
   B. Inactivation of enzymes: gastric hyperacidity, Zollinger-Ellison syndrome
   C. Lack of digestive enzymes: exocrine pancreatic insufficiency
   D. Deficiency of bile salts: cholestatic liver disease, obstruction of common bile duct, or loss of bile salts as a result of ileal disease
   E. Bacterial overgrowth in the small intestine resulting in cobalamin deficiency, deconjugation of bile salts, and impairment of intestinal mucosal function
III. Mucosal causes include the following disorders:
   A. Deficiencies of mucosal (brush border) enzymes: trehalase deficiency in cats, lactose deficiency
   B. Disturbances in uptake of luminal substrate across the mucosa from congenital lack of transport protein: intrinsic factor receptor absence
   C. Severe mucosal disease: IBD, neoplasia, etc.
   D. Defects in enterocytes resulting in abnormal transport: villous atrophy, abetalipoproteinemia, inflammatory or infectious diseases affecting enterocytes
IV. There is often considerable overlap between the classes of disorders.
V. Some of the more important individual causes of malabsorption include the following:
   A. Inflammatory bowel diseases: lymphocytic plasmacytic enteritis, eosinophilic enteritis, granulomatous enteritis, etc.
   B. Neoplasia: lymphosarcoma, leiomyosarcoma, adenocarcinoma, etc.
   C. Chronic infectious enteropathies: histoplasmosis, giardiasis, pythiosis, small intestinal bacterial overgrowth
   D. Villous atrophy: idiopathic, secondary to IBD, etc.
   E. Dietary hypersensitivity: dietary allergy, wheat-sensitive enteropathy, dietary intolerance
   F. Short bowel syndrome: congenital or secondary to massive bowel resection
   G. Lymphangiectasia: primary, secondary to other intestinal disease
   H. Idiopathic PLE

Clinical Signs

I. Signs of intestinal malabsorption are varied in both severity and presentation, and range from mild diarrhea or weight loss to severe diarrhea, weight loss, abnormal appetite, and edema or ascites from hypoproteinemia.
II. Diarrhea is the most consistent abnormality.
   A. Occasional soft feces to severe watery diarrhea
   B. Hematochezia and/or melena with severe inflammatory diseases
   C. Light or gray fecal color with maldigestion or a lack of bile salts
III. Weight loss may be the only clinical sign in some cases, and it can be significant.
IV. Other variable clinical signs include alterations in appetite, abdominal discomfort, depression, increased intestinal gas production (borborygmus, belching, flatus), or vomiting.
V. Severe lymphangiectasia may result in edema or ascites from severe hypoproteinemia from PLE, and may rarely be associated with a chylous effusion in the abdomen or thorax.

VI. Protein and fat malnutrition may result in poor skin and hair coat.
VII. Increased risk of bleeding may occur with severe malabsorption and vitamin K deficiency or with loss of clotting proteins secondary to intestinal protein loss.

Diagnosis

I. Rule out extraintestinal causes of diarrhea and weight loss (complete blood count, biochemistry profile, urinalysis), and assess of thyroid, adrenal, and liver function.
   A. Hematological findings are nonspecific, but may include lymphopenia, eosinophilia, neutrophilia, or anemia of chronic disease.
   B. Serum biochemistry profile results are often nonspecific.
      1. With severe malabsorptive disease, hypocholesterolemia, hypoproteinemia, and hypoalbuminemia indicate PLE.
      2. Cats or dogs with IBD may have elevations of liver enzymes and/or hyperglobulinemia.
      3. Electrolyte concentrations are variable, depending on the degree and severity of diarrhea, but hypokalemia is common with severe small bowel diarrhea.
      4. Hypomagnesemia, hypochloremia, and hyponatremia can also occur.
      5. Hypocalcemia (true or pseudo) is a common finding in dogs with PLE from lymphangiectasia (Kimmel et al., 2000).
      6. Serum bile acid concentrations may be increased from concurrent hepatic disease, or may be falsely low owing to deconjugation and loss of bile salts in the GI tract.
II. Fecal examinations are essential.
   A. Perform multiple fecal flotations (more than three) using different flotation media (salt, sugar, zinc sulfate [$ZnSO_4$]), and different methods (direct examination, cytology of fecal smears, Baermann's).
      1. *Giardia* spp. are best detected using a minimum of three $ZnSO_4$ flotations, sugar flotation, or ELISA for giardial antigen.
      2. Diarrhea caused by clostridial overgrowth and enterotoxin production is suggested by finding enterotoxin in the feces using an ELISA assay (Marks and Kather, 2003).
      3. *Cryptosporidia* spp. are difficult to identify because their extremely small oocysts require special microscopy, so an assay for the toxin is the best diagnostic approach.
      4. Fecal cytology may also be useful in identification of *Campylobacter* spp., *Tritrichomonas* spp., *Histoplasma* spp., and other enteric pathogens.
   B. Fecal cultures are important if specific bacterial pathogens are suspected; however, cultures should be followed by PCR assays.
   C. Fecal α_1-protease inhibitor assay detects fecal protein loss in dogs with PLE.
      1. This protein is not affected by intestinal or bacterial degradative processes, but is similar in size to albumin and is lost into the lumen if there is intestinal protein leakage.
      2. The assay has been validated in dogs but not in cats, and requires obtaining three separate, defecated fecal samples.
      3. Send samples directly to the Gastrointestinal Laboratory at Texas A&M University for processing using special collection kits provided.
      4. The assay can be falsely elevated in animals with parasites and other GI disturbances, and from collection problems.
   D. Other fecal tests (fecal fat, proteolytic activity, occult blood) are nonspecific, insensitive, and not recommended.
III. Other serum tests may be helpful in identifying intestinal, pancreatic, or hepatic disease associated with malabsorption.
   A. Trypsin-like immunoreactivity (TLI)
      1. The TLI assay is a species-specific assay for the pancreatic acinar cell enzymes, trypsinogen and trypsin.
      2. Normal serum TLI of dogs is 5.2 to 35 μg/L and of cats is 12 to 82 μg/L.
      3. Serum TLI is unaffected by small intestinal disease, but is markedly low in dogs or cats with exocrine pancreatic insufficiency.
      4. Elevated levels correlate poorly in dogs and only moderately well in cats with acute pancreatitis.
      5. Serum is collected following a fast for 6 to 12 hours.
   B. Serum vitamin concentrations (folate and cobalamin)
      1. Decreased levels of folate occur with severe proximal or diffuse small intestinal disease.
      2. Increased folate levels are observed in animals on parenteral supplementation, and in dogs with exocrine pancreatic insufficiency or with antibiotic responsive enteritis.
      3. Increased levels of folate are also present in hemolyzed blood samples from leakage of the vitamin from RBCs.
      4. A cobalamin deficiency reflects ileal disease, exocrine pancreatic insufficiency, or may occur in the presence of antibiotic responsive enteritis (dogs).
      5. Elevated levels of cobalamin have unknown clinical significance, but may occur with excess parenteral supplementation.
      6. Assays for both cobalamin and folate must be validated and normal values established for each species.
         a. Samples are collected after a 6- to 12-hour fast and stored in darkness, because cobalamin is light sensitive.
         b. Because serum vitamin concentrations can be low in animals with both exocrine pancreatic insufficiency and small intestinal disease, simultaneous serum TLI assay is recommended.
      7. Cats may be more susceptible to cobalamin deficiency because of their increased need for cobalamin.
   C. Measurements of intestinal permeability

1. Tests of intestinal permeability are used to noninvasively determine the presence of intestinal mucosal damage from gluten enteropathy, acute gastroenteritis, IBD, neoplasia, and other diseases.
2. The standard test uses the probe ^{51}Cr-labeled EDTA; however, the marker is not suitable for use in private clinical practice or many referral practices.
3. Other tests use two sugars, one disaccharide (cellobiose, lactulose) and one monosaccharide (mannitol, rhamnose) to determine intestinal permeability by measuring the amount excreted in urine and expression of the results as a ratio.

D. d-Xylose absorption test
1. It has a very low sensitivity for small intestinal disease.
2. It is impractical and cumbersome to perform in most clinical settings and is not recommended.

E. Tests for antibiotic responsive enteritis (previously referred to as *small intestinal bacterial overgrowth*)
1. Increased serum folate and decreased serum cobalamin levels are suggestive but not specific for the problem.
2. Serum unconjugated bile acids increase 10 to 20 times in affected dogs, but an assay is not yet commercially available.
3. At this time, the best diagnostic test is culture of intestinal contents to quantitate bacterial numbers, and isolate known or potential pathogens.
   a. Recent evidence indicates that this method is inadequate for identification of bacterial numbers and species in the intestinal tract (Suchodolski et al., 2005).
   b. DNA technology may be the most reliable and accurate means of identifying and enumerating the wide variety of bacterial species colonizing the intestinal tract, but is only available at research laboratories.

IV. Imaging studies are indicated, but may give nonspecific results and are used to rule out other diseases.
A. Survey abdominal radiography is often normal.
B. Upper GI contrast studies may reveal foreign bodies, masses, intestinal obstruction or intussusception, and gastric or intestinal ulcers (see Chapter 4).
C. Abdominal ultrasonography is used to detect changes in echogenicity of abdominal organs and bowel thickness or irregularities, for identifying lymphadenopathy or other intraabdominal masses, and for obtaining biopsies and aspirates.

V. Endoscopic examination permits direct visualization of the mucosa and provides an opportunity to obtain multiple samples for cytology, biopsy, and culture.
A. In animals with weight loss or chronic diarrhea, samples for biopsy are obtained from multiple sites (stomach, duodenum, ileum, colon).
B. Properly obtained biopsies include submucosa and intact mucosa in the proper orientation (i.e., carefully uncurled and lying flat on a biopsy sponge to maintain orientation).
C. In some cases, endoscopic biopsies may not be sufficient for diagnosis (e.g., focal disease in jejunum unreachable by the endoscope, serosal disease, edematous changes), and full-thickness biopsies may be required.
D. Cytological examination of endoscopically obtained tissue can often be used to make a rapid diagnosis of inflammatory changes present in the mucosa (Jergens, 2003).

VI. Histological examination is essential to document villous atrophy and other architectural changes; verify that lymphatic dilatation is consistent with lymphangiectasia; and confirm neoplastic, inflammatory, or other infiltrative diseases.

VII. Intestinal samples can also be submitted for specialized assays, including analysis for marker enzymes (e.g., lactase, alkaline phosphatase) or cell surface markers cluster differentiation (CD; e.g., CD4, CD8) to help distinguish neoplastic from inflammatory infiltrates.

Differential Diagnosis

I. Exocrine pancreatic insufficiency
II. Hepatopathy resulting in reduced bile production or bile flow
III. Endocrinopathies
A. Hyperthyroidism in cats
B. Diabetes mellitus
C. Hypoadrenocorticism
IV. Dietary intolerance or sensitivity
V. Severe parasitism: heterobilharziasis, giardiasis
VI. Other enteric pathogens: protothecosis, pythiosis

Treatment

I. Specific therapy is directed at correcting or controlling the underlying cause.
A. Exocrine pancreatic insufficiency: see Chapter 36
B. IBD: see the following section
C. PLE and lymphangiectasia: see Protein-Losing Enteropathies
D. Neoplasia: see the following section
E. Parasitic, bacterial, or fungal enteropathies: see earlier
F. Dietary sensitivity: see Chapters 85 and 122
G. Antibiotic responsive enteropathy
1. Antibiotic therapy is most effective if based on culture of intestinal fluid.
2. Antibiotics commonly used for empirical treatment in dogs are as follows:
   a. Tetracycline 10 to 20 mg/kg PO TID for 21 to 28 days
   b. Tylosin 40 to 80 mg/kg PO SID to BID in food
   c. Metronidazole 5 to 15 mg/kg PO BID
   d. Trimethoprim-sulfadiazine 15 mg/kg PO BID
   e. Enrofloxacin 2.5 to 10 mg/kg PO SID to BID

II. General supportive care of malabsorptive diseases involves many options.
A. Feed a highly digestible, low-fat, novel or hydrolyzed protein, low-fiber, or an elemental diet in small quantities.

1. In general, fat is the limiting ingredient, so selection of a diet containing the lowest fat is essential.
2. The lowest fat, highest digestible diet is Royal Canin Low Fat (1.95 g/100 kcal fat).
3. The next lowest diets are Purina Veterinary Diets EN (2.8 g/100 kcal) and Eukanuba Low Residue (2.5 g/100 kcal).
4. In dogs with severe malabsorptive disease, commercially available diets may be inadequate, so homemade novel protein, ultra-low fat diets are needed.

B. Parenteral nutrition is required initially if PLE is severe or until the bowel has time to develop adaptive processes.
C. In dogs with severe PLE and ascites or edema, colloid therapy with hetastarch (5 to 20 mL/kg IV) is helpful.
D. Antibiotic therapy is used to control overgrowth of bacteria.
E. Parenteral vitamin supplementation may be indicated.
1. Cobalamin 250 μg SC, IM weekly or 1 mg SC every 2 weeks for 1 to 3 months
2. Folic acid 1 to 5 mg PO, SC weekly for 1 month
3. Thiamine 10 mg/kg SC, IM SID for 3 to 4 days
4. Tocopherol 100 to 500 IU IM, PO SID with food
5. Vitamin K_1 2 mg/kg PO SID

F. In animals with IBD or lymphangiectasia, antiinflammatory or immunosuppressive therapy with steroids is indicated (see IBD).
G. Histamine$_2$-receptor blockers or proton pump inhibitors are used to control gastric hypersecretion and prevent ulcer development.
1. Ranitidine 0.5 to 1 mg/kg PO, SC SID to BID
2. Famotidine 0.5 to 1 mg/kg PO, SC SID
3. Omeprazole 0.5 mg/kg PO SID

H. Cholestyramine 200 to 300 mg/kg PO BID is administered in dogs to bind bile acids.
I. Loperamide 0.08 mg/kg PO BID to TID is used in dogs for persistent diarrhea not from infectious causes.
J. Special therapy of fungal infection (histoplasmosis) is described earlier.

Monitoring of Animal

I. Warn owners that many cases of malabsorption do not respond immediately to therapy, may require some trial-and-error dietary regimens to achieve a full response, or may not be responsive to therapy at all.
II. Frequent reevaluation is necessary to assess response to therapy, and to make adjustments in the diagnostic and therapeutic approach.
A. Reassessment provides new information when the diagnosis is not apparent on the initial evaluation.
B. Reevaluate serum biochemical and vitamin levels to determine if the therapy has been appropriate.

DIETARY SENSITIVITY AND INTOLERANCE

See Chapters 85 and 122.

INFLAMMATORY BOWEL DISEASES

Definition

I. Eosinophilic enterocolitis is characterized by increased numbers of eosinophils in the stomach, small intestine, or colon.
II. Lymphocytic plasmacytic enteritis (LPE) is characterized by infiltration of the bowel with lymphocytes and plasma cells, and can affect the stomach, small intestine, colon, or all of them.
III. Granulomatous enteritis is characterized by infiltration of macrophages or histiocytes in the lamina propria, and is more common in the distal small intestine and colon of boxers.
IV. Neutrophilic enteritis is characterized by infiltration of neutrophils, may occur at any location in the small or large intestine, and is uncommon in idiopathic IBD.

Causes

I. The etiology of eosinophilic enteritis is unknown, but proposed causes include parasitic infestation, dietary hypersensitivity, and idiopathic disease.
II. Many different causes of intestinal infiltration of lymphocytes and plasma cells exist.
A. Dietary sensitivity
B. Parasitism
C. Bacterial toxins
D. Neoplasia
E. Idiopathic disease

III. Basenjis have a severe, hereditary form of lymphoplasmatic enteropathy (see Table 33-1).
IV. Soft-coated wheaten terriers have a familial PLE that is characterized by severe LPE, lymphangiectasia, and hypoproteinemia; may also be associated with a concurrent PLE; and is most likely an immune-mediated disease with a genetic basis (see Table 33-1).
V. A gluten (wheat)-sensitive enteropathy occurs in Irish setters as an autosomal recessive trait, and is characterized by intestinal infiltration of lymphocytes and plasma cells.
VI. No etiological agent or cause is known for granulomatous or neutrophilic enteritis, or for idiopathic LPE.

Pathophysiology

I. The presence of increased eosinophils, lymphocytes, or plasma cells is likely an immune response to the presence of antigen.
II. If the inflammatory response is significant, it may result in malabsorption owing to changes in the absorptive surface (villous blunting or fusion, crypt abscesses, or fibrosis), lymphatic obstruction, or exudation of protein from the inflammatory effects on epithelial cell function.
III. Eosinophils are chemotactic for other cells, including mast cells, and may result in a local type I hypersensitivity or delayed hypersensitivity reaction to antigens presented to the GI mucosa.
IV. Although the exact etiology of LPE is unknown, an aberrant immune response to luminal antigen (bacterial, parasitic, dietary) is presumed to be the triggering event.

A. Once the mucosa is infiltrated with inflammatory cells, mediators (C-reactive protein, cytokines) are released and trigger the pathogenic effects observed.
B. Intestinal inflammation may be mild or severe, but the effects of the inflammatory changes in the mucosa include malabsorption, vomiting, diarrhea, weight loss, hypoproteinemia, or more widespread effects, such as cholangiohepatitis or pancreatitis.

Clinical Signs

I. Anorexia, weight loss, vomiting, and diarrhea are common signs.
II. Diarrhea may be small bowel, large bowel, or a combination.
III. Enterocolitis is common in cats with eosinophilic IBD.
IV. Melena or hematochezia is observed more frequently with eosinophilic enteritis than with LPE.
V. Doberman pinschers, boxers, and German shepherd dogs may be predisposed to eosinophilic IBD.
VI. Thickened bowel loops may be palpable in cats with severe LPE.
VII. Severe IBD may be associated with concurrent ascites, coagulopathies, cholangiohepatitis, thromboembolic disease, and nephropathies.
VIII. Histiocytic enterocolitis in boxers causes severe hematochezia and large-bowel diarrhea.

Diagnosis

I. See the diagnostic approach for Disorders of Malabsorption.
II. There are no specific hematological or biochemical abnormalities.
   A. Occasionally, neutrophilia or eosinophilia are observed.
   B. In cats, if eosinophilia is significant, hypereosinophilic syndrome (HES) must be considered.
   C. Dogs with severe eosinophilic enteritis are more likely to have significant anemia or hypoproteinemia (from gastroduodenal ulceration or mucosal bleeding).
   D. In LPE, nonregenerative anemia (from chronic inflammation or intestinal blood loss) and mild thrombocytopenia are relatively common changes.
   E. There are no pathognomic changes in serum biochemistries, but abnormalities include hypoproteinemia, hypoalbuminemia, hyperglobulinemia, elevations in liver enzyme concentrations, and electrolyte abnormalities.
III. Fecal examinations are essential for eliminating endoparasites and protozoal infections.
IV. Serum folate and cobalamin concentrations are important indicators of the severity of mucosal disease.
   A. Subnormal folate concentrations occur in proximal disease, whereas low concentrations of cobalamin (vitamin B_{12}) are associated with distal small bowel disease.
   B. Although not diagnostic for IBD, they indicate the need for further evaluation (biopsy) and supplementation.
V. Diagnostic imaging is important to document disease outside the GI tract, further define the extent of intestinal disease, and identify changes compatible IBD, such as mesenteric lymphadenopathy, thickened bowel loops, and concurrent pancreatic inflammation or liver changes (occasionally in cats).
VI. Definitive diagnosis of IBD requires biopsy of the affected bowel.
   A. Biopsy may be obtained via endoscopy or laparotomy.
   B. Surgical biopsies are indicated if there is multiple organ involvement, if endoscopic biopsies are nondiagnostic, or if the disease is distal.
   C. Classic findings in IBD are increased numbers of inflammatory cells infiltrating the lamina propria and submucosal tissues of the intestine in association with changes of mucosal architecture.
   D. Severe IBD is associated with villous blunting, mucosal ulceration, and other severe mucosal irregularities, which may include lymphangiectasia.

Differential Diagnosis

I. Causes of chronic intestinal inflammation: *Giardia* spp., histoplasmosis, protothecosis, pathogenic bacteria, etc.
II. Dietary sensitivity or intolerance
III. Cancers of the small bowel causing LPE-like changes, especially lymphoma
IV. Other primary GI diseases, such as lymphangiectasia
V. HES in cats
   A. Infiltration of eosinophils occurs in multiple organs, including the bone marrow, spleen, liver, intestines, and lymph nodes.
   B. Signs mimic eosinophilic IBD (diarrhea, vomiting, weight loss, anorexia) and may involve other organ systems (splenomegaly, anemia, dermatologic signs).
   C. HES can be distinguished from eosinophilic leukemia by mature eosinophils instead of the immature or blast cells observed with leukemia.
   D. Response to treatment with prednisolone is poor in HES, whereas a good response is expected in eosinophilic IBD.

Treatment

I. Hypoallergenic or novel protein diets, elimination diets, or hydrolyzed protein diets are recommended.
   A. Dietary therapy alone may result in resolution when dietary hypersensitivity is the cause of the inflammatory infiltrates.
   B. Novel, single-antigen or hydrolyzed protein diets reduce the antigenic stimulus and are recommended even when dietary hypersensitivity is ruled out.
   C. Low-residue or highly digestible diets are also alternatives, especially when a low-fat diet is required to prevent further malabsorption.
   D. If homemade diets are used in dogs, well-cooked rice, potatoes, and tapioca are highly digestible, gluten-free carbohydrate sources.
II. Administer appropriate treatment for intestinal parasitism, because it is difficult to identify all parasites with fecal examination.

A. Fenbendazole 50 mg/kg PO SID for 3 to 5 days is appropriate for most intestinal parasites of dogs and cats.
B. Pyrantel pamoate has a narrower spectrum of activity, but is safer in sick dogs or cats.
1. Cats: 10 mg/kg (1 mL/5 lb) PO once
2. Dogs: 5 mg/kg (1 mL/10 lb) PO once

III. Immunosuppressive doses of prednisone reduce the inflammatory and immunological stimulus within the GI tracts once infectious or parasitic causes are ruled out.
A. Give prednisolone 1 to 2 mg/kg PO BID for 3 to 6 weeks in dogs and 2 to 3 mg/kg PO BID in cats, then taper over several months.
B. In cats, methylprednisolone at 1 mg/kg PO BID may be more effective.
C. Some animals require long-term therapy to control the clinical disease, whereas others can be tapered to low QOD doses.
D. A few animals are eventually maintained with diet alone, but these are likely to be animals with a primary dietary sensitivity, not idiopathic eosinophilic IBD.

IV. Antibacterial therapy is generally justified in IBD since secondary overgrowth of bacteria or development of antibiotic responsive enteritis is relatively common, and because bacterial antigens are believed to be of major importance in the development of IBD.
A. Metronidazole is the preferred drug in both dogs and cats for initial therapy.
B. Tylosin may also be effective and has immunomodulatory effects (similar to metronidazole).
C. In severe cases of IBD, fluoroquinolones (enrofloxacin) may be indicated.
D. Bacterial overgrowth is not recognized in cats, but antibiotic therapy with metronidazole is often helpful in the management of IBD.

V. In animals that do not respond to steroid therapy, or have severe steroid-associated side effects, other immunosuppressive drugs may be tried.
A. Dogs: azathioprine 1 to 2.5 mg/kg PO SID to QOD; bone marrow toxicity monitored via frequent CBCs
B. Dogs: cyclosporine 5 mg/kg BID PO; efficacy variable, toxicity problematic, requires blood level monitoring
C. Cats: chlorambucil 1.5 mg/m^2 PO SID to QOD

Monitoring of Animal

I. The prognosis for dogs and cats with eosinophilic IBD is good, and a positive response to therapy can be expected.
A. The more extensive the lesions and severe the disease (e.g., ulcerations, villous atrophy), the more difficult it is to achieve remission.
B. German shepherd dogs are more difficult to control and are more likely to have other concurrent GI abnormalities.

II. The prognosis for LPE varies, depending on the severity of clinical disease, histological changes, and initial response to therapy.
A. In some cases, a single course of drug therapy is all that is required to achieve an apparent cure, whereas others may require lifelong (diet and/or immunosuppressive) therapy.
B. Rarely, cats with LPE develop alimentary lymphoma.

III. In animals with familial or genetic enteropathies, the prognosis is guarded to poor (see Table 33-1).

IV. The prognosis for granulomatous and neutrophilic IBD is unpredictable, but may be guarded depending on the severity and initial response to therapy.

PROTEIN-LOSING ENTEROPATHIES

Definition and Causes

I. PLEs are characterized by increased loss of both small (albumin) and large (globulin) proteins into the GI tract.

II. PLE may be primary or secondary to diseases affecting the bowel (Peterson and Willard, 2003).
A. Examples of inflammatory diseases: IBD, histoplasmosis, other granulomatous diseases
B. Diseases causing villous atrophy: gluten enteropathy, severe viral enteritis, bacterial enteritides
C. Severe parasitic enteropathies in young animals
D. Giardiasis in heavily infested adult dogs
E. Chronic obstructive diseases: intussusception, neoplasia
F. Diseases causing intestinal ulceration or erosion (Table 33-3)
G. Diseases affecting the intestinal lymphatic system
1. Lymphangiectasia is characterized by dilated submucosal, subserosal, and/or mesenteric lymphatics.
2. Primary or congenital lymphangiectasia may occur.
a. Lymphangiectasia is seen in the Norwegian lundehund and small terrier breeds (e.g., Yorkshire, Maltese).
b. Even though the disease is congenital, clinical signs do not occur until lipogranulomatous lymphangitis develops, which is progressive.
3. Acquired or secondary lymphangiectasia may be idiopathic (intestinal lymphatic obstruction from an unknown cause) or may develop secondary to other diseases of the GI tract (e.g., neoplasia, IBD) that cause obstruction of the lymphatics, to thoracic duct obstruction, or to right-sided congestive heart failure.

Pathophysiology

I. It is normal for protein to be lost into the small intestine; however, this protein is usually digested, absorbed, and reused to make new protein.

II. Loss of protein is accelerated in animals with intestinal mucosal or malabsorptive diseases, or lymphatic obstruction.

III. Hypoproteinemia occurs when the rate of GI loss of protein exceeds the liver's ability to synthesize protein.

IV. Hypoproteinemia manifests initially as hypoalbuminemia, with a subsequent reduction in plasma oncotic pressure, but eventually larger proteins are lost and hypoglobulinemia also occurs.

TABLE 33–3

Ulcerogenic Diseases of the Small Intestine

CAUSES	CLINCAL SIGNS	DIAGNOSIS	TREATMENT
Neoplasia Mast cell tumors and mastocytosis Gastrin-secreting tumors (gastrinoma) Hypergastrinemia Secondary to liver disease Secondary to renal disease Drug induced: prolonged use of H_2 blockers or antacids Drug induced NSAIDs Corticosteroids Idiopathic Hypovolemic shock with ischemia	Diarrhea ± gross melena Vomiting with or without hematemesis Weight loss, and anorexia or decreased appetite common Abdominal pain in severe cases Anemia in animals with chronic or severe blood loss	History and appropriate clinical signs are suggestive Lab findings nonspecific but support blood loss (elevated BUN, normal creatinine, decreased total protein and albumin) Liver or renal disease causing hypergastrinemia are supportive. Severe hypergastrinemia from gastrin-secreting tumor is rare, but measurement of serum gastrin is suggestive The definitive diagnosis of ulcerative disease is by visualization of the mucosal defects (endoscopy, specialized imaging studies, or surgery)	Replace blood loss with whole blood if animal is in shock or in respiratory distress Stop all medications that may cause ulcers Decrease gastric acid secretion: Omeprazole 0.5-1.0 mg/kg PO, SC SID Famotidine 0.5-1 mg/kg PO, SC, or IV SID-BID Ranitidine 1-4 mg/kg PO, SC BID-TID Control vomiting Metoclopramide 0.2-0.5 mg/kg PO, SC, or IV TID-QID Prochlorperazine 0.25-0.5 mg/kg IM BID-TID Ondansetron 0.5-1.0 mg/kg IM BID-TID Dolasetron 0.3-0.6 mg/kg SC SID-BID Provide mucosal protection with sucralfate 1 g/25 kg PO TID Withhold food until vomiting is controlled for 24-48 hr Institute specific treatment of primary disease

H_2, Histamine$_2$; *NSAIDs*, nonsteroidal antiinflammatory drugs; *BUN*, blood urea nitrogen.

V. Because coagulation proteins and immunoglobulins are also lost, a dysfunction of the clotting system or abnormal immune responses may arise.

Clinical Signs

I. The most common presenting clinical sign is weight loss.
II. Chronic diarrhea may occur, but is inconsistent and depends on the cause and duration.
III. Diarrhea may be intermittent or continuous, is usually small bowel in character, and may be associated with hematochezia.
IV. Vomiting, anorexia, and lethargy are variable, depending on the cause.
V. Severe PLE may cause peripheral edema, ascites, or pleural effusion, and may be associated with abnormal clotting (increased risk of thromboembolism).

Diagnosis

I. Although signs of diarrhea or vomiting may not occur, most affected animals have weight loss, so an initial assessment must include a work-up for weight loss.
II. Classic abnormalities on hematology and biochemistry profiles include hypoalbuminemia, hypoglobulinemia, hypocholesterolemia, hypocalcemia (true or pseudo), hypomagnesemia, lymphopenia, and mild anemia of chronic disease.
III. Ascites is a pure transudate if it arises from pure loss of albumin, but may be a modified transudate if right heart failure is present, and in rare cases may be chylous if there is a thoracic duct lesion.
IV. Other causes of hypoproteinemia (liver disease, protein-losing nephropathy) must be excluded.
   A. Urinalysis, urine protein: creatinine ratio
   B. Measurement of serum bile acids, other assessments of liver function
   C. Analysis of any ascitic fluid to further identify a cause
   D. Fecal α_1-protease inhibitor assay to assess the presence of GI protein loss (see Disorders of Malabsorption)
V. Also assess for other causes of GI disease (see Disorders of Malabsorption or Inflammatory Bowel Diseases).
VI. Definitive diagnosis of intestinal protein loss is supported by histological evidence of disease(s).

A. Because hypoproteinemia may decrease healing and increase the risk of leakage of biopsy sites or dehiscence of the incisions, endoscopic examination is preferred in animals with severe hypoproteinemia.
B. Some dogs with lipogranulomatous lymphangitis do not have significant mucosal abnormalities in the early stages of the disease; in these dogs, full-thickness biopsies are needed to obtain a definitive diagnosis.
C. Many animals with PLE have a normal-appearing intestinal tract at endoscopy or surgery, so it is imperative that biopsies be taken.
D. Endoscopic evaluation of a classic lymphangiectasia reveals lipid droplets on the surface or prominent, chyle (lipid)-filled villous tips.
E. In dogs with severe edema or ascites from hypoproteinemia, mucosal edema must be corrected with hetastarch before biopsy to assure that diagnostic specimens are obtained.
F. Feeding corn oil (1 tbsp) 6 to 8 hours before the endoscopic or surgical biopsy procedure results in maximum dilation of the lacteals, and may increase the likelihood of obtaining a diagnosis.

Treatment and Monitoring

I. When identified, correct the primary cause of the enteropathy (i.e., administer immunosuppressive therapy for IBD and lipogranulomatous lymphangitis or antifungal therapy for histoplasmosis).
II. The most important aspect of dietary therapy is to feed a low-fat, highly digestible diet to minimize fat malabsorption and lymphatic leakage (Zoran, 2003).
   A. A homemade diet is often the best choice for dogs with severe PLE that have a selective appetite, because it can be formulated to include ultra-low–fat content, novel protein, and highly digestible carbohydrate sources.
      1. One example consists of no-fat cottage cheese, egg whites, or turkey breast as the protein sources, and boiled potatoes (without the skins) or well-cooked white rice as the carbohydrate sources.
      2. Initially, no other fat source is added, but eventually, a small amount of oil (corn oil) must be added to provide essential fatty acids in the diet.
   B. Commercially available, ultra-low–fat (<3 g/100 kcal fat) diets may be adequate in less severe cases.
      1. The lowest fat, commercially available diet that is not also a high-fiber diet is Royal Canin Low Fat.
      2. Hydrolyzed diets also may be well tolerated, but they are not all low in fat.
      3. Purina Veterinary Diets H/A has the lowest fat content of the commercially available hydrolyzed diets.
   C. In dogs that are unable to eat (vomiting, severe diarrhea) nutritional support via total parenteral or partial parenteral nutrition may be needed, especially in dogs that are severely cachetic and edematous.
   D. If hypoproteinemia is severe, but the animal is able to eat, low-fat elemental diets (e.g., *Vivonex*) may be used instead of or in addition to commercial diets.
III. For dogs with severe coagulation protein loss that have a coagulopathy, plasma therapy (10 to 20 mL/kg IV) can be used to provide these proteins, but it is ineffective in increasing serum protein levels.
IV. Following diagnosis and institution of appropriate therapy, reevaluate body weight, serum protein concentrations, and any biochemical abnormalities found on initial presentation.

ULCEROGENIC DISEASES

See Table 33-3.

INTESTINAL OBSTRUCTION

Definition

I. Partial or complete obstructions of the small intestine are caused by intraluminal, intramural, or extramural lesions that slow or prevent passage of intestinal contents.
II. Functional obstruction is caused by ileus arising from neurogenic, myogenic, or humoral mechanisms.
III. Obstructions are also classified as to whether they are partial or complete, and whether they are simple or strangulated.
IV. Complete or strangulated obstructions result in a medical and surgical emergency necessitating an immediate response (see Chapter 39).

Causes

I. Intraluminal causes include neoplasia, polyps, foreign bodies (both linear and other), and intussusception.
II. Intramural obstruction is caused by neoplasia, abscesses, granulomas, congenital stenosis and atresia, and inflammatory lesions.
III. Extramural lesions include adhesions, strangulation (mesenteric or organ volvulus), strictures (secondary to surgery), and neoplastic masses incarcerating the bowel or adjacent structures.
IV. Functional obstruction of the bowel is caused by hypomotility and ileus, which may be idiopathic or may occur secondary to infectious or inflammatory diseases (e.g., parvovirus).

Pathophysiology

I. Obstructions in the bowel are also classified according to their location and their relative effects on fluid, electrolyte, and acid-base balance.
   A. High small intestinal obstructions of the duodenum or upper jejunum result in frequent vomiting and a rapid onset of dehydration with severe hypokalemia and metabolic acidosis.
   B. If the high obstruction is a gastric outflow obstruction, hypochloremic metabolic alkalosis is observed.
   C. Lower small intestinal obstructions are often associated with a slower onset of dehydration and vomiting, but diarrhea may be common.
      1. These cases frequently have hypokalemia, hyponatremia, hypochloremia, and metabolic acidosis.

2. Cats are more prone to develop low obstructions.

II. Another effect is alteration in normal GI motility, with subsequent alterations in bacteria and/or bacterial overgrowth, increased bacterial absorption, and development of endotoxemia and septicemia.

III. Intestinal strangulation, intussusception, or incarceration interfere with vascular integrity, resulting in segmental bowel stasis or death, and the animal is often presented in shock or a state of collapse.

IV. Partial, low obstruction or sliding intussusception may be chronic and cause intermittent clinical signs of malabsorption or small intestinal bacterial overgrowth.

Clinical Signs

I. Signs depend on the location, severity, and amount and location of bowel affected.

II. Duration of the process and effects on bowel integrity and function, as well as bacterial translocation, are also important factors in determining the clinical signs.

III. The most common signs are vomiting, anorexia, and lethargy.

IV. Other signs may include diarrhea (especially with lower obstructions), abdominal pain (with bowel strangulation or loss of vascular integrity), and severe dehydration or collapse from hypovolemia, endotoxemia, or septicemia.

Diagnosis

I. Compatible history, signalment, and physical examination findings are suggestive.

II. Palpation may reveal abdominal pain, a mass lesion, intestinal bunching (typical of string foreign bodies) or intussusception.

III. Laboratory findings are variable.
   A. The hemogram is often normal, but neutrophilia or neutropenia, a left shift, evidence of toxic change, and anemia of chronic disease may all be observed.
   B. The biochemical profile is used to rule out other causes of vomiting and anorexia (e.g., pancreatitis, liver disease, renal failure) and to assess electrolyte abnormalities (especially potassium, chloride, sodium, and magnesium).
   C. Prerenal azotemia or hepatic enzyme elevations are common in severely dehydrated or sick animals.

IV. Imaging studies are necessary when palpation is nondiagnostic.
   A. Plain radiography may reveal dilated loops of bowel present proximal to the obstruction, radiopaque foreign objects, intestinal pleating typical of linear foreign bodies, and/or evidence of functional obstruction (ileus of all bowel loops).
   B. Horizontal beam radiography (standing lateral) may show an interface of fluid and gas, with a complete obstruction having gas caps at different levels.
   C. Positive contrast studies can be used to identify obstructions that are partial, low, or intermittent, especially when survey films are inconclusive; however, in vomiting animals aspiration of the material can be life-threatening.
   D. Ultrasonography is used to identify partial or low obstructions, intussusceptions, and mesenteric volvulus or strangulation of bowel.

V. Exploratory laparotomy is necessary if the clinical signs or laboratory data indicate an obstruction, but imaging studies are inconclusive.
   A. Surgery is an acceptable means of confirming the diagnosis, especially if the clinical status is deteriorating in the face of no diagnosis.
   B. Intestinal volvulus, strangulation, and sliding intussusceptions are difficult to diagnose and may only be seen at surgery.

Differential Diagnosis

I. Pancreatitis

II. Hypoadrenocorticism

III. Acute renal or hepatic failure

IV. Severe infectious or inflammatory intestinal diseases

V. Ingestion of toxins

VI. Other causes of acute abdomen (see Chapter 39)

Treatment

I. Stabilize the animal with aggressive fluid therapy and electrolyte supplementation.
   A. Crystalloid therapy (lactated Ringer's solution, Normosol-R) is adequate in most cases, but hetastarch or other colloids are important in severely hypovolemic or shocky animals.
   B. Potassium supplementation (10 to 40 mEq/L) is essential if hypokalemia is present.

II. Parenteral broad-spectrum antibiotic therapy is initiated to combat bacterial overgrowth or translocation, and endotoxemia or septicemia (see Viral or Bacterial Infections).

III. Antiemetics may be considered to control vomiting, but some (metoclopramide) are contraindicated in animals with complete intestinal obstruction or must be used with caution (chlorpromazine) in severe hypovolemia.

IV. Aggressively treat hypoglycemia, systemic inflammatory response syndrome, and DIC arising from endotoxemia.

V. Definitive therapy is surgical intervention.
   A. A variety of surgical remedies are available, including enterotomy, resection and anastomosis, reduction of the intussusception and bowel plication, repair of hernias, and volvulus and mesenteric repair.
   B. Intestinal biopsies are obtained if there is any doubt about the possible cause of the problem.

Monitoring of Animal

I. Careful postoperative monitoring is essential for a successful outcome, especially in those animals that are endotoxemic or septic.
   A. Monitor PCV, TP, vital signs, electrolytes, blood glucose, and fluid status (CVP, capillary refill time, body weight, urine output) closely.
   B. With significant bowel resection or disturbance, oral alimentation is initiated as soon as possible (12 to 18 hours postoperatively) to provide nutrition for the

GI tract, help prevent postoperative ileus, and provide support for recovery and healing.
C. If the animal refuses to eat or is unable to eat because of persistent vomiting, parenteral nutrition must be considered.

II. The prognosis is guarded to good, depending on the severity of the obstruction, the cause, and the presence of any complicating factors (e.g., DIC, endotoxemia, peritonitis).

NEOPLASIA

Definition and Causes

I. The most common malignant tumors of the small intestine in dogs and cats are adenocarcinoma and lymphosarcoma (LSA).
A. Intestinal adenocarcinoma only accounts for 1% of all tumors, so it is relatively rare.
B. Adenocarcinomas appear to be more common in the boxer, collie, poodle, West Highland white terrier, German shepherd dog, Doberman pinscher, and Siamese cats.

II. GI lymphoma is the second most common form of LSA in dogs and the most common form in cats.
A. Intestinal LSA may be of B or T cell origin or a large granular lymphocyte subtype, and the behavior of the tumor is dependent on its type.
B. There is no apparent breed predisposition in cats, but in dogs, the boxer, shar-pei, golden retriever, English springer spaniel, Doberman pinscher, Labrador retriever, and German shepherd dog appear to be predisposed.

III. Other malignant neoplasms affecting the small intestine include mast cell tumors (cats), leiomyosarcomas, and carcinoid tumors.

IV. Leiomyosarcomas are more common in large-breed dogs, especially German shepherd dogs.

V. Benign tumors of the intestinal tract include leiomyomas, polyps, fibromas, lipomas, and adenomas.

VI. The inciting cause of intestinal neoplasia is unknown; however, LSA may be observed in cats with chronic IBD or previous exposure to FeLV (most cats are FeLV negative).

Pathophysiology

I. The etiology of small intestinal adenocarcinoma is unknown, but a genetic predisposition is likely.
A. These tumors typically cause an obstruction of the intestine because they form annular, constrictive lesions.
B. They can form in any segment of the intestine, but are most common in the distal jejunum or ileum in cats and in the colon in dogs.

II. The etiology of LSA is unknown in most cases, but IBD may be a predisposing factor.
A. LSA of the small intestine may occur as a diffuse, infiltrative lesion affecting large segments of bowel with thickening of the bowel wall, as a classic malabsorptive syndrome, or as an obstructive mass.
B. LSA in the cat may arise as a low-grade disease that grows slowly over months or years and may be difficult to distinguish from IBD.
C. LSA may occur in both dogs and cats as a rapidly advancing, high-grade malignancy.

III. Leiomyosarcomas tend to create large masses and have been more often associated with paraneoplastic hypoglycemia.

IV. Mast cell tumors (especially in cats) tend to be infiltrative.

Clinical Signs

I. Clinical signs are dependent on the location of the lesion, the type of lesion (mass effect or infiltrative disease), the rate of development, and other effects initiated by the presence of the tumor.
A. Intestinal adenocarcinoma is often slow growing, so weight loss in the absence of other signs is a frequent finding in the early stages, which may be months.
1. Once an obstructive lesion develops, vomiting or diarrhea (with or without blood) occurs.
2. Metastasis to the liver, mesenteric lymph nodes, peritoneal cavity, other intestinal sites or lungs is common and has usually occurred by the time of diagnosis.
B. Signs of GI LSA are variable.
1. Solitary mass lesions may cause signs of an obstruction, including vomiting or diarrhea, anorexia, and weight loss.
2. Diffuse small-cell LSA may be very insidious, resulting in weight loss, signs of malabsorption or diarrhea (especially in cats), and is easily confused with IBD.
3. Dogs with LSA tend to have a more acute illness and are more likely to develop hypercalcemia.
4. Lymphoblastic LSA may develop very quickly and is often associated with severe malabsorptive disease, melena, and other GI signs.
C. Other intestinal tumors typically cause signs of obstruction (e.g., vomiting, diarrhea, anorexia, weight loss) and may result in a nonregenerative anemia of blood loss.
D. Intestinal mastocytosis of cats is more likely to be associated with intestinal blood loss than other GI tumors.

II. Clinical signs of weight loss or diarrhea in an older animal should warrant an investigation.

III. Physical examination may reveal weight loss or thin body condition (especially cats), but may be otherwise unremarkable.
A. Alternatively, diffuse intestinal thickening or intestinal or abdominal masses may be palpated.
B. In dogs or cats with diffuse abdominal carcinomatosis, ascites or peritonitis may be present.
C. Hepatosplenomegaly is also possible in dogs with diffuse, multicentric LSA.

IV. The most common clinical signs are vomiting, diarrhea, anorexia, and weight loss.

Diagnosis

I. A compatible history, signalment, and physical examination findings are suggestive.

II. Laboratory results are often variable and nonspecific.

A. The hemogram may be normal, or a nonregenerative anemia of chronic disease or iron deficiency may be seen.
B. The biochemistry profile is used to assess albumin levels (intestinal protein loss), electrolytes (loss), or other organ system dysfunction.
C. Specific testing, to rule out pancreatitis (see Chapter 36) may be needed in some cases.
D. Abdominal radiography frequently reveals intestinal abnormalities, masses, abnormal organ position, or abnormal gas patterns.
E. Thoracic radiography is used to rule out metastatic disease.
F. Abdominal ultrasonography is also used to identify masses, abdominal lymphadenopathy, or obstructive lesions in the bowel wall.

III. Definitive diagnosis is made by histopathologic evaluation of biopsies.

Differential Diagnosis

I. Lymphoma: IBD, chronic giardiasis, chronic pancreatitis (cats), cholangiohepatitis (cats), other infiltrative GI diseases or PLE (dogs), severe bacterial overgrowth
II. Adenocarcinoma: foreign body, intussusception, pythiosis granuloma, IBD, LSA, mast cell tumor in the cat, smooth muscle tumors
III. Other intestinal neoplasms: causes of intestinal obstruction, malabsorptive disease

Treatment and Monitoring

I. LSA
A. Focal LSA may be cured with complete surgical resection if margins are clean, but most LSA that is diffuse or has nodal or hepatic involvement requires chemotherapy to provide a good quality of life for a prolonged period.
B. Specific chemotherapy depends on the type and location of LSA (see Treatment and Monitoring under Neoplasia in Chapter 31; see also Chapter 69).

II. Adenocarcinoma
A. Surgical resection is the treatment of choice for intestinal adenocarcinoma.
B. Recurrence is likely even with wide surgical margins, but may provide clinical remission for 6 to 12 months.
C. Chemotherapy is generally unsuccessful.

III. Leiomyosarcoma: surgical resection may provide long-term survival (slow growing).
IV. Intestinal mast cell tumors (cats)
A. Surgical resection is beneficial, but early metastasis is common.
B. Chemotherapy is necessary in diffuse mastocytosis or in cats in which resection is not associated with clean margins.

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CHAPTER 34

Diseases of the Large Intestine

Lisa E. Moore | Rhea V. Morgan

CONGENITAL DISORDERS

See Table 34-1.

DEGENERATIVE DISORDERS

Megacolon

Definition

I. Megacolon is flaccid distension and enlargement of the colon and rectum.
II. It usually arises from either mechanical obstruction or functional abnormalities of the distal colon, rectum, or anus.
III. Although congenital forms are rarely recognized, megacolon is usually an acquired disorder.

Causes

I. Mechanical obstructions
  A. Narrowing of the pelvic canal
    1. Pelvic fractures or luxations
    2. Prostatomegaly
    3. Enlargement of the iliac lymph nodes
    4. Neoplasia: bony, prostatic, urogenital
  B. Distal colonic or rectal foreign body
  C. Colonic or rectal neoplasia, granulomas
  D. Strictures
  E. Chronic, recurrent obstipation
II. Functional disorders
  A. Dysautonomia (rare)
  B. Sacral spinal cord or pelvic nerve dysfunction
  C. Autonomic ganglioneuritis in dogs (rare)
III. Idiopathic acquired megacolon of cats

Pathophysiology

I. In acquired megacolon, generalized dysfunction of the colonic smooth muscle occurs.
  A. In some cases, abnormalities of smooth muscle myofilaments cause disruption of colonic motility, which results in constipation and obstipation, and subsequent distension of the colon.
  B. In other cases a permanent functional abnormality may arise after recurrent or chronic constipation and obstipation from varying causes.
  C. The exact pathogenesis of acquired megacolon in cats is not well understood, but may involve both mechanisms.
II. Water continues to be absorbed from retained fecal matter, which results in very hard feces that cannot be passed.

Clinical Signs

I. History of prior pelvic trauma, prostatic diseases, recurrent episodes of constipation or obstipation
II. Unsuccessful attempts to defecate
III. Passage of only small amounts of liquid feces
IV. Possible fresh blood in the fecal material
V. Anorexia, vomiting
VI. Lethargy, dehydration
VII. ± Weight loss in affected cats

Diagnosis

I. On palpation the colon is grossly enlarged and filled with hard feces.
II. Rectal examination is essential to help determine an underlying cause.
  A. Evidence of anal or rectal strictures or masses
  B. Narrowing of the pelvic canal from fractures
  C. Detection of prostatomegaly or lymphadenopathy
  D. Palpable masses of the vagina or urethra
III. Radiography may reveal the following:
  A. Recent or healed pelvic fractures or luxations
  B. Colon distended with dense feces
  C. Possible colonic foreign material (including ingested bones)
  D. Organomegaly of adjacent structures
  E. Fractures, separation of the tail, or other spinal abnormalities
IV. Colonoscopy, biopsy, and histopathology may be required to definitively diagnose neoplasia and other causes.

Differential Diagnosis

I. Other causes of tenesmus, especially colitis and proctitis
II. Causes of stranguria (which is misinterpreted as tenesmus)

Treatment

I. Fluid therapy is indicated for dehydrated animals.
II. Impacted fecal material is removed when the animal is stable.

TABLE 34–1

Uncommon Disorders of the Large Intestine in Dogs and Cats

DISORDERS, SIGNS	DIAGNOSIS	TREATMENT
Disorders That Cause Acute Diarrhea		
Infectious agents		
Giardiasis	Fecal smear, $ZnSO_4$ concentration, antigen test	Fenbendazole
Salmonella spp.	Blood and fecal culture (special media)	Enrofloxacin, amoxicillin, trimethoprim–sulfa
Campylobacter spp.	Fecal smear, culture (special media)	Erythromycin, aminoglycosides
Yersinia enterocolitica	Blood and fecal culture (special media)	Chloramphenicol, aminoglycosides, cephalosporin
Entamoeba histolytica	Fecal smear with methylene blue	Metronidazole
Balantidium coli	$ZnSO_4$ concentration, fecal smear	Metronidazole, tetracycline
Heterobilharzia americana	Fecal smear, biopsy	Fenbendazole ± praziquantel
Cryptosporidium spp.	Fecal smear with special stain*	Controversial—possibly tylosin
Corticosteroid-associated ulceration in dogs with neurological disease	Physical examination, colonoscopy	Discontinue corticosteroid therapy as soon as possible; abdominal surgery may be needed
Secondary to severe pancreatitis	Physical examination, ultrasonography (see Chapter 36)	Manage pancreatitis aggressively (see Chapter 36)
Disorders That Cause Chronic Diarrhea		
Congenital abnormalities		
Vascular ectasia	Colonoscopy, biopsy	Surgical resection of the affected area
Short colon	Colonoscopy, barium enema	Low-residue diet
Enterocyst	Ultrasonography, exploratory surgery	Surgical resection
Histoplasmosis	Rectal scraping for cytology, biopsy	Itraconazole (see Chapter 111)
Protothecosis (dogs)	Rectal biopsy	Itraconazole
Ileocolic intussusception	Ultrasonography, exploratory surgery	Surgical resection
Cecal inversion	Ultrasonography, exploratory surgery	Surgical resection
Extramedullary plasmacytoma	Ultrasonography, exploratory surgery	Melphalan, prednisone
Disorders That Cause Constipation		
Congenital abnormalities		
Atresia, stenosis	Physical examination	Reconstructive surgery
Colonic duplication	Colonoscopy, barium enema	Surgical resection
Dysautonomia	Physical examination, pharmacological ocular function testing, plasma catecholamine levels	Supportive care (see Chapter 105)
Colorectal diverticulum	Rectal examination, barium enema	Surgical resection
Benign colorectal stricture	Colonoscopy, biopsy	Surgical resection; treatment of underlying cause

Modified from Bunch SE, Jergens AE: Diseases of the large intestines. p. 377. In Morgan RV, Bright RN, Swartout MS (eds): Handbook of Small Animal Practice. 4th Ed. WB Saunders, Philadelphia, 2003.
*Carbol-fuchsin, crystal violet.

A. Initially, warm-water enemas may be tried, but these efforts are usually successful only if the fecal mass is relatively soft.
B. General anesthesia, colonic lubrication, and digital evacuation are often needed.
   1. The feces are broken up by a combination of infusion of lubricating liquid (e.g., warm soapy water, diluted water-soluble jelly) and digital manipulation.
   2. Care must be taken to avoid damaging the colonic mucosa and perirectal tissues, especially if forceps are used to extract fecal material.

III. The underlying cause must also be addressed.
IV. Preventative measures are instituted because recurrences are common, especially with functional disorders or when the underlying cause is difficult to rectify.
   A. Add fiber in the form of psyllium, oat bran, or canned pumpkin to the diet.

B. Encourage frequent defecation.
C. Consider laxative therapy.
   1. Lactulose 2 to 10 mL PO TID titrated to maintain soft stools
   2. Docusate sodium (dioctyl sodium sulfosuccinate [DSS]) 50 mg PO SID to BID
D. Administer a smooth-muscle prokinetic agent, such as cisapride (not available commercially).
   1. In vitro studies of normal cats indicate that cisapride effectively stimulates longitudinal contractions.
   2. If given early, cisapride may prevent progression of constipation and dilated colon in cats (Washabau and Holt, 1999).
   3. Cisapride may not be beneficial in severe cases.
   4. Dose in cats is 2.5 to 5 mg PO BID to TID.
   5. Dose in dogs is 0.1 mg/kg PO BID to TID.
E. Erythromycin at 0.5 to 1.0 mg/kg PO TID may stimulate colonic motility in dogs.
F. Nizatidine 2.5 to 5 mg/kg PO SID and ranitidine 1 to 2 mg/kg PO BID may also stimulate colonic motility in cats (Washabau et al., 1996).

V. Surgical subtotal colectomy is indicated for cats with idiopathic megacolon that fail to respond to medical therapy and experience recurrent, severe obstipation.
   A. Many cats have normal enteric function and require minimal continued medical management after surgery.
   B. Soft or diarrheic stools are not common sequelae.
   C. The procedure is done less frequently in dogs, so data on outcomes are lacking.

Monitoring of Animal

I. Clinical signs and consistency of bowel movements are monitored closely to determine efficacy of medical therapy.
II. Aggressive medical management is usually required in cats with idiopathic megacolon and, even with therapy, many affected cats eventually require subtotal colectomy.

ACUTE INFLAMMATORY DISORDERS

Acute Colitis

Definition

I. Acute colitis is the sudden onset of large intestinal diarrhea.
II. It may be a nonspecific disease or arise in association with numerous infections or inflammatory conditions of the cecum, colon, and rectum.

Causes

I. Ingestion of abnormal foodstuffs (e.g., table scraps, garbage) or foreign matter (e.g., bones, rocks)
II. Abrupt exposure to a different diet
III. Certain protozoal and bacterial agents: see Table 34-1, Chapters 31, 33, 116
IV. Parasites: see under Trichuriasis
V. *Clostridium perfringens* type A enterotoxicosis
   A. Overgrowth of normal, anaerobic intestinal bacteria
   B. May be a hospital-acquired infection
   C. Develops soon after discharge from hospital
VI. Stress: hospitalization, travel, boarding, sudden changes in environment, etc.
VII. Drugs: corticosteroids, nonsteroidal antiinflammatory drugs (NSAIDs), etc.
VIII. Other medical conditions: pancreatitis, abdominal surgery or procedures, etc.
IX. More common in dogs than in cats

Pathophysiology

I. Ingestion or exposure to osmotically active material, and bacterial action on that material result in the movement of water in the colon, increased fermentation products, and hypomotility.
II. Spoiled food may contain endotoxins and certain bacteria may generate harmful enterotoxins.
III. Undigested foreign material (e.g., bones, metal particles) can cause direct mucosal injury.
IV. Inflammatory mediators (e.g., kinins, prostaglandins) are released and cause further degradation of the protective mucosal barrier, decreased absorption, and loss of electrolytes.
V. Bleeding and increased production of mucus may occur.
VI. Inflammation stimulates the defecation reflex, which increases the frequency of defecation and often results in tenesmus and dyschezia.

Clinical Signs

I. Acute onset of markedly increased frequency of defecation of a small volume of feces is a hallmark sign.
II. Defecation is often accompanied by tenesmus and/or dyschezia.
III. The feces typically contain mucus and/or fresh blood, and foreign matter may be seen.
IV. A temporal association may occur between feeding a different diet, exposure to some stressful event, hospitalization, administration of an antiprostaglandin drug, and the sudden onset of large intestinal signs.
V. The animal may show signs of discomfort (i.e., pacing, drooling).
VI. Signs of upper gastrointestinal (GI) involvement may also occur, including vomiting, small intestinal diarrhea, and inappetence.
VII. In many cases the physical examination is normal, and the animal is bright and alert.
   A. Mild depression or abdominal discomfort upon palpation may be noted.
   B. Dehydration and vomiting are uncommon unless the upper GI tract is also involved.
   C. The perineum may be stained with fresh blood and/or mucus.
   D. Digital rectal examination may elicit pain or tenesmus, or reveal bloody fluid, mucus, and/or foreign material.

Diagnosis

I. A presumptive diagnosis of large bowel disease is based on tenesmus, dyschezia, fresh blood and mucus in the stool, and an absence of other GI signs.

II. Fecal smears, flotations, or antigen tests are conducted to rule out parasitic and clostridial causes of acute large intestinal diarrhea (see Table 34-1).
   A. Thin fecal smears are made and stained with a Diff-Quik–type stain to identify the presence of high numbers of clostridial spores, which is supportive of the diagnosis.
   B. Gram or Wright-Giemsa stains demonstrate excess numbers of a uniform population of positively stained rods.
   C. Greater than five spores per high-power field is considered abnormal.
III. A positive response to treatment is supportive, as signs usually resolve rapidly after removal of the offending substance and symptomatic care.
IV. Failure to respond to therapy necessitates further diagnostic testing (Figure 34-1).
   A. A complete blood count (CBC) and biochemistry profile to rule out other systemic disease
   B. Bacterial culture, possibly using specialized media
   C. Abdominal radiography ± ultrasonography
   D. Colonoscopy and biopsy
   E. Identification of enterotoxin with reverse passive latex agglutination assays
      1. Only a small volume of fresh feces is needed; it is suspended in buffered saline, and 25 mL of the supernatant is used to detect enterotoxin.
      2. The presence of enterotoxin is not specific for clostridial colitis, because enterotoxin may also be produced in healthy dogs.

Differential Diagnosis

I. Acute, small intestinal diarrhea, especially hemorrhagic gastroenteritis: see Chapter 33
II. Chronic colitis: see Chronic Idiopathic Colitis

Treatment

I. Withhold food for 12 to 24 hours initially.
II. Allow access to water if the animal is not vomiting.
III. Consider subcutaneous fluids for mild dehydration.
IV. After 24 hours, provide small amounts TID to QID of a low-fat, highly digestible diet, such as rice with boiled chicken or low-fat cottage cheese, or prescription diets designed for large intestinal disorders.
V. Fiber may also be added in the form of psyllium or oat bran.
VI. The animal's normal diet may be slowly reinstituted after 3 to 5 days.
VII. Symptomatic medications may be needed to relieve pain, encourage rest, and decrease excess intestinal secretion.
   A. Motility modifiers
      1. Narcotic analgesics may be used for 24 to 48 hours, after GI obstruction has been ruled out.

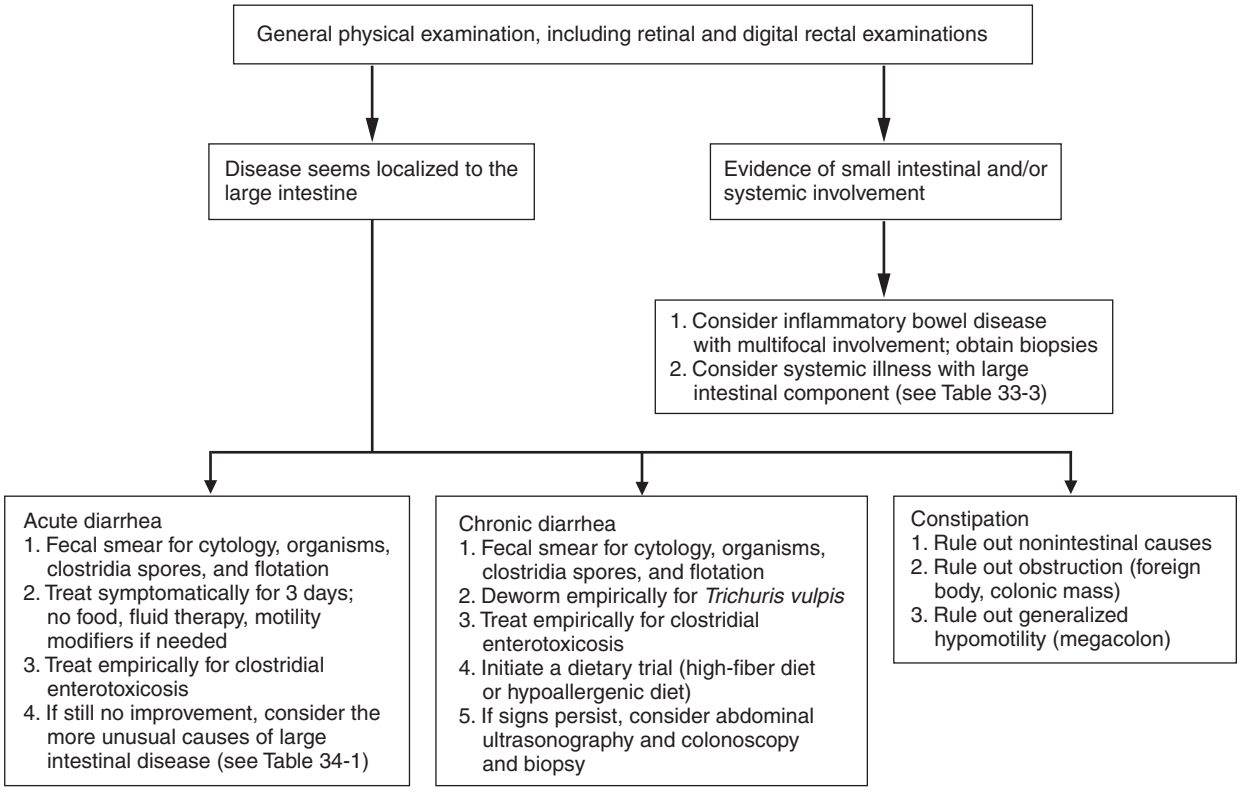

FIGURE 34-1 Diagnostic approach for animals with a history consistent with large intestinal disease. *Reprinted with permission from Bunch SE, Jergens AE: Diseases of the large intestines. p. 377. In Morgan RV, Bright RN, Swartout MS (eds): Handbook of Small Animal Practice. 4th Ed. WB Saunders, Philadelphia, 2003.*

a. Loperamide: 0.08 to 0.2 mg/kg PO TID to QID for dogs, 0.04 mg/kg PO SID to BID *cautiously* for cats
b. Diphenoxylate (with atropine to discourage abuse): 0.05 to 0.1 mg/kg PO TID to QID for dogs, 0.063 mg/kg PO TID for cats

2. They are contraindicated in diarrhea associated with endotoxin or enterotoxin, because they delay evacuation of toxic substances.

B. Antisecretory agents
1. Consider bismuth subsalicylate 1 to 2 mL/kg PO TID for dogs.
2. It causes the feces to appear very dark in color, which does not indicate melena.
3. It must be used cautiously in cats because of their inherent sensitivity to salicylates.

VIII. Specific therapies are instituted for any identified causes.
A. Clostridial enterotoxicosis, salmonellosis, campylobacteriosis, and other bacterial infections
1. Ampicillin or amoxicillin 22 mg/kg PO BID to TID
2. Metronidazole 10 to 15 mg/kg PO BID
3. Tylosin tartrate (2.27 g of tylosin per teaspoon) 10 to 20 mg/kg BID mixed in food

B. Discontinuance of any offending drugs
C. Antiparasitical agents: fenbendazole, praziquantel
D. Manual removal of foreign material, as needed
E. Removal of all identified stressors
F. Appropriate treatment for associated systemic diseases

Monitoring of Animal

I. Most cases of acute colitis resolve within 2 to 3 days with symptomatic or appropriate, specific therapy.
II. Recurrences are possible depending upon the cause, and some cases may become chronic (see Chronic Inflammatory Disorders).

Trichuriasis

Definition and Causes

I. Large bowel diarrhea may be caused by *Trichuris vulpis,* a widespread nematode parasite of dogs in North America.
II. Heavy infestations may involve the ileum, cecum, and colon.

Pathophysiology

I. The nematode burrows into the submucosa and causes varying degrees of mononuclear cell infiltration.
II. Parasite burden and location (focal versus diffuse), as well as the health status of the host, contribute to the degree of illness.
III. Heavy infestations may result in anemia from mucosal bleeding.
IV. The parasite may cause both acute and chronic large bowel diarrhea, owing to the following (Bunch and Jergens, 2003):
A. Hardiness of *Trichuris* spp. ova in the environment and likelihood of reinfection
B. Intermittent shedding of ova
C. Long prepatent period: 70 to 100 days
D. Longevity of the adult organism: months to years
E. Variations in host response and interaction with other parasites

Clinical Signs

I. Infection may be inapparent or signs of systemic illness may occur.
II. Parasite burden does not necessarily correlate with severity of clinical manifestations.
III. Most dogs have signs of large intestinal diarrhea.
IV. Weight loss, weakness, anorexia, polydipsia, and abdominal discomfort may be noted.
V. Dehydration, bradycardia, and hypothermia may be detected in animals with systemic signs.

Diagnosis

I. Ova may be found on fecal flotation, but infection cannot be ruled out with a single negative fecal flotation, as the nematode may only shed ova intermittently.
II. Rectal examination, performed to rule out other causes of hematochezia, is usually normal.
III. Response to empirical treatment in animals with a typical history, signs, and environmental risk for trichuriasis may also be diagnostic.
IV. Adult parasites can be visualized incidentally during colonoscopy.
V. Animals with systemic signs may have findings on a biochemistry profile similar to mineralocorticoid deficiency.
A. These include hypochloremia, hyponatremia, hyperkalemia, azotemia, poor urine concentrating ability, and metabolic acidosis.
B. Infected animals have normal adrenal responsiveness (both cortisol and aldosterone) after adrenocorticotropic hormone stimulation testing, however.

Differential Diagnosis

I. Other causes of acute and chronic colitis
II. Other intestinal parasites
III. Hypoadrenocorticism
IV. Cecal inversion
V. Colonic polyps or neoplasia
VI. Colonic motility disorders

Treatment

I. Fenbendazole is given at 50 mg/kg PO SID for 3 consecutive days.
II. Treatment is repeated in 3 weeks if other common GI parasites are present, and again 3 months later for *T. vulpis.*
III. Other supportive care (e.g., fluid therapy for dehydration) is provided as needed.

Monitoring of Animal

I. Because of intermittent shedding of ova, posttreatment fecal flotation cannot be used to judge treatment efficacy.
II. Retreatment is recommended if signs return, with or without a positive fecal flotation result.

III. For recurrences, or if reinfection is likely, heartworm preventive products that also include agents active against *T. vulpis* are recommended.
   A. Milbemycin oxime *(Interceptor)* 0.5 mg/kg PO once monthly
   B. Diethylcarbamazine with oxibendazole *(Filaribits Plus)* 6 mg/kg PO SID; possible adverse hepatic idiosyncratic reactions to this combination of drugs

CHRONIC INFLAMMATORY DISORDERS

Chronic Idiopathic Colitis

Definition

I. Chronic idiopathic colitis is also referred to as *inflammatory bowel disease* (IBD) and may be composed of three different forms of disease.
   A. In dogs and cats, lymphocytic-plasmacytic colitis is the most common form.
      1. Histologically, the lamina propria has inflammatory infiltrates of predominantly plasma cells and lymphocytes, with lesser numbers of neutrophils and eosinophils.
      2. Crypt dilatation and loss of epithelium are also common.
   B. Eosinophilic and histiocytic ulcerative colitis occur less frequently.
      1. Eosinophilic colitis is characterized by infiltration of the lamina propria with eosinophils.
      2. In cats, eosinophilic colitis may occur as a single entity or be a component of hypereosinophilic syndrome.
      3. Histiocytic, ulcerative colitis is an uncommon disease characterized by colonic mucosal ulceration and inflammation with periodic acid-Schiff (PAS)-positive histiocytes (macrophages).
      4. Histiocytic colitis of the boxer may also be referred to as *granulomatous colitis of boxers.*
   C. Granulomatous and suppurative colitis are uncommon entities.

II. Familial tendencies have been noted in some of these diseases.
   A. Basenji: lymphocytic-plasmacytic colitis (immunoproliferative enteropathy)
   B. Purebred cats: lymphocytic-plasmacytic colitis
   C. Boxer and French bulldog: histiocytic, ulcerative colitis
   D. Sporadic reports of ulcerative colitis: bull mastiff, Alaskan malamute, English bulldog, Doberman pinscher, a cat

Causes and Pathophysiology

I. The pathogenesis of idiopathic colitis or IBD may be immunologic because of the character of the most common cellular infiltrates and the positive response to treatment with immunosuppressive drugs or hypoallergenic diets.

II. Infection with adherent, invasive *Escherichia coli* may be associated with granulomatous colitis of boxers (Simpson et al., 2006; Van Kruiningen et al., 2005).

III. Regardless of the inciting cause, goblet cell hyperplasia with excess mucus production, mucosal inflammation and erosion, and hematochezia are common features.

IV. Inflammatory cell infiltrates can occur only in the large intestine or may involve the stomach and small intestine (see Chapters 31 and 33).

V. The degree and type of cellular infiltrate do not seem to correlate with severity of clinical signs.

Clinical Signs

I. Episodes of or prolonged (weeks) large bowel diarrhea occur.

II. Most affected dogs and cats are middle-aged.

III. Boxers with ulcerative colitis are often <2 years of age.

IV. Anorexia, vomiting, dehydration, and weight loss may occur if the large intestinal disease is severe or if the upper GI tract is involved.

V. Systemic signs (weight loss, debilitation) may be evident in boxers with histiocytic ulcerative colitis.

Diagnosis

I. Physical examination is often normal, except for digital rectal examination.
   A. Rectal examination may reveal thickened, irregular mucosa, mucus and fresh blood, and may precipitate tenesmus.
   B. It is also helpful to rule out other causes of large intestinal signs, such as masses, strictures, foreign bodies, perineal hernias, anal sac disease, and perianal fistulas.

II. A CBC, biochemistry profile, urinalysis, fecal flotation, and rectal cytology are indicated (see Figure 34-1).
   A. Laboratory test results are usually unremarkable.
   B. Eosinophilia may be seen with trichuriasis, eosinophilic colitis of dogs, and disseminated hypereosinophilic syndrome of cats.
   C. Neutrophilia, mild anemia, and hypoalbuminemia may be seen in some dogs with ulcerative colitis.
   D. Monoclonal or polyclonal gammopathy may accompany eosinophilic or plasmacytic enterocolitis.
   E. High serum alanine transaminase activity is often seen in cats.
   F. Rectal cytology may identify another causative agent (e.g., *Histoplasma* spp., *Prototheca* spp., *Cryptosporidium* spp.).

III. Cats are tested for feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV).

IV. A more aggressive diagnostic approach is undertaken in animals that do not respond to empirical treatment (see Treatment).
   A. Survey abdominal radiographs are usually unremarkable.
   B. Abdominal ultrasonography may show thickening of the walls of the large and small intestines and regional lymphadenopathy.
   C. Colonoscopy allows direct visualization of the mucosa, identification of masses, and biopsy of any identified lesions.
      1. The animal must be prepared adequately before colonoscopy.

a. Withhold food for 24 to 36 hours.
b. Administer an oral lavage solution (20 to 30 mL/kg divided in two doses 2 to 4 hours apart) the afternoon before the procedure.
c. Give 1 to 2 warm-water enemas the morning of the procedure.

2. Position the animal in left lateral recumbency.
3. Use a flexible fiberoptic endoscope to permit the most complete examination.
4. Take multiple biopsy specimens from several locations.
5. With lymphocytic-plasmacytic colitis, the colon may grossly appear normal or the mucosa may be hyperemic, with pale areas (cellular infiltrates).
6. With ulcerative colitis, colonoscopy reveals patchy red foci (pinpoint ulcerations), overt ulceration, thick mucosal folds, areas of granulation tissue, and strictures.

D. See additional tests described under Acute Colitis.

Differential Diagnosis

I. Acute colitis and its various causes
II. Trichuriasis: dogs
III. Infectious causes of chronic colitis (see Table 34-1)
  A. *Tritrichomonas foetus*: cat
  B. Histoplasmosis: dog, cat
  C. Protothecosis: dog
  D. FeLV, FIV: cat
IV. Antibiotic-responsive colitis: bacterial adherence or overgrowth
V. Dietary intolerance or allergy
VI. Cecal inversion or ileocolic intussusception
VII. Colonic polyps and neoplasms
VIII. Colonic strictures
IX. Irritable bowel syndrome
X. Small intestinal diarrhea and its causes: see Chapter 33
XI. Perianal fistulas in dogs
XII. Complication of pelvic irradiation

Treatment

I. Empirical treatment can be tried and helps to rule out other causes of chronic colitis.
  A. Dogs are dewormed for trichuriasis.
  B. Dogs (and perhaps cats) may also be treated empirically for clostridial enterotoxicosis (see Acute Colitis).
  C. Cats may be treated with metronidazole or fenbendazole for tritrichomoniasis.
  D. Dogs and cats are changed to a different, high-quality, easily digestible diet for 4 to 6 weeks.
    1. Several commercial products are available and marketed as large intestinal diets.
    2. Fiber is added to the diet in the form of soluble fiber, such as oat bran or psyllium,
      a. Add $^1/_4$ to 3 tablespoons/day PO.
      b. Some commercial diets already contain a soluble fiber.
  E. Novel protein diets that contain protein and carbohydrate sources not commonly found in commercial foods (e.g., duck, venison, rabbit) may also be tried.
  F. Hypoallergenic diets that contain hydrolysated protein may be tried.
II. Drugs that contain 5-aminosalicylic acid (5-ASA) are considered the preferred treatment for dogs with lymphocytic-plasmacytic and suppurative colitis.
  A. Sulfasalazine is initially given at 15 to 20 mg/kg PO TID and requires monitoring for side effects (e.g., keratoconjunctivitis sicca, polyarthritis, thrombocytopenia).
  B. Olsalazine does not contain a sulfa component, so there are fewer side effects, but the drug is more expensive.
    1. Initial dosage in dog is 5 to 10 mg/kg PO BID.
    2. The dosage may be tapered after signs are controlled for at least 1 to 2 weeks (usually after 3 to 4 weeks of treatment), and then decreased to the lowest effective dose.
  C. These drugs must be used very cautiously, and at reduced dosages and frequencies in cats because of their sensitivity to salicylates.
III. Other drugs can be added or tried for lymphocytic-plasmacytic colitis if clinical signs persist.
  A. Prednisone 2 mg/kg PO SID or divided BID in dogs and 2 to 4 mg/kg PO SID or divided BID in cats.
    1. It is the preferred drug in cats.
    2. It may allow the sulfasalazine dosage to be reduced further in dogs.
  B. Metronidazole may also be used at 10 to 15 mg/kg PO BID, then tapered to the lowest effective dose for long-term use.
  C. Tylosin tartrate (2.27 g of tylosin per teaspoon) may be used at 10 to 20 mg/kg PO BID mixed in food.
    1. It is safe for long-term use (weeks to months).
    2. Cats generally do not like the taste, so the powder may be compounded into a capsule.
  D. Probiotic bacteria (e.g., *FortiFlora*) may be tried SID in dogs and can be given long-term.
IV. Prednisone (see doses, discussed previously) is the drug of choice for eosinophilic and granulomatous (regional) colitis in dogs and cats.
V. Treatment for histiocytic ulcerative colitis in dogs initially involves adding soluble fiber to the diet and starting antimicrobial therapy.
  A. Supplement the existing diet with psyllium $^1/_2$ to 3 tablespoons/day PO, or change to a specially formulated diet containing soluble fiber.
  B. First choice antibiotics include the following:
    1. Enrofloxacin 5 to 15 mg/kg PO BID alone or with metronidazole and amoxicillin
    2. Metronidazole 15 mg/kg PO BID
    3. Tylosin 45 mg/kg PO SID to BID
  C. Antiinflammatory and/or immunosuppressive drugs may be tried if antimicrobials are ineffective.
    1. Prednisone 2 mg/kg PO SID or divided BID until clinical remission, then tapered slowly over 4 to 6 months
    2. Sulfasalazine 25 to 40 mg/kg PO TID

3. Azathioprine 2 mg/kg PO SID for 2 weeks then QOD

D. Anticholinergics are avoided, as they may worsen the clinical signs.

Monitoring of Animal

I. Drug therapy (5-ASA drugs and/or prednisone) may be tapered after signs have been resolved for at least 2 weeks.
II. Some animals require drug therapy for life, whereas in others the disease is controlled with diet alone (after drug discontinuation).
III. Keratoconjunctivitis sicca is a common adverse reaction to sulfonamide use, but may be reversible if detected early.
   A. Baseline Schirmer tear testing is performed before initiating therapy with sulfasalazine.
   B. Tear production is then assessed every 2 to 4 weeks in dogs receiving long-term sulfasalazine.

Fiber-Responsive Colitis

Definition and Causes

I. This term is used for cases of chronic colitis that respond well to only soluble fiber supplementation.
II. The cause is unknown.

Pathophysiology

I. Fiber administration has several beneficial effects on the colon.
II. Soluble fiber traps water and delays intestinal transit time, allowing excess water to be absorbed and fermented by intestinal bacteria, yielding more bacterial by-products.
III. Together with insoluble fiber, which is not digested, these effects increase fecal bulk.
IV. Increased fecal bulk stimulates rhythmic segmental contractions, further prolonging fecal transit time.
V. Both types of fiber bind bile acids, some of which are injurious to colonic mucosa.
VI. Anaerobic bacteria in the colon metabolize fiber, yielding short-chain fatty acids, such as butyric acid.

Clinical Signs

I. Clinical signs are generally intermittent.
II. Increased frequency of defecation of small amounts of feces mixed with fresh blood and/or mucus is the primary sign.
III. Signs of systemic illness are very uncommon.
IV. Results of the general physical examination are normal.
V. Digital rectal examination may be normal or reveal mild pain, fresh blood, or excessive mucus.

Diagnosis

I. The diagnosis is one of exclusion.
II. Affected animals usually do not respond to deworming for *Trichuris* spp., treatment for *Clostridium* enterotoxicosis, or use of a bland or hypoallergenic diet.
III. All diagnostic testing, including colonoscopy and biopsy, is unremarkable.

Differential Diagnosis

I. Other causes of chronic colitis: see Idiopathic Chronic Colitis
II. Other causes of acute colitis
III. Systemic illnesses that may affect the colon: histoplasmosis, protothecosis, etc.

Treatment and Monitoring

I. Add soluble fiber to the diet.
II. Supplement the existing diet with psyllium 1/2 to 3 tablespoons/day PO.
III. Alternatively, change to a specially formulated diet containing soluble fiber.
IV. Most signs resolve within a few days.

Irritable Bowel Syndrome

Definition and Causes

I. The disease resembles irritable bowel syndrome in humans, but dogs and cats do not have constipation as part of the disease.
II. It is not known whether the disorder represents undiagnosed clostridial enterotoxicosis or if it is a true motility disorder.

Clinical Signs

I. Signs of large bowel diarrhea occur intermittently.
II. A relationship with stressful events (e.g., boarding, travel, grooming, new members in the household, separation from the owner, or visits to the veterinarian) may be elucidated by careful questioning of the owner.
III. Affected animals may not outwardly appear excitable or overly anxious.
IV. There is no evidence of systemic illness, and results of a general physical examination are usually normal.
V. Digital rectal examination may be normal or reveal fresh blood or excessive mucus.

Diagnosis

I. The diagnosis is one of exclusion.
II. Affected animals usually do not respond to deworming for *Trichuris* spp., treatment for *Clostridium* enterotoxicosis, or use of a bland or hypoallergenic diet.
III. All diagnostic testing, including colonoscopy and biopsy, is unremarkable.

Differential Diagnosis

I. Other causes of chronic colitis: see Idiopathic Chronic Colitis
II. Other causes of acute colitis

Treatment and Monitoring

I. Soluble fiber is added to the diet.
   A. Supplement the existing diet with psyllium 1/2 to 3 tablespoons/day PO.
   B. Alternatively, change to a specially formulated diet containing soluble fiber.

II. If necessary, motility-modifying agents can be given to control acute episodes (see Acute Colitis).
III. An antianxiety agent may be tried in dogs.
  A. A combination of 5 mg chlordiazepoxide hydrochloride and 2.5 mg clidinium bromide *(Librax)* is available.
  B. Dosage is 0.10 to 0.25 mg/kg of clidinium PO BID to TID.
IV. The disorder is not life-threatening, but may be challenging to control.

NEOPLASIA

Definition

I. Many colonic tumors are malignant in dogs, and virtually all are malignant in cats.
II. Most primary tumors are solitary.
III. Mucosal adenomas (polyps) are the most common benign tumors.
  A. Small polyps are unlikely to represent premalignant lesions, although they can be multiple.
  B. Leiomyomas and other tumors have been reported sporadically.
IV. Adenocarcinoma is the most common malignant, primary tumor of dogs and often occurs in pedunculated or annular intraluminal forms in the rectum.
V. GI lymphoma may involve the small and/or large intestine and is the most common malignant tumor of cats.
  A. The large intestine may also be affected in multicentric lymphoma.
  B. Lesions may be focal and nodular or diffuse and infiltrative.
VI. Other primary tumors include leiomyosarcoma (especially cecal), carcinoid, extramedullary plasmacytoma, and mast cell tumor.

Causes and Pathophysiology

I. No causative factors have been identified in large intestinal cancer of dogs and cats.
II. Most cats with GI lymphoma are FeLV negative.
III. Most benign tumors are slow growing and cause intermittent signs for up to 12 months before diagnosis.
IV. Malignant tumors are usually detected within 3 months.

Clinical Signs

I. Male, medium- to large-breed dogs or domestic shorthair cats >9 years of age are most likely to have malignant tumors.
II. Hematochezia is the most common sign (82% of cases) (Valerius et al., 1997).
III. GI signs are those of chronic large intestinal diarrhea.
IV. Annular adenocarcinoma often causes tenesmus and constipation.
V. Persistent tenesmus can cause rectal prolapse.
VI. Occasionally prolapsed polypoid tumors may protrude from the anus.
VII. Some tumors (cecum) result in perforation and signs of septic peritonitis.
VIII. Upon abdominal palpation, large colonic tumors or general thickening (lymphoma) of the colon may be detected.
IX. On digital rectal examination a rectal adenocarcinoma often forms an annular constrictive lesion, which must be differentiated from inflammatory strictures from proctitis or colitis.
X. Systemic signs are variable and may include vomiting, dehydration, anemia, anorexia, and weight loss.

Diagnosis

I. Results of a CBC, biochemistry profile, and urinalysis are usually normal.
II. Extreme neutrophilia has been reported in a dog with a rectal adenomatous polyp (Thompson, 1992).
III. Survey radiographs are often normal.
IV. Abdominal ultrasonography may differentiate focal from diffuse lesions, and identify regional lymphadenopathy or involvement of the liver.
V. The most common malignant large intestinal tumors do not often disseminate to the lungs, but thoracic radiography is still recommended.
VI. Colonoscopy is useful to visualize tumors and to obtain multiple biopsies.
VII. Not all tumors are identified from endoscopic biopsy, so exploratory laparotomy and full-thickness biopsies may be required to achieve a diagnosis.

Treatment

I. Some tumors can be treated with surgical resection.
  A. Rectal adenoma (polyp)
  B. Distal rectal polypoid adenocarcinoma
  C. Solitary cecal or colonic tumor of any cell type (with wide margins)
II. Large intestinal lymphoma is not as responsive as the multicentric form, but chemotherapy may be tried (see Chapter 69).
  A. Small-cell lymphoma in cats is usually treated with prednisone (or prednisolone) and chlorambucil, and long-term remissions may be achieved in these cats.
  B. Start prednisone at 5 mg PO BID and chlorambucil at 15 mg/m^2 PO SID for 4 days then and repeated every 3 weeks.
  C. Alternatively, give chlorambucil at 6 mg/m^2 PO QOD.
III. Annular rectal adenocarcinoma is difficult to treat.
  A. Local resection and cryosurgery may offer longer survival times than radical resection.
  B. Radiation therapy has been successful in a small number of dogs (Straw, 1996).
  C. Palliative therapy with stool softeners or a colostomy may be tried because distant metastasis is unusual.
  D. Local recurrence is the most common cause of euthanasia.

Monitoring of Animal

I. Recurrence is common (41% of cases) (Valerius et al., 1997), with signs of hematochezia, dyschezia, tenesmus, and mucoid stools.

II. Recurrence is higher in dogs with multiple masses, diffuse disease, or carcinoma in situ (Valerius et al., 1997).
III. Increased survival times are seen in dogs with adenomas, carcinoma in situ, noninvasive carcinomas, and wide, clean margins after surgical excision (Wolf et al., 1997).

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CHAPTER 35

Diseases of the Anus and Perianal Region

Eric R. Pope

CONGENITAL DISORDERS

Imperforate Anus

Definition and Causes

I. *Imperforate anus* is the general term used to describe a group of abnormalities that result in either a reduced ability or inability to pass feces from the rectal tube.
II. Four types have been documents (Vianna and Tobias, 2005).
  A. Congenital anal stenosis
  B. Imperforate anus alone
  C. Imperforate anus with termination of rectum as a blind pouch
  D. Discontinuity of the proximal rectum with normal anal and terminal rectal development (atresia ani)
III. Atresia ani occurs as a failure of the cloacal membrane that separates the anal invagination and rectum to resorb.
IV. All types usually have an intact external anal sphincter and associated nerve supply, as well as normally developed anal sacs.

Pathophysiology

I. The inability or reduced ability to pass feces results in abdominal distention and ultimately signs of a lower intestinal obstruction.
II. As the abdominal distention worsens, the puppy or kitten becomes restless and anorexic.

Clinical Signs

I. Congenital anal stenosis
  A. Clinical signs may not become apparent before weaning.
  B. Tenesmus and constipation develop.
II. Atresia ani
  A. Tenesmus
  B. A bulging anal dimple in the absence of an anal orifice
  C. Absence of feces
  D. Abdominal distention and/or discomfort
  E. Restlessness, decreased vigor

Diagnosis

I. Signalment
  A. Females at greater risk
  B. Breed predisposition: poodle, Boston terrier
II. Suspicious history and clinical signs
III. Compatible physical examination findings
  A. Bulging perineum and anal dimple with atresia ani
  B. Possibly abdominal distention
IV. Horizontal-beam radiography
  A. It aids in determining point of termination of the rectum.
  B. Elevate hind end.
  C. Migration of gas to distal colon and rectum helps to define the limits of the rectal pouch.
  D. The reliability of the technique depends on the following:
    1. Amount of gas used: air introduced into stomach by tube can migrate caudally
    2. Consistency of feces in terminal rectum: possible decreased migration of gas

Differential Diagnosis

I. Congenital rectal stricture
II. Congenital anal stenosis

Treatment

I. For atresia ani, incise skin over the anus with a cruciate incision.
II. Identify and avoid the external anal sphincter and anal sac openings.
III. Mobilize the rectal pouch and incise in a cruciate pattern over the imperforate rectum.
IV. Suture the rectum to subcutaneous tissues and skin with interrupted sutures.

Monitoring of Animal

I. Fecal incontinence may be a sequela.
  A. Normal anal sphincter function may be absent depending on the amount of damage caused by the surgical reconstruction.
  B. Incontinence can also result from lack of normal sensation in the rectal segment.
II. Small and debilitated animals may not survive the surgical correction.

DEGENERATIVE DISORDERS

Fecal Incontinence

Definition

Fecal incontinence is the inability of the animal to retain feces until defecation is appropriate.

Causes

I. Sphincter mechanism dysfunction
   A. Neurological dysfunction from damage to the lower sacral (S) spinal cord (S1 through S3 cord segments) or to local innervation of the anorectal area
      1. External anal sphincter damage
         a. Fractures of the lower lumbar and/or sacral vertebrae
         b. Sacrococcygeal luxations
         c. Spinal cord disease: fibrocartilaginous emboli, neoplasia
         d. Surgical trauma: perineal hernia repair in dogs, perineal urethrostomy in cats
         e. Penetrating wounds: bite wounds, gunshots
      2. Internal anal sphincter damage
         a. Most causes of internal anal sphincter dysfunction are ill defined.
         b. It is occasionally encountered as an isolated disorder in aged dogs.
   B. Sensory incontinence
      1. Sensory receptors in the wall of the rectum and pararectal musculature respond to dilatation of the rectum by feces.
      2. Interruption of interplay between these receptors results in inappropriate defecation, because an increase in the tone of the external anal sphincter does not occur.
   C. Nonneurogenic causes
      1. Inflammatory diseases of the perianal and anorectal area
      2. Surgical trauma to sphincter musculature
      3. Neoplasia
II. Loss of reservoir function following resection of proximal two thirds or more of the colon

Pathophysiology

I. The internal anal sphincter is controlled by the autonomic nervous system and maintains a high level of tone that is primarily responsible for continence at rest.
II. The external anal sphincter is tonically active, with contraction occurring during peristaltic activity to prevent inappropriate defecation.
III. Dysfunction or loss of sensory receptors in the rectal muscularis and pararectal muscles or their afferent nerve fibers interrupts the coordination between the internal and external anal sphincters.
IV. Dysfunction of the spinal cord segments S1 through S3 or their somatic efferents destroys function of the external anal sphincter.
   A. Unilateral damage of peripheral efferents causes only transient incontinence.
   B. Incontinence is transient because of decussation of muscle fibers and cross-innervation.
V. Dysfunction or disruption of the hypogastric nerves or pelvic plexus interferes with internal anal sphincter function.

Clinical Signs

I. Sphincter mechanism dysfunction
   A. Flatulence with usually normal stool consistency
   B. Involuntary or inappropriate defecation
      1. It occurs with exercising, barking, or becoming excited.
      2. Animal is unaware that feces are being passed and does not posture normally.
   C. Soiling of perineal region between defecations
II. Loss of reservoir function: frequent passage of abnormally soft, unformed, or liquid feces

Diagnosis

I. History
   A. Owner complaint of unconscious defecation by the animal
   B. Known spinal cord disease, previous lumbar or sacrococcygeal trauma
   C. Inflammatory disease of the colon or rectum
   D. Perianal fistulas
   E. Previous surgery to anorectal or perineal region: congenital anorectal disease, perineal hernia, perianal fistulas, anal or rectal neoplasia
II. Physical examination
   A. Sphincter mechanism incontinence
      1. Anus is dilated on visual inspection.
      2. Soiling of the perineal region is common, especially if the tail is flaccid.
      3. Decreased or absent anal sphincter tone is detected on rectal examination.
      4. Decreased or absent perianal reflex is noted.
      5. With nonneurogenic causes, the perianal reflex may be intact, but anal constriction is impaired mechanically.
      6. A thorough neurological examination may reveal sensory and motor deficits to other perineal structures, such as the tail, pelvic limbs, and urinary bladder.
   B. Sensory incontinence
      1. Normal external anal sphincter tone
      2. Soiling of perineal region, indiscriminate passage of feces
III. Other tests
   A. Radiography is indicated to investigate possible spinal cord disease and musculoskeletal injuries.
   B. Electromyographic studies may be helpful for demonstrating denervation, as suggested by positive sharp waves and fibrillation potentials.

Treatment

I. Denervation of the external anal sphincter is often a permanent, untreatable condition.

II. Reinnervation may be possible if the neurolemmal sheath and nerve cell bodies are intact.
III. If other neurological deficits exist, the animal may no longer be a functional pet.
IV. Symptomatic care for mild or nonneurogenic incontinence includes the following measures:
   A. Give multiple feedings per day of a low-bulk diet.
   B. Exercise the dog immediately after eating to encourage elimination.
   C. Walk frequently during the day.
   D. Do not feed the animal near bedtime.
   E. Tail amputation may make husbandry easier if the tail is paralyzed.
V. A silicone elastomer sling is effective in restoring continence in normal dogs with experimentally created fecal incontinence, but results in clinical cases have been mixed (Dean et al., 1988).
VI. Sensory incontinence is permanent.
VII. Intestinal adaptation generally results in significant improvement of clinical signs over time in animals with reservoir incontinence.

Monitoring of Animal

I. Incontinence may be transient or permanent, depending on the etiology (e.g., inflammatory, postsurgical).
II. Prognosis is guarded to poor regardless of cause.
III. Most causes of incontinence related to surgery can be avoided with careful dissection by an experienced surgeon.

Rectal Deviation and Sacculation

Definition

I. Rectal deviation is an S-shape or similar curve in the rectal tube.
II. Rectal sacculation is a dilatation of the lateral rectum, usually at its terminal extent.

Causes and Pathophysiology

I. Rectal deviation and sacculation are most commonly associated with perineal hernia (see later in this chapter)
II. The muscles of the pelvic diaphragm normally provide the support that prevents the rectum from deviating laterally or bulging out as peristaltic contractions push feces caudally.

Clinical Signs

I. Tenesmus and dyschezia may be present.
II. A large bulge occurs lateral and cranial to the anorectal junction, especially when defecating.

Diagnosis

I. History of tenesmus
II. Physical examination findings
   A. Bulging rectum
   B. Palpation of a feces-filled pouch in the rectum just proximal to the anus
   C. ± Palpable hernial ring
III. Barium enema demonstrating an outpouching
IV. Proctoscopy and/or colonoscopy to confirm the diagnosis

Differential Diagnosis

I. Perineal hernia with retroflexed urinary bladder
II. Prostatic disease with perineal location of a prostatic or paraprostatic cyst
III. Prior trauma
IV. Neoplasia, especially tumors of the perineum or pelvic canal

Treatment

I. Correct the underlying cause.
II. Correcting a perineal hernia restores the lateral support of the rectal wall, facilitating defecation.
III. Low-residue diets and stool softeners may alleviate symptoms in some dogs.
IV. A colopexy performed with cranial traction on the rectum helps palliate signs of rectal deviation and sacculation if perineal herniorrhaphy is unsuccessful.

Monitoring of Animal

I. Deviation and/or sacculation may recur if associated with a perineal hernia and the repair fails.
II. Imbrication or excision of affected tissue is seldom indicated and carries an additional risk of infection caused by subcutaneous exposure to colonic contents.

Anorectal Stenosis and Stricture

Definition

I. Anorectal stenosis is a partial obstruction of the anal or rectal lumen by intraluminal or extraluminal lesions.
II. Anorectal stricture is diminution in size of the anal or rectal lumen, either from cicatricial contracture or deposition of abnormal tissue.

Causes

I. Secondary to underlying diseases
   A. Anorectal abscesses
   B. Perianal fistulas, chronic anusitis, or proctitis
   C. Neoplasia
II. Trauma
   A. Accidental injuries
   B. Surgical complication, especially after perianal fistula surgery and rectal resection for prolapse or neoplasia
   C. Ingestion or malicious placement of a foreign object

Pathophysiology

I. Diseases affecting >50% of the circumference of the anus or rectum result in partial or complete obstruction.
II. Any disease or trauma evoking an inflammatory response in the anorectal region can cause a constricting ring of scar tissue to form.
III. Rectal adenocarcinomas often involve the rectal wall circumferentially as they increase in size.

Clinical Signs

I. Thin, ribbon-type stools
II. Tenesmus, dyschezia, hematochezia
III. Megacolon with constipation
IV. Incontinence

Diagnosis

I. History and clinical signs are helpful.
II. Rectal palpation reveals a mass obstructing part of the rectal lumen.
III. A constricting ring that does not relax when the animal is under anesthesia is found on rectal palpation.
IV. If the obstruction or stricture is more cranial, contrast radiography (barium enema) aids in the diagnosis.
    A. It helps delineate the extent of the stricture.
    B. It may also demonstrate megacolon rostral to the stricture.
V. Proctoscopy allows direct visualization of intraluminal lesions.
    A. It helps in determining the exact location and extent of the lesion.
    B. It aids in obtaining a biopsy specimen to rule out neoplasia.
VI. Computed tomography (CT) can be used to assess the extent of involvement of extraluminal disease processes.

Differential Diagnosis

I. Spastic rectum (functional stricture) associated with proctitis or anal sac disease that disappears with a surgical plane of anesthesia
II. Extraluminal masses within the pelvic canal
    A. Urogenital tract
    B. Pelvis
    C. Pelvic musculature
    D. Soft tissues: sarcomas

Treatment

I. Dietary management includes stool softeners and a low-residue diet.
II. If tumor is suspected, a biopsy is performed before any surgical intervention.
III. If malignancy is diagnosed, a work-up for metastasis is indicated with thoracic and abdominal radiographs, ultrasonography, and CT scan.
IV. Simple circular rectal strictures may respond to repeated balloon dilatation with concurrent use of prednisone 1 mg/kg PO BID for 14 days and then tapered.
V. Surgery is indicated if dietary management and balloon dilatation are unsuccessful in alleviating the signs or if neoplasia is diagnosed; however, the risk of causing damage to the external anal sphincter must always be considered when deciding to do surgery in this region.
VI. Surgical techniques include the following:
    A. Anal stricture
        1. If the stricture is not too severe, two to four longitudinal incisions made through the stricture site are sutured transversely to enlarge the anal opening.
        2. With more extensive lesions, excise the fibrotic ring and suture the rectal mucosa to the anal skin (modified rectal pull-through) in an effort to preserve anal sphincter function.
    B. Rectal stricture
        1. Longitudinal incisions made through the stricture at the 12, 3, 6, and 9 o'clock positions are closed transversely.
        2. With more severe lesions, excise the stricture completely and anastomose the rectum with simple interrupted appositional sutures.
            a. Strictures located near the anorectal junction may be accessible through the anus.
            b. More cranial lesions are exposed using the dorsal approach to the anus (Holt et al., 1991).
        3. Treat rectal and colonic strictures secondary to neoplasia palliatively by inserting an intraluminal stent (Hume et al., 2006).

Monitoring of Animal

I. Simple circular strictures often respond to balloon dilation, but it may be necessary to repeat this procedure several times.
II. If surgery is performed, recurrence of the stricture is possible regardless of the procedure used.
III. Tenesmus and rectal prolapse may occur postoperatively secondary to the inflammation of surgery and the presence of suture material in the rectum.
IV. Incontinence may be a sequela to any corrective surgery.
V. Prognosis is guarded to poor if the underlying cause is rectal carcinoma.
VI. High-risk patients and those with inoperable disease may be managed successfully with dietary changes, including stool softeners, low-residue foods, or laxatives.

Perineal Hernia

Definition

A perineal hernia is a disruption of the pelvic diaphragm musculature that allows contents of the pelvic canal and/or abdominal cavity to herniate into the perineal subcutaneous tissues.

Causes

I. The exact etiology is unknown.
II. Degenerative changes of the muscles of the pelvic diaphragm occur, especially the levator ani muscle.
III. Imbalance of androgenic and estrogenic hormone levels or alteration in their receptors in the pelvic diaphragm musculature may be present.
IV. The levator ani is thinner and narrower and has a weaker fascial attachment to the external anal sphincter and rectal wall in the male dog, which may be a contributing factor.
V. Prostatic disease (e.g., benign prostatic hyperplasia) causing tenesmus can lead to a hernia.
VI. Tenesmus secondary to chronic constipation and obstipation from various causes also lead to pelvic musculature weakness.

VII. It is a rare but potential surgical complication after perineal urethrostomy in cats.

Pathophysiology

I. Partial or total rupture of the muscles forming the pelvic diaphragm is likely, especially the levator ani muscle.
II. Four types of hernia have been described, namely the caudal, dorsal, ventral, and sciatic.
III. The caudal type is most common and occurs between the external anal sphincter and the levator ani.
IV. Loss of support of the rectal wall allows the rectum to deviate, interfering with normal defecation.
V. Retroflexion of the urinary bladder into the hernia results in urinary obstruction that can lead to a life-threatening nephropathy.

Clinical Signs

I. Soft, reducible, nonpainful swelling in the ventrolateral perineum on one or both sides of the anus
II. Constipation, tenesmus
III. Dyschezia, fecal incontinence
IV. Dysuria if bladder is retroflexed into the ischiorectal space
V. Systemic signs associated with organ entrapment (e.g., uremia) or concurrent disease (e.g., prostatitis)

Diagnosis

I. Signalment and history
   A. Intact middle-aged to older male dog
   B. Constipation, straining to defecate, or bulge in perineum
II. Compatible clinical signs
III. Palpation of a defect in the pelvic diaphragm externally, after manual reduction of the hernial contents
IV. Palpable defect of the pelvic diaphragm musculature on rectal examination
V. The presence of impacted feces in a rectal sacculation
VI. Nonreducible, painful, fluid-filled perineal mass with signs of uremia and the inability to pass a urinary catheter (urinary bladder retroflexion)
VII. Discoloration of the skin overlying a retroflexed bladder
VIII. Radiography
   A. Survey radiographs show a soft-tissue mass or fecal material in the perineal area.
   B. Barium enema demonstrates a rectal deviation or sacculation.
   C. Urethrocystogram sometimes demonstrates a misplaced bladder or prostate.

Differential Diagnosis

I. Rectal diverticulum without a perineal hernia
II. Neoplasia
III. Caudally located paraprostatic cyst

Treatment

I. Dietary management
   A. Low-residue food
   B. Stool softeners
   C. May be tried as primary management in dogs with minimal signs or in those instances in which the anesthetic risk is too great for surgical correction
   D. As an adjunct to surgical therapy
II. Digital removal of feces and enemas during episodes of obstipation or tenesmus
III. Castration to help decrease the size of the prostate
IV. Treatment of choice: herniorrhaphy
   A. Reduce the hernia using blunt dissection.
   B. Remove the hernial sac and excessive fat.
   C. Protect the pudendal nerve and internal pudendal artery and vein, located in the ischiorectal fossa on the ventrolateral surface of the coccygeus muscle.
   D. Be aware of the location of the caudal rectal nerves and anal sacs during placement of sutures in the external anal sphincter.
   E. Use the thick perineal subcutaneous tissue (perineal fascia) to provide additional support to the primary repair technique.
   F. Standard suture reconstruction consists of suturing together muscles that normally form the pelvic diaphragm, including the external anal sphincter, lateral coccygeus, and internal obturator muscles.
   G. Internal obturator muscle flap transposition is the most reliable surgical technique, particularly for large and bilateral hernias, and is associated with a low rate of recurrence.
   H. Implants can be used to augment the previously mentioned repairs or when other techniques fail.
      1. Synthetic materials, such as polypropylene mesh
      2. Biological implant (processed swine intestinal submucosa) (Stoll et al., 2001)
   I. Salvage procedures are used when primary repair is not indicated or has failed.
      1. Semitendinosus muscle flap for ventrally located hernias (Mann and Constantinescu, 1998)
      2. Colopexy and cystopexy
         a. Colopexy eliminates or reduces severity of rectal deviation or sacculation, thereby facilitating defecation.
         b. Cystopexy prevents retroflexion of urinary bladder.
   J. Retroflexion of the urinary bladder into the ischiorectal fossa is an emergency and is managed as follows:
      1. Attempt catheterization of the bladder and, if unsuccessful, perform cystocentesis percutaneously to reduce size of the bladder, and then repeat catheterization attempt.
      2. Stabilize animal and treat for uremia before performing definitive repair of the hernia.
      3. If the urinary bladder is incarcerated and cannot be catheterized or repositioned, perform perineal herniorrhaphy on an emergency basis.

Monitoring of Animal

I. Animals exhibiting excessive pain or signs of sciatic nerve paralysis should be evaluated for potential nerve entrapment by sutures.

II. Withhold food and water for 1 day postoperatively.
III. Place on a low-residue diet and stool softeners for 2 to 4 weeks.
IV. Recurrence is possible and is affected by the technique used and the experience of the surgeon.
V. Fecal incontinence is more likely if the repair is bilateral.
VI. Rectal prolapse can be a transient problem, particularly if sutures penetrate the rectal lumen.
VII. Wound infection may occur.
   A. Because infection may be related to sutures being placed in the colon, suture removal and exploration of the infected wound is necessary.
   B. Antibiotics help prevent a postoperative infection caused by contamination at the time of surgery.
   C. Give cefoxitin 30 mg/kg IV 30 minutes before surgery, and two more injections IM at 1.5-hour intervals thereafter.

INFLAMMATORY AND INFECTIOUS DISEASES

Proctitis

Definition and Causes

I. Inflammation of the rectum
II. Arises with infectious or inflammatory diseases involving the colon and other portions of the intestinal tract
III. Occurs secondary to foreign bodies, such as sharp objects
IV. May follow surgical trauma involving the rectum

Clinical Signs

I. Unproductive tenesmus
II. Assuming the posture for defecation for prolonged periods of time
III. Hematochezia, dyschezia

Diagnosis

I. History of ingesting a foreign body, concurrent intestinal disease, or recent surgery to the region
II. Thickening of the rectal mucosa on digital rectal examination
III. Fresh hemorrhage following digital examination
IV. Proctoscopy revealing inflamed, swollen, or ulcerated rectal mucosa
V. Colonoscopy and fecal cultures to identify more diffuse involvement
VI. Plain radiography revealing a foreign body if it is radiopaque
VII. Biopsy and histopathology necessary to confirm the diagnosis

Differential Diagnosis

I. Lower bowel disease
II. Rectal neoplasia
III. Anorectal stricture
IV. Masses in the pelvic canal
V. Prostatomegaly

Treatment

I. Treat or eliminate the underlying cause.
II. Hydrocortisone retention enemas may decrease inflammation.
III. Local anesthetic gel in the rectum may help reduce tenesmus.
IV. Feed low-residue foods and stool softeners for 7 to 10 days.

Monitoring of Animal

I. A good prognosis is expected if stricture is not a sequela.
II. Proctitis is often a self-limiting disease if the cause is removed (e.g., foreign body).

Rectal Prolapse

Definition

I. Eversion of one or more layers of the rectal wall through the anus
II. Complete: all layers involved
III. Incomplete: only rectal mucosa everted

Causes

I. Persistent straining caused by intestinal or urogenital disease
   A. Severe enteritis, including that caused by endoparasites
   B. Foreign bodies
   C. Neoplasia of rectum or distal colon
   D. Rectal deviation
   E. Dystocia
   F. Feline urologic syndrome
   G. Prostatic disease
II. Breed predisposition: Boston terrier, Manx cats
III. Prior rectal or perineal surgery

Clinical Signs

I. Incomplete prolapse
   A. Only a slight protrusion of mucosa
   B. Worsens immediately after defecation
II. Complete prolapse
   A. Prolapsed tubular mass with a depression in the end
   B. Everted rectal tissue swollen, edematous, and reddened
   C. Possible areas of ulceration or necrosis secondary to chronic exposure or vascular compromise
   D. Most commonly occurs in kittens and puppies <4 months of age
III. Possible tenesmus or pain

Diagnosis

I. Based on history and clinical signs
II. Confirmed by physical examination findings

Differential Diagnosis

I. Prolapsed ileocolic or colonic intussusception must be considered.
II. Grossly, rectal prolapse and prolapsed intussusception appear similar, but signs of partial or complete obstruction usually accompany the latter.

III. With rectal prolapse, a lubricated probe does not pass between the rectal wall and the prolapsed mass.
IV. With prolapsed ileocolic or colonic intussusception, the probe passes freely between the protruding mass and the rectal wall.

Treatment

I. Treat or remove any underlying cause.
II. Conservative management of rectal prolapse is attempted if the prolapse is viable and reducible.
  A. Apply a warm isotonic or hypertonic solution to the mucosa.
  B. Gently massage prolapsed mucosa to remove edema.
  C. Reduce the prolapse and place a loose, purse-string suture in the anus using 2-0 monofilament nonabsorbable suture material.
  D. A thermometer or syringe casing of appropriate size is used to avoid overtightening of the purse-string suture.
  E. Feed a low-residue diet and give stool softeners.
  F. Remove purse-string suture in 7 to 10 days.
  G. Continue dietary management and stool softeners until the underlying cause is corrected.
III. Surgical correction is indicated if the prolapse recurs, or if it is nonviable or irreducible.
  A. Use colopexy to treat and prevent recurrent rectal prolapse.
  B. Amputation of the prolapsed rectum may be indicated.
    1. Amputation is the treatment of choice if the rectal mucosa is necrotic, lacerated, or irreducible.
    2. Perform amputation if more conservative methods fail (purse-string or colopexy).
    3. Administer cefoxitin 30 mg/kg IV 30 minutes before surgery, followed by 30 mg/kg IM at 1.5-hour intervals for two more doses.

Monitoring of Animal

I. Recurrence is likely with more conservative methods, especially if the underlying cause is not addressed concomitantly.
II. Stenosis or incontinence is not uncommon after rectal surgery; therefore, more conservative methods of treatment are tried first whenever possible.

Anal Sac Disease

Definition

I. Anal sac impaction: retention of anal gland secretions
II. Anal sacculitis: inflammation and/or infection within the anal sac
III. Anal sac abscess formation: rupture of the anal sac secondary to obstruction of the duct or stasis of secretions and secondary infection

Causes

I. Not fully understood, but related to changes in the ability to empty anal sacs normally
II. Environmental and dietary factors (e.g., a high-fat diet leading to loose stools)
III. Breed predisposition: more common in small breeds, especially the poodle and Chihuahua
IV. Abnormally small duct system leading to obstruction
V. External anal sphincter dysfunction
VI. Hypersecretion of anal glands, possibly related to seborrhea
VII. Change in character of the secretions
VIII. Chronic diarrhea

Pathophysiology

I. Retained secretions evoke an inflammatory response within the anal sac.
II. Bacteria proliferate in the trapped secretions.
III. Severe cellulitis ensues, followed by potential abscess formation.
IV. Anal sacculitis and abscessation can be extremely painful, causing reluctance to defecate and constipation.

Clinical Signs

I. Licking and biting at tailhead region or tail chasing
II. Rubbing anus on ground or "scooting"
III. Discomfort when sitting or reluctance to sit
IV. Tenesmus, pain, or reluctance to defecate
V. Redness and/or swelling over anal sac region
VI. Perianal draining tract from abscessation

Diagnosis

I. Clinical signs often localize the disorder to the perianal area or specifically to the anal sacs.
II. Physical examination reveals one of the following:
  A. Impaction
    1. Firm, swollen anal sac
    2. Difficult or impossible to express contents
    3. Secretions thick and pasty
  B. Hypersecretion: voluminous secretion that is more liquid than normal
  C. Sacculitis
    1. Foul, purulent, and/or bloody material expressed from sac
    2. Overlying skin possibly reddened and painful on palpation
  D. Abscess formation
    1. Presence of an open wound or draining tract that communicates with the sac
    2. Usually unilateral

Differential Diagnosis

I. Anal sac neoplasia
II. Perianal gland neoplasia
III. Perianal fistulas
IV. Perianal trauma, especially bite wounds
V. Urinary tract or perivulvar infections in the female

Treatment

I. Anal sac impaction
  A. Express anal sacs by squeezing the skin overlying the anal sac or by internal compression applied by a finger inserted into the rectum.

B. If unsuccessful, consider sedation to facilitate further treatment.
C. If secretions are inspissated, instill saline or mineral oil to soften them before expression.
D. Flush out sacs with saline or antiseptic solution (0.1% povidone-iodine, 0.05% to 0.1% chlorhexidine).
E. Repeat manual expression weekly for 3 to 4 weeks.
F. If secretions remain thick or impaction is recurrent, anal sacculectomy may be necessary.

II. Anal sacculitis
A. Manually express the anal sacs every 5 to 7 days for three to four treatments.
B. Sedation is usually necessary because of pain.
C. Irrigate with antiseptic solution as for anal sac impaction, but only after samples for culture and sensitivity testing are taken, especially if the infection is recurrent.
D. Antibiotic solutions can be instilled into the anal sacs after irrigation.
E. Institute oral antibiotics for 10 to 14 days.
F. Instruct owner to apply hot compresses BID for 5 to 7 days.
G. Anal sacculectomy may be necessary, especially if repeated expressions, flushes, and antibiotic instillations are unsuccessful in controlling either anal sac impaction or infection.

III. Abscess formation
A. Heavily sedate or anesthetize the animal to allow thorough inspection and treatment.
B. Lance abscess and express anal sac rectally if eruption and drainage has not occurred spontaneously.
C. If already ruptured, cannulate duct and flush area well with antiseptic solution.
D. Submission of specimens for culture and sensitivity is ideal, but empirical treatment with broad-spectrum antibiotics can also be performed, particularly if it is a first occurrence.
E. Instruct owner to apply hot compresses BID for 5 to 7 days.
F. Irrigate abscess cavity with antiseptic solution BID for 3 to 5 days (longer if wound remains open or discharge persists).
G. If abscessation is recurrent, consider anal sacculectomy after abscess has healed.
H. Bilateral anal sacculectomy is recommended even if only one side appears to be involved.

Monitoring of Animal

I. Anal sac impaction and inflammation often recur.
II. It is important to maintain a regular schedule of anal sac expression if the animal is prone to recurrence (e.g., every 4 to 6 weeks).
III. In some instances, the owner can be taught how to express the anal sacs.
IV. A change in diet that allows more normal stool consistency may help control impaction (e.g., changing from a canned food diet to a dry ration, lowering fat content, etc.).
V. Draining tracts that develop after anal sacculectomy are usually the result of incomplete removal and may require exploratory surgery with excision of any remaining tissue to achieve complete resolution.
VI. Fecal incontinence is a potential complication of anal sacculectomy, especially when done bilaterally.

Perianal Fistula

Definition

I. Chronic, painful, inflammatory condition involving the perianal tissues
II. Results in ulcerative lesions in the skin and deeper draining tracts with a malodorous discharge

Causes

I. Genetic predisposition
A. It is reported in many breeds, but the German shepherd dog and Irish setter are most commonly affected.
B. Although conformation may contribute (broad, flat tailhead resulting in a fecal film over the perineal area), only a small percentage of dogs with this conformation are affected.

II. Immunological defect (Wyatt, 1998)
III. Concurrent colitis, especially in German shepherd dogs (Harkin et al., 1996)

Pathophysiology

I. Lesions begin as periappendageal inflammation in the dermis, with infiltration of lymphocytes, plasma cells, and eosinophils.
II. Progression of the inflammation leads to the development of ulcerative lesions and draining tracts (sinuses) of variable depth.
III. True rectal-cutaneous fistulas are uncommon.
IV. The fibrosis that develops with chronic lesions may lead to anal stenosis and stricture.

Clinical Signs

I. Onset often insidious and may go unnoticed
II. Excessive licking of the perianal region
III. Single or multiple draining tracts with thick, malodorous discharge
IV. Perianal hemorrhage
V. Dyschezia
VI. Tenesmus or constipation
VII. Personality change
VIII. Pain on raising tail and with rectal palpation

Diagnosis

I. Breed of dog is suggestive.
II. Physical examination shows typical lesions, and removal of hair often reveals a greater extent of involvement.
III. Proctoscopy and colonoscopy are performed to identify concurrent colonic involvement.

Differential Diagnosis

I. Anal sac abscesses with fistulas directly overlying the anal sac

II. Perianal tumors, especially squamous cell carcinoma and adenocarcinoma
III. Autoimmune skin disease
IV. Anusitis
V. Perianal irritation from caustic or thermal injury and trauma

Treatment

I. Medical management is recommended as the initial treatment for most cases.
   A. Immunosuppressive drugs
      1. Cyclosporine
         a. Dosage is 4 to 8 mg/kg PO BID initially (6 to 12 weeks) and then tapered, for a total of 18 to 20 weeks of treatment (Patterson and Campbell, 2005).
         b. Treating with the higher initial dose and then tapering over a longer time period may provide a faster resolution and fewer relapses.
      2. Prednisone
         a. Give 3 to 4 mg/kg PO SID for 3 to 6 weeks, then slowly taper to 1 mg/kg SID to QOD.
         b. Monitor for relapses as the dose is tapered (Patterson and Campbell, 2005).
         c. Prednisone is recommended primarily for dogs with mild lesions.
      3. Azathioprine
         a. Dose is 50 mg PO SID (Tisdall et al., 1999).
         b. Treat for 4 to 6 weeks or until no further improvement is seen.
         c. Complete resolution is unlikely, but the drug simplifies the surgery needed to eliminate residual disease.
         d. It can be used with prednisone at a dose of 1.5 to 2.2 mg/kg PO SID for 2 to 4 weeks then QOD. (Patterson and Campbell, 2005).
      4. Topical tacrolimus (0.1%)
         a. Primary treatment for mild lesions (Patterson and Campbell, 2005)
         b. Adjunct to cyclosporine therapy so induction dose of cyclosporine can be reduced
   B. Antibiotics
      1. Secondary infection of the fistulas is common.
      2. They reduce odor and amount of discharge.
      3. Consider metronidazole 15 mg/kg PO BID for 7 to 10 days.
      4. Consider cephalexin 20 mg/kg PO BID for 7 to 10 days.
   C. Dietary modification (hypoallergenic diets) for evidence of colitis
II. Surgical management is indicated when medical management fails.
   A. Anal sacculectomy is recommended in all cases, because the sacs often become secondarily involved.
   B. Excise all diseased tissue via surgical dissection, electrosurgery, or carbon dioxide laser.
   C. Perform primary closure unless excessive tension is present.
   D. Tail amputation may alter the local environment if there is a recurrence (van Ee, 1993).

Monitoring of Animal

I. Monitor for complications of immunosuppressive therapy.
II. Fecal incontinence is a possible sequela to surgery depending on the severity of the fistulas and depth of involvement.
III. Recurrence of the fistulas is possible.

NEOPLASIA

Perianal Adenoma

Definition and Causes

I. A benign, androgen-dependent tumor arising from circumanal hepatoid glands
II. Most common in older, intact male dogs
III. Can arise from a number of sites around the anus, tailhead, and genitalia
IV. Occasionally occurs in older spayed females

Pathophysiology

I. It is a benign neoplasm of primarily hepatoid glandular tissue, with a sebaceous component, in the dermis of the perianal skin.
II. Continued growth results in raised masses that often ulcerate and become secondarily infected.

Clinical Signs

I. Excessive licking of the perianal area
II. Single or multiple firm mass(es) in the perianal dermis
III. Possible masses around the anus, tailhead, inguinal region, and prepuce
IV. Ulceration leading to bleeding and secondary infection with larger masses
V. Sometimes an incidental finding

Diagnosis

I. Physical appearance and location of the mass is usually diagnostic.
II. Rectal examination rules out anal sac neoplasia.
III. Cytological examination of fine-needle aspirates reveals typical hepatoid cells.
IV. Histopathologic examination of the excised mass is necessary to differentiate benign lesions from malignant ones.
V. The testicles should be carefully evaluated for evidence of accompanying neoplasia.

Differential Diagnosis

I. Perianal adenocarcinomas
   A. Much less common, but often clinically indistinguishable from benign tumors
   B. Carry a poor prognosis and commonly metastasize to regional lymph nodes, especially sublumbar nodes
II. Anal sac adenocarcinoma
III. Diffuse hypertrophy of circumanal hepatoid glands in older male dogs

IV. Perianal fistulas
V. Anal sac abscess
VI. Other benign perirectal neoplasms: lipoma, fibroma, trichoepithelioma, leiomyoma

Treatment

I. Castration is the therapy of choice, whether alone or in combination with excision.
II. Submit testicles for histopathology to rule out androgen-secreting tumors (Leydig cell tumor).
III. Surgical excision is indicated under certain conditions.
   A. The tumor is ulcerated, necrotic, hemorrhaging, or getting progressively larger.
   B. The tumor occurs in a female dog.
   C. Excision is typically performed at the time of castration.
IV. Estrogen therapy is not recommended because of its myelosuppressive effects.
V. Radiation therapy is effective, but expensive.
VI. Cryosurgery is effective, but not commonly used.

Monitoring of Animal

I. Most dogs respond well to castration alone, especially if the tumors are small.
II. Surgical excision and cryotherapy may have some complications.
   A. Wound dehiscence and wound infection
   B. Anal stricture with extensive dissection or freezing
   C. Fecal incontinence unlikely unless the lesions are very deep
III. Anusitis, proctitis, or anal stricture may arise after radiation therapy.
IV. Perianal adenocarcinoma is suspected if the tumors fail to regress or continue to grow.

Perianal Adenocarcinoma

Definition and Cause

I. Malignant tumor of the circumanal hepatoid glands
II. Growth not androgen dependent

Pathophysiology

I. Locally invasive malignant tumor of the circumanal hepatoid glands
II. Metastasis to regional lymphatic and lymph nodes common

Clinical Signs

I. Signs are similar to those of perianal adenoma.
II. Males are most commonly affected.
III. Enlarged sublumbar lymph nodes may be palpable by abdominal or rectal palpation.
IV. Interference with defecation occurs with severe regional lymph node enlargement.

Diagnosis

I. Histopathologic evaluation of biopsy specimens (core biopsy specimen)
II. Abdominal radiography and ultrasonography to detect metastases
III. CT scan to search for metastases

Differential Diagnosis

I. Perianal adenoma
II. Anal sac adenocarcinoma
III. Other perirectal masses

Treatment

I. Wide surgical excision of primary tumor if small and metastasis not detected
II. Excision of enlarged lymph nodes (for palliation)
III. Radiation therapy
IV. Chemotherapy with cisplatin or doxorubicin possibly helpful (Withrow, 2001)

Monitoring of Animal

I. Warn owner of the potential for recurrence and metastasis.
II. Reexamine every 3 months for new tumor formation or perianal ulceration.
III. Metastasis occurs to regional lymph nodes, liver, and numerous subcutaneous sites, usually within 6 months.
IV. Complete excision of small lesions may be curative.

Anal Carcinoma

Definition and Cause

I. Aggressive form of squamous cell carcinoma in the intermediate cutaneous zone around the anus
II. A highly malignant and metastatic tumor that initially may appear like perianal fistulas

Pathophysiology

I. Ulcerative or proliferative-ulcerative lesions in the skin around the anus
II. Rapidly progressive lesions resulting in pain, tenesmus, and bleeding

Clinical Signs

I. Flat, ulcerative lesions in the perianal skin
II. Tenesmus, dyschezia
III. Perianal bleeding
IV. Extension into the pelvic cavity on rectal palpation

Differential Diagnosis

I. Anusitis, proctitis
II. Perianal fistulas
III. Other perianal neoplasia

Treatment

I. Wide excision of early lesions
II. Radiation therapy

Monitoring of Animal

I. Aggressive surgery may result in fecal incontinence.
II. Prognosis is poor.

Anal Sac Neoplasia

Definition and Causes

I. These are aggressive tumors that originate from the apocrine glands of the anal sac.
II. The cause is unknown.
III. Early studies indicated higher incidence in females, but more recent studies showed no gender predisposition (Turek et al., 2003).

Pathophysiology

I. The tumors originate in glandular epithelium of the anal sac and are initially confined to this structure.
II. Extension to local tissues occurs as the mass enlarges.
III. Early metastasis to the regional lymph nodes (especially pelvic canal and sublumbar nodes) is common.
IV. Distant metastasis to liver, spleen, and other organs occurs.
V. Hypercalcemia from production of parathyroid hormone-related protein (PTH-RP) is not uncommon.
VI. Metastatic lesions are often functional and produce PTH-RP.

Clinical Signs

I. Small masses asymptomatic and discovered on physical examination
II. Bulging ventrolateral to anus with larger masses
III. Usually unilateral
IV. Licking at the anal area
V. Dyschezia, tenesmus
VI. Constipation
VII. Systemic signs caused by hypercalcemia (see Chapter 43)

Diagnosis

I. Signalment and history often increase the index of suspicion.
II. Palpable mass is present in anal sac or a visible mass is seen in the perineum.
III. Sublumbar lymph node enlargement raises suspicion that the mass is malignant.
IV. Hypercalcemia, hypophosphatemia, and secondary renal insufficiency may be documented on biochemical profile.
V. Increased PTH-RP may be detected.
VI. Obtain chest and abdominal radiographs to check for metastasis.
VII. Abdominal ultrasonography and CT scan are used to assess the extent of metastasis.
VIII. Excision followed by histopathologic evaluation is necessary to confirm the diagnosis.

Differential Diagnosis

I. Anal sac impaction and infection
II. Perianal gland adenoma and adenocarcinoma
   A. Usually more superficial
   B. Anal sac still palpable
III. Other tumors of the perineum

Treatment

I. Surgical excision is the treatment of choice, including sublumbar lymph node removal.
II. Adjunctive radiation therapy of the primary site and regional lymph nodes can be effective (Withrow, 2001).
III. Chemotherapy can be attempted, but efficacy is not established.
IV. Mitoxantrone combined with radiation therapy has improved overall survival time compared with surgery alone (Turek et al., 2003).
V. Treat hypercalcemia and renal insufficiency.

Monitoring of Animal

I. Asymptomatic dogs with complete excision and no evidence of local invasion or metastasis have a good to guarded prognosis (DeNovo and Bright, 2000).
II. If metastatic disease is identified, the long-term prognosis is poor.
III. Hypercalcemia should resolve following complete excision.
IV. Recurrence of hypercalcemia is indicative of either recurrence of the primary tumor or metastatic disease.
V. Acute and chronic complications are common after radiation therapy

Rectal Neoplasia

See Chapter 34.

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CHAPTER 36

Diseases of the Exocrine Pancreas

Craig G. Ruaux

INFLAMMATORY DISEASES

Acute Pancreatitis

Definition

I. It is an inflammatory condition of the exocrine pancreatic tissue, with infiltration by inflammatory cells and interstitial damage by pancreatic enzymes.
   A. Several mechanisms exist to prevent damage to pancreatic tissue from digestive enzymes, and defects in any of these mechanisms can potentially lead to pancreatitis.
      1. Proteolytic enzymes are synthesized as inactive precursors (zymogens).
      2. Zymogens are isolated in secretory granules before secretion.
      3. Local proteins inhibit or inactivate any zymogens that become activated within the secretory granules.
      4. Secretion of the secretory granules is localized, usually only through the apex of the acinar cell into the acinus.
   B. With excessive stimulation of the pancreas, ischemia, or excess hydrostatic pressure in the pancreatic duct, enzyme/proenzyme transport is disturbed.
      1. Excretion of zymogen granules into the intercellular space and interstitium exposes pancreatic tissue to damaging effects from these enzymes.
      2. Damage to the pancreatic interstitium by digestive enzymes causes release of cytokines that attract inflammatory cells to the pancreas.
   C. The pancreas is a source of cytokines released during pancreatitis.
      1. Tumor necrosis factor-α, interleukin 6, and interleukin 10 are produced by inflamed pancreatic acinar tissue (Brivet et al., 1999).
      2. Pancreatic production of proinflammatory cytokines may lead to systemic inflammatory response and distant organ failure (Ruaux, 2000).

II. Acute pancreatitis can range from a mild, self-limiting disease to fulminant, rapidly lethal disease.
   A. Complications are common in severe, acute pancreatitis.
   B. Acute pancreatitis is diagnosed in both dogs and cats.
      1. Cats often present with more subtle signs of disease, possibly only inappetence or occasional vomiting.
      2. Cats are more commonly affected with chronic, relapsing pancreatitis rather than single bouts of severe, acute pancreatitis.

Causes

I. Nutritional factors
   A. Obese dogs are at greater risk of developing acute pancreatitis.
   B. Lower fat diets reduce the risk of relapse in recovering animals.
   C. History of consumption of a high-fat meal is common in dogs with acute pancreatitis.

II. Hyperlipidemia
   A. There is a high frequency of pancreatitis in miniature schnauzers, which commonly have marked hyperlipoproteinemia.
   B. Very high concentrations of triglycerides may lead to lipid thrombi in the pancreatic circulation, thereby causing or worsening pancreatic ischemic injury.
   C. Hyperlipidemia may also result from abdominal fat necrosis.

III. Trauma
   A. Surgical or blunt abdominal trauma may precipitate pancreatic inflammation.
   B. Hypovolemia, ischemia, and reperfusion injury are most likely responsible.
   C. Pancreatic biopsy alone is rarely associated with significant pancreatic inflammation in hemodynamically stable animals.

IV. Hepatobiliary disease: possible extension of inflammatory disease to pancreas

V. Small intestinal disease: extension of inflammatory disease to pancreas

VI. Pancreatic duct reflux
   A. It is considered rare.
   B. It is only likely with high intraduodenal pressure (e.g., during vomiting).
   C. As vomiting is a common sequela of pancreatitis, the role of ductal reflux in initiation of the disease is difficult to assess.

VII. Pancreatic duct obstruction
   A. It may arise with neoplasia, trauma, surgery, and parasite migration.
   B. Compression of the duct and resultant back pressure damages pancreatic acinar tissue.

C. Frequency of pancreatitis from duct obstruction is low.

VIII. Drugs
- A. Many drugs have been implicated, mainly in limited observational studies.
- B. Glucocorticoids are commonly considered to cause pancreatitis, but no experimental evidence is available.
  1. High-dose glucocorticoids are often given to animals with hemodynamic compromise (e.g., shock, intervertebral disc disease).
  2. Ischemia and reperfusion injury of the pancreas from the concurrent condition is a more likely cause of pancreatitis.
- C. Hyperadrenocorticism may increase the risk of acute pancreatitis by increasing food intake and dietary indiscretion.

IX. Babesiosis: possible ischemia and reperfusion injury (Mohr et al., 2000)

X. Conditions associated with acute pancreatitis in cats
- A. Inflammatory bowel disease (IBD)
- B. Cholangitis, cholangiohepatitis (Mansfield and Jones, 2001)
- C. Infections: *Toxoplasma gondii,* parvovirus, feline infectious peritonitis (FIP)
- D. Hepatic lipidosis: 59% of acute cases (Hill and Van Winkle, 1993)
- E. Organophosphates, drug toxicities
- F. Abdominal trauma: high-rise syndrome

Pathophysiology

I. Within the pancreatic parenchyma, ischemia/reperfusion injury or excessive stimulation lead to abnormal release of zymogen granules.

II. Lipase and elastase-mediated damage to the pancreatic interstitium triggers inflammation within the gland.

III. Release of pancreatic enzymes into the interstitium and peritoneal space establishes a chemical peritonitis.

IV. Up-regulation of inflammatory cells occurs from pancreatic cytokine release, leading to a state of systemic inflammation.

V. Fluid losses from vomiting, ileus, and severe systemic inflammatory changes can lead to organ failure.

VI. There is no experimental evidence that circulating pancreatic enzymes contribute to organ failure in naturally occurring acute pancreatitis.

VII. Secondary hepatic injury is common in acute pancreatitis.
- A. Pancreatic swelling can obstruct the common bile duct, leading to extrahepatic cholestasis.
- B. Local release of pancreatic enzymes and cytokines, and degranulation of neutrophils can lead to hepatocellular injury.
- C. Splanchnic congestion and circulatory compromise also occur.

Clinical Signs

I. The clinical signs of pancreatitis are variable and nonspecific.

II. The following are common signs observed in dogs:
- A. Acute vomiting, often following a high-fat meal
- B. Cranial abdominal pain
  1. Splinting on palpation of the abdomen, particularly in the right cranial quadrant
  2. Restlessness, pacing, adoption of the "prayer position"
- C. Fever
- D. Obtundation

III. Less common signs in dogs are as follows:
- A. Diarrhea
- B. Abdominal mass or distension, hepatomegaly
- C. Icterus, petechiation, coagulopathy
- D. Weakness, tachycardia, tachypnea, pulmonary edema
- E. Injected mucous membranes

IV. Clinical signs in cats are often more subtle, but commonly include the following:
- A. Vomiting, inappetence, weight loss, diarrhea, icterus, lethargy, dehydration, hypothermia, dyspnea
- B. ± Palpable abdominal masses and cardiovascular shock
- C. Diarrhea with intestinal disease

Diagnosis

I. No diagnostic test is 100% sensitive and specific for acute pancreatitis.

II. Pancreatic inflammation often has a patchy distribution and varying severity within the gland (Newman et al., 2004).

III. A presumptive diagnosis can be made from physical findings, history, presence of predisposing factors, laboratory results, and/or imaging findings.

IV. Laboratory investigation may show the following changes:
- A. Complete blood count (CBC)
  1. Neutrophilia, with or without a left shift
  2. Neutropenia and degenerative left shift from severe systemic inflammation, sepsis, peritonitis, pancreatic necrosis
  3. Decreased platelets and red blood cell fragments with disseminated intravascular coagulopathy (DIC)
  4. Increased packed cell volume (PCV) and total protein from dehydration
- B. Routine biochemistry assays
  1. Elevated total bilirubin with secondary hepatopathy or cholestasis
  2. Azotemia: prerenal (dehydration), acute renal failure
  3. Hyperglycemia
     - a. It is common and may be secondary to increased glucagon secretion, insulin resistance, and stress-related cortisol and catecholamine release.
     - b. Cats are particularly susceptible to stress-induced hyperglycemia.
  4. ± Elevated alkaline phosphatase and alanine transaminase
     - a. Secondary hepatitis, hepatic ischemia, local peritonitis
     - b. Cholestasis or cholangiohepatitis

5. Hypercholesterolemia, hypertriglyceridemia, gross lipemia common
6. Possible hypocalcemia
   a. Calcium consumption
   b. Low serum albumin concentrations with systemic endothelial dysfunction
   c. Intracellular shifts of calcium

C. Digestive enzyme activities
1. Amylase and lipase may be elevated in dogs.
2. Amylase and lipase are of no clinical value in cats.
3. Elevations of amylase or lipase and compatible clinical signs support the diagnosis, but sensitivity and specificity are low.
4. The diagnosis cannot be ruled out in the presence of normal amylase and lipase.
5. Renal failure may cause a three-fold elevation in serum lipase.

D. Trypsin-like immunoreactivity (TLI)
1. Trypsin/trypsinogen is exclusively pancreatic in origin, and there is no significant reabsorption from the intestinal tract.
   a. Elevations are consistent with increased pancreatic acinar cell permeability as occurs with pancreatitis.
   b. They are markedly elevated in the early stages of experimental acute pancreatitis, but return to normal or are subnormal within the first 24 hours (Williams et al., 1996).
   c. Trypsinogen is cleared by renal mechanisms, and active trypsin is cleared extremely rapidly by plasma anti-proteinases and the reticuloendothelial system.
2. TLI is cleared by renal mechanisms, so renal insufficiency may lead to elevated serum TLI in the absence of pancreatic disease.
3. Serum TLI has poor diagnostic accuracy in both dogs and cats, and it is not recommended for this disease (Ruaux and Atwell, 1999; Swift et al., 2000).
4. The reference range (normal values) for serum TLI in dogs is 5 to 35 μg/L, and in cats it is 12 to 82 μg/L.
5. Values >50 μg/L in dogs and >200 μg/L in cats are recommended for the diagnosis of acute pancreatitis.

E. Pancreatic lipase immunoreactivity (PLI)
1. The pancreas produces a structurally distinct lipase.
2. PLI assays are available for both dogs and cats.
3. Pancreatic lipase is cleared from the circulation slower than TLI, which increases the sensitivity of this test for acute pancreatitis (Williams et al., 2003).
4. The normal values for PLI are 0 to 200 μg/L in dogs (using the IDEXX specPL assay) and 2.0 to 6.8 μg/L in cats.
5. Values >400 μg/L in dogs and >12 μg/L in cats support a diagnosis of pancreatitis.

V. Abdominal radiography is indicated when acute pancreatitis is suspected and may show the following signs:
   A. Diminished contrast and increased soft-tissue density in the cranial abdomen, often with a granular appearance ("ground glass" appearance)
   B. A widening of the angle between the pylorus and descending duodenum, or the presence of a mass medial to the descending duodenum
   C. Gas distension of the stomach
   D. Presence of a static gas pattern in the descending duodenum and/or transverse colon
   E. Caudal displacement of the transverse colon

VI. Abdominal ultrasonography has become increasingly useful in the diagnosis of pancreatitis, and the following findings are suggestive:
   A. Loss of echodensity or mottled echogenicity in the area of the pancreas
      1. Hypoechoic areas are commonly seen in hemorrhagic forms of the disease, with surrounding hyperechoic regions representing pancreatic edema.
      2. Peripancreatic fat is often hyperechoic.
   B. Mass effect in the area of the pancreas
   C. Localized peritoneal effusion
   D. Biliary obstruction secondary to pancreatic inflammation
   E. Pancreatic pseudocysts or abscesses
      1. Cystic masses may contain necrotic pancreatic tissue, pancreatic secretions, and inflammatory exudates.
      2. Pseudocysts and abscesses may be seen distant from the body of the pancreas.

VII. Computed tomography (CT) is of limited value (Gerhardt et al., 2001; Jaeger et al., 2003).

VIII. Abdominocentesis, exploratory laparotomy and laparoscopy may all be considered if the diagnosis is unclear.
   A. Therapeutic actions should not be delayed by these diagnostic steps.
   B. The pancreas can be viewed laparoscopically via a ventral or right lateral approach.
   C. The pancreas can be biopsied with punch-type biopsy forceps, avoiding the center of the gland.
   D. Complications of laparoscopic biopsy are rare.

Differential Diagnosis

I. Other causes of acute abdomen syndrome: see Chapter 39

II. Other gastrointestinal (GI) diseases
   A. Intestinal obstruction, foreign bodies, intussusception, volvulus
   B. Intestinal infarction
   C. Viral infections: parvovirus, canine distemper, infectious canine hepatitis
   D. Systemic infections: leptospirosis, salmonellosis, sepsis
   E. Acute cholecystitis
   F. Hemorrhagic gastroenteritis
   G. Hepatic infarction

III. Other nongastrointestinal diseases
   A. Acute pyelonephritis
   B. Acute renal failure (possible complication of pancreatitis)

C. Rupture of the urinary bladder, post-renal obstruction from feline urologic syndrome, ureteral calculi
D. Prostatitis
E. Ketoacidotic diabetes mellitus (possible complication of pancreatitis)
F. Peritonitis
G. Hypoadrenocorticism
H. Pyometra, acute metritis
I. Testicular torsion

Treatment

I. The major goals of therapy are as follows:
   A. To correct and maintain normal fluid balance and electrolytes
   B. To control vomiting
   C. To control abdominal pain
   D. To maintain the integrity of the pancreatic microcirculation
   E. To anticipate and manage complications
II. Therapeutic planning begins with rational determination of the severity of the condition.
   A. Loss of all exocrine pancreatic function is not acutely life-threatening.
   B. Death from acute pancreatitis is secondary to distant organ failure rather than exocrine pancreatic gland failure.
      1. Assessment of the CBC and biochemistry panel allows detection of other organ problems.
      2. Compromise of multiple organs is associated with more severe disease and a worse prognosis.
III. Medical management of mild acute pancreatitis involves the following:
   A. Attempt to eliminate any predisposing factors (see Causes).
   B. Assess state of hydration.
   C. Fluid losses in pancreatitis are often greater than anticipated because of ileus.
   D. Institute fluid replacement therapy with a balanced electrolyte solution (e.g., lactated Ringer's, Normosol) at a rate calculated to replace deficits and meet maintenance requirements.
      1. Consider potential for ongoing losses if vomiting or diarrhea continues.
      2. Subcutaneous fluids may be used in some very mild cases treated as outpatients, but hospitalized animals should receive parenteral fluids.
      3. Addition of 20 mEq KCl/L of fluids is recommended because of potassium loss with vomiting.
      4. Mild acidosis resolves with fluid therapy, rehydration, and increased renal perfusion in most uncomplicated cases.
   E. If vomiting continues, consider antiemetics.
      1. Metoclopramide may be given at 0.2 to 0.5 mg/kg SC TID to QID, or as a constant rate infusion of 1 to 2 mg/kg /24 hours IV (preferred).
      2. If vomiting is not controlled with metoclopramide, ondansetron *(Zofran)* or dolasetron *(Anzemet)* is given at 0.6 mg/kg IV SID.
   F. Give nothing per os (NPO) for 48 to 96 hours.
      1. Maintain hydration with fluid therapy.
      2. Offer water 24 hours after vomiting stops.
      3. If water is tolerated, gradual reintroduction of a high-carbohydrate, low-fat diet is indicated.
      4. Initial diets may be either homemade or commercially available low-fat products.
      5. Feed small amounts often.
      6. If food is tolerated while hospitalized, discharge with instructions to avoid high-fat foods.
      7. Table scraps must be diligently avoided.
   G. Institute effective pain control.
      1. Butorphanol 0.2 to 0.4 mg/kg SC every 4 to 6 hours
      2. Oxymorphone 0.05 to 0.1 mg/kg SC, IM, IV every 4 to 6 hours (use low dose in cats)
      3. Avoid nonsteroidal antiinflammatory drugs (NSAIDs) because of risk for GI ulceration
   H. Manage complications.
      1. There is little evidence of bacterial infection in most cases of mild acute pancreatitis, so antibiotics are not recommended in routine cases.
      2. Any decline in PCV and total protein warrants further investigation.
IV. Medical management of severe, acute pancreatitis can be challenging.
   A. It often involves failure or compromise of multiple organ systems and is a medical emergency.
   B. Treatment requires 24-hour care and intensive monitoring.
   C. The major causes of death are hypovolemia and cardiovascular shock.
      1. Following resuscitation for cardiovascular shock, affected animals are at high risk for renal, pulmonary, and hepatic insufficiency, as well as DIC.
      2. Initial resuscitation therapy must be aggressive, so administer crystalloid fluids at shock rates (up to 90 mL/kg/hr IV) for the first hour.
      3. Monitor PCV and total protein.
      4. If total protein is declining, consider a plasma transfusion or colloidal fluids (hetastarch, dextrans) for support of plasma oncotic pressure (see Chapter 71).
         a. They may reduce pancreatic edema, help maintain pancreatic microcirculation, and reduce or mitigate pulmonary edema and pleural effusion.
         b. Plasma replenishes coagulation proteins and reduces the risk of DIC.
      5. Whole blood transfusion may be indicated for severe intraabdominal hemorrhage (see Chapter 71).
      6. Proteinase inhibitors (e.g., aprotinin) have provided no benefit in spontaneous acute pancreatitis and are not recommended.
   D. Administer effective analgesia.
      1. Butorphanol 0.2 to 0.4 mg/kg SC every 4 to 6 hours
      2. Oxymorphone 0.05 to 0.1 mg/kg SC, IM, IV every 4 to 6 hours (use low dose in cats)
      3. NSAIDs avoided because of the risk for GI ulceration
   E. Most animals are inappetent for several days.

1. Maintain NPO for 48 hours after cessation of vomiting.
2. If NPO >5 days, or if >10% body weight is lost while receiving adequate fluid therapy, nutritional support is indicated.
   a. Enteral feeding is preferred, to maintain gut function.
   b. Feeding of an elemental diet by jejunostomy catheter may be considered.
   c. Total parenteral nutrition may be necessary in some cases.

F. Control vomiting as described previously.

V. Surgical intervention may be indicated for management of peritonitis, with open peritoneal drainage and lavage.
   A. Surgical management of complications following pancreatitis has been described elsewhere (Bellenger et al., 1989; Barnhart and Smeak, 1998; Marchevsky et al., 2000).
   B. Ultrasound-guided percutaneous drainage of pseudocysts may be attempted (Smith and Biller, 1998).

Monitoring of Animal

I. The following complications are anticipated with severe pancreatitis, and early recognition is important for their successful management:
   A. Acute renal failure
   B. DIC
   C. Pancreatic abscessation, pseudocyst development
   D. Sepsis
      1. Ileus, circulatory compromise, and GI inflammation compromise the gut's barrier function.
      2. Devitalized pancreatic tissue may become infected following bacterial translocation or pancreatic duct reflux (during vomiting).
   E. Pulmonary insufficiency and thromboembolism
   F. Cardiac arrhythmias
   G. Diabetes mellitus, ketoacidosis
      1. They are relatively common, transient phenomena.
      2. Hyperglycemia and acidosis often resolve with fluid therapy.
      3. Institute insulin for diabetic ketoacidosis.
   H. Jaundice
      1. It may arise from direct hepatic injury, secondary inflammation, obstruction of extrahepatic biliary duct, or hemolysis.
      2. Persistent jaundice despite aggressive therapy indicates a need for exploratory laparotomy.
   I. Exocrine pancreatic insufficiency
      1. It is uncommon in dogs after a single episode of severe, acute pancreatitis.
      2. It may develop after recurrent bouts of mild to severe, acute pancreatitis.

II. Mild, edematous pancreatitis has a fair to good prognosis.

III. Severe, hemorrhagic, or necrotizing pancreatitis has a poorer prognosis.

Chronic Pancreatitis

Definition and Causes

I. Chronic pancreatitis is characterized by either recurrent episodes of inflammation or persistent clinical signs.

II. Chronic pancreatitis may occur with improper dietary management following acute pancreatitis.

III. Chronic, subclinical pancreatitis is the most common form of pancreatitis in the domestic cat.

IV. Chronic pancreatitis may accompany other systemic illnesses.
   A. Dogs: hyperadrenocorticism, diabetes mellitus, hyperlipidemia
   B. Cats: toxoplasmosis, FIP, panleukopenia, IBD, cholangiohepatitis

Pathophysiology

I. Recurrent inflammatory episodes may lead to progressive destruction of pancreatic parenchyma, with fibrosis and loss of acinar cellular mass.
   A. Progressive loss of pancreatic tissue may cause permanent impairment of pancreatic or hepatic function.
   B. Subclinical chronic pancreatitis is the main cause of exocrine pancreatic insufficiency in cats.
   C. Diabetes mellitus may develop with loss of islet cells.
   D. Extrahepatic bile duct obstruction may lead to obstructive cholestasis.

II. In cats, chronic pancreatitis and cholangiohepatitis or hepatic lipidosis may coexist because of the connection between the pancreatic and common bile ducts.

III. Miniature schnauzers are at increased risk for development of chronic pancreatitis and often have hyperlipidemia.
   A. Marked breed predisposition suggests a genetic component in these dogs.
   B. No mutations have yet been detected in trypsinogen or lipoprotein lipases in affected dogs (Bishop and Steiner, 2002).

Clinical Signs

I. Anorexia, chronic intermittent vomiting

II. Intermittent pyrexia, abdominal pain

III. Weight loss, diarrhea

Diagnosis

I. Clinical signs are often vague and nonspecific.

II. History usually indicates a waxing and waning general malaise.

III. Clinical pathologic results are highly variable and often unremarkable.
   A. The serum PLI test is often useful in confirming the diagnosis, with elevations persisting for several days following episodes of pancreatic inflammation (Williams et al., 2003).
   B. Mildly elevated PLI in animals with consistent clinical signs is supportive of the diagnosis.
   C. Traditional serum lipase assays are of no value.

D. Rule out toxoplasmosis and FIP in cats.

IV. Abdominal ultrasonography may show changes similar to those described for acute pancreatitis, and the pancreatic duct may be dilated (>1 mm) in cats (Leveille et al., 1996).

Differential Diagnosis

I. Other causes of chronic vomiting: chronic gastritis, renal failure, GI foreign body, or gastric neoplasia

II. Other causes of chronic intestinal signs: IBD, hypoadrenocorticism, intestinal neoplasia

III. Other causes of chronic inappetence: cholangiohepatitis (cats)

Treatment and Monitoring

I. During episodes of acute signs, treatment is similar to that for acute pancreatitis, as described earlier.
   A. Many cases recover rapidly with outpatient therapy (pain control, pancreatic rest).
   B. Persistence of vomiting or presence of dehydration warrants hospitalization and treatment as for acute pancreatitis.

II. Long-term management revolves around dietary changes.
   A. For dogs, higher carbohydrate and fat-restricted diets are recommended.
   B. Cats may benefit from a novel protein source and moderate fat restriction.
   C. Requirements for dietary arachidonic acid limit the long-term use of very low-fat diets in cats.

III. In some cases where dietary management is not effective, oral prednisone at antiinflammatory doses (0.5 to 1.0 mg/kg PO SID to QOD) may be considered.

IV. There is no objective evidence of benefit from oral supplementation with pancreatic enzymes in these cases.

V. Prognosis is fair to good if dietary management is successful and other predisposing factors (e.g., hyperlipoproteinemia) can be controlled.

NONINFLAMMATORY DISEASES

Exocrine Pancreatic Insufficiency

Definition

I. Loss of pancreatic acinar tissue results in a syndrome of malabsorption, maldigestion, malassimilation, and small intestinal diarrhea.

II. Clinical signs do not develop until approximately 85% to 90% of the exocrine pancreatic secretory function is lost (Westermarck et al., 1993; Wiberg and Westermarck, 2002).

III. Exocrine pancreatic insufficiency (EPI) occurs in both dogs and cats, but the frequency in cats is lower.

Causes

I. The most common cause in young dogs is pancreatic acinar atrophy.
   A. Numerous breeds are affected; large breeds are affected most often.
   B. The German shepherd dog has a high prevalence, and the disease is most likely inherited in an autosomal recessive manner (Moeller et al., 2002).
   C. Lymphocytic infiltration of the pancreas precedes pancreatic acinar atrophy in German shepherd dogs and rough-coated collies (Wiberg et al., 1999; Wiberg et al., 2000; Wiberg, 2004).

II. Chronic pancreatitis is the most common cause of EPI in the cat, because the end stage of chronic pancreatitis is fibrosis and acinar atrophy.

III. Pancreatic neoplasia, congenital pancreatic hypoplasia or aplasia, and pancreatic duct obstruction, although rare, can all lead to exocrine insufficiency.

IV. EPI can occur with some nonpancreatic diseases (e.g., duodenal hyperacidity, severe protein-calorie malnutrition).

Pathophysiology

I. Loss of pancreatic acinar tissue results in reduced secretion of digestive enzymes into the small intestine.

II. Failure of small intestinal digestion results in nutrient malabsorption.
   A. Concomitant changes occur in small intestinal mucosal function and morphology, contributing to malabsorption.
   B. Mucosal enzyme defects lead to abnormal transport of sugars, amino acids, and fatty acids.
   C. Loss of trophic factors in pancreatic secretions may result in villous atrophy and inflammatory infiltration.
   D. Bacterial overgrowth may occur, leading to nutrient competition.
   E. Global malnutrition has an adverse effect on the GI mucosa.

III. With EPI secondary to chronic pancreatitis (typically cats), diabetes mellitus may occur from islet cell loss.

Clinical Signs

I. Signalment
   A. In dogs, signs are usually seen in young adults, typically <2 years of age.
   B. Pancreatitis-induced EPI in dogs can occur at any age, but is more common in middle-aged to older dogs and in smaller breeds.
   C. In cats, signs usually develop in middle-aged to older cats, reflecting the more chronic etiology.
   D. There is no sex predilection.

II. Common clinical signs and physical examination findings
   A. Young adult dogs are usually bright, alert, and active, but underweight for their age.
   B. Cats typically have chronic weight loss as well as a waxing and waning appetite, which reflect underlying chronic pancreatitis.
   C. Mild to moderate weight loss is noted.
      1. Weight loss occurs despite a good to ravenous appetite and polyphagia.
      2. Pica and coprophagia may occur in dogs.
      3. Some dogs are emaciated, with muscle wasting and severely reduced body fat.

D. Diarrhea is a common clinical sign.
   1. Decreased digestion and malabsorption result in an increased osmotic gradient into the GI lumen.
   2. Protein and carbohydrates in the lumen undergo bacterial fermentation with production of diarrheagenic products.
   3. The diarrhea is typically voluminous, poorly formed, and may have a rancid odor.
   4. As fatty acids are a major osmotic agent, the diarrhea may show some improvement with a low-fat diet.
   5. With indoor–outdoor cats, diarrhea may not be observed.
E. Vomiting is an occasional clinical sign in dogs, but it is more common in cats.
F. Borborygmus and flatulence may be noted.
G. The hair coat is often of poor quality.
H. Oily staining of the perineum is common in cats and may be noted in dogs.
I. Polydipsia and polyuria may occur with diabetes mellitus.

Diagnosis

I. Typical history and clinical signs, particularly in young large-breed dogs, are suggestive.
   A. Clinical signs are nonspecific, and the diagnosis must be confirmed.
   B. Confirmation is important because treatment is expensive in large-breed dogs.
II. Many laboratory tests have been used to diagnose EPI in dogs and cats.
   A. Clinical biochemistries are usually unremarkable.
   B. Traditional diagnostic tests, such as the oral N-benzoyl-L-tyrosyl-para-amino-benzoic acid (BT-PABA) test, fecal fat determination, and fecal proteolytic activity, are of poor sensitivity and specificity and are not recommended.
III. The most reliable test in both dogs and cats is serum TLI concentration.
   A. Reduced TLI concentration is highly sensitive and specific for EPI.
   B. Prior administration of pancreatic extracts does not interfere with the assay.
   C. Canine TLI assays are widely available.
   D. Feline TLI assay is only available from the Gastrointestinal Laboratory at the College of Veterinary Medicine and Biomedical Sciences, Texas A&M University.
   E. Interpretation of TLI results is straightforward in most cases.
      1. Serum TLI is markedly decreased in dogs (<2 μg/L) and cats (<8 μg/L) with EPI.
      2. Dogs with small intestinal disease usually have normal serum TLI concentrations (5 to 35 μg/L).
      3. Cats with small intestinal disease often have mild elevations in serum TLI concentrations (100 to 200 μg/L).
      4. Subclinical EPI in dogs is diagnosed with persistent serum TLI concentrations <5 μg/L in the absence of clinical signs (Wiberg and Westermarck, 2002; Westermarck and Wiberg, 2003).
IV. Serum PLI is inferior for the diagnosis of EPI (Steiner et al., 2001).
V. Measurement of serum folate and cobalamin concentrations is indicated.
   A. Serum folate may be elevated from increased bacterial biomass.
   B. Serum cobalamin may be reduced owing to ileal mucosal disease and intrinsic factor deficiency.
   C. In the cat, the pancreas is the sole source of intrinsic factor, so essentially all cats with EPI have marked cobalamin deficiency (Ruaux et al., 2001, 2005).
   D. Fecal elastase enzyme-linked immunosorbent assay has lower sensitivity and specificity than serum TLI and is not recommended for the diagnosis of EPI.

Differential Diagnosis

I. The major differential diagnoses for EPI are diffuse, infiltrative small intestinal diseases (see Chapter 33).
II. Many cats with clinical signs suggestive of EPI have normal to elevated serum TLI concentrations and significant small intestinal disease.

Treatment

I. Goals
   A. Replacement of pancreatic digestive enzymes
   B. Restoration of an adequate nutritional state
      1. Replacement of fat-soluble vitamins
      2. Replacement of water-soluble vitamins, such as cobalamin
II. Digestive enzyme replacement
   A. Pancreatic enzyme supplements are commercially available and are usually extracts from porcine pancreata.
   B. Enteric-coated preparations are less effective in dogs and cats.
   C. Preincubation of food with enzymes does not increase effectiveness and may lead to food aversion in cats.
   D. Addition of bile salts, antacids, or sodium bicarbonate to the meal has no benefit.
   E. Dosages of powdered pancreatic enzymes are as follows:
      1. In dogs, start with 2 tsp/20 kg body weight with each meal.
      2. In cats, start with $^1/_2$ tsp/5 kg.
   F. Mix enzymes with a maintenance diet immediately before feeding.
   G. Two meals a day are usually adequate to promote rapid weight gain in affected dogs.
      1. Diarrhea usually resolves within 2 to 3 days.
      2. Once improvement is seen, determine minimal effective dose via slow tapering.
      3. Strict maintenance of dietary routines is critical.
   H. High doses of pancreatic enzymes may lead to periodontal bleeding and ulceration in dogs, necessitating dosage reduction (Rutz et al., 2002).
III. Restoration of nutritional state

A. Maintenance dog and cat foods are usually adequate with appropriate enzyme replacement therapy.
B. Higher fiber diets are not recommended as they may adversely impact the activity of supplemented digestive enzymes.
C. A low-fat, highly digestible diet may be beneficial for initial stabilization, but the utility of these diets is not universally accepted (Simpson et al., 1994; Westermarck et al., 1995).
D. Consider supplementation with fat-soluble vitamins in severely affected animals.
   1. Coagulopathy from vitamin K deficiency has been documented in a cat (Perry et al., 1991).
   2. Deficiency of fat-soluble vitamins is common in affected German shepherd dogs (Rutz et al., 2001).
E. In cats with cobalamin deficiency (<300 pg/L), parenteral supplementation is instituted at 250 μg SC every 7 days for 6 weeks, then 250 μg SC every 14 days for 6 weeks, then 250 μg SC every 28 days thereafter (Ruaux et al., 2002, 2005).
F. Medium-chain triglyceride (MCT) oil, 1 to 2 mL/kg/day PO in combination with a severely fat restricted diet may be used in dogs if steatorrhea continues.
G. Severe fat restriction is done with caution in cats because of their obligate requirement for dietary arachidonic acid.
H. Reduction of gastric acid secretion is not recommended in most cases.
I. Antibiotic therapy may be considered for dogs.
   1. If there is evidence of intestinal bacterial overgrowth, antibiotic therapy may be indicated.
   2. Tylosin (25 mg/kg PO BID) or metronidazole (10 to 15 mg/kg PO BID) are reasonable choices.
J. If there is poor response to therapy, prednisone at 1 to 2 mg/kg PO SID for 14 days, then tapered, may be beneficial because lymphocytic-plasmacytic enteritis often coexists with EPI.

Monitoring of Animal

I. Monitor body weight
   A. Rapid weight gain is expected with adequate enzyme replacement therapy.
   B. Some dogs fail to regain full body weight even if steatorrhea and polyphagia resolve.
II. Lifelong treatment is usually required.
III. Prognosis is generally good for dogs with EPI.
   A. Response to therapy is variable, but >50% show improvement (Wiberg et al., 1998).
      1. Poor responses are seen in 20% of affected dogs.
      2. Dermatological disorders are common.
   B. Because EPI requires lifelong therapy and is more common in large-breed dogs, financial constraints may be an issue for some owners.
   C. A high prevalence (10%) of fatal mesenteric torsion has been seen in German shepherd dogs with EPI in Finland (Westermarck and Rimaila-Parnanen, 1989).
IV. Prognosis is more guarded for cats with EPI.
   A. Food aversion may occur when mixed with digestive enzymes.
   B. Cats may also develop diabetes mellitus, which is more difficult to manage than usual because of poor nutrient uptake.
   C. Owner compliance and administration of enzymes, antibiotics, etc. is often poorer than with dogs.

PARASITIC DISEASES

Definition and Causes

I. Parasitic infestation is an uncommon cause of pancreatic disease in cats.
II. Cats may contract a pancreatic fluke, *Eurytrema procyonis*.
   A. It is normally found in the pancreatic ducts of raccoons and foxes.
   B. Infection is most likely through consumption of an infected intermediate host.
III. Cats may also develop pancreatic duct parasitism by the hepatic fluke, *Amphimerus pseudofelinus.*

Pathophysiology

I. Chronic infestation of the pancreatic duct system may lead to enlargement and fibrosis of the pancreatic ducts.
II. Duct obstruction may produce chronic pancreatitis through increased back pressure on the pancreatic acinar tissue.
III. Chronic inflammation and fibrosis may lead to pancreatic atrophy and decreased pancreatic secretory capacity.

Clinical Signs

I. Infection may be clinically silent or signs may be vague and nonspecific.
II. See discussion of clinical signs under Chronic Pancreatitis.
III. Signs consistent with pancreatitis have been described in a cat infected with *E. procyonis* (Anderson et al., 1987), and rare case reports describe pancreatitis in cats with *A. pseudofelinus* infections (Rothenbacher and Lindquist, 1963; Lewis et al., 1991).

Diagnosis

I. Without a high index of suspicion, these infections remain undiagnosed.
II. Diagnosis is made by demonstration of characteristic parasite ova in fecal flotation preparations.
III. The ova of *A. pseudofelinus* are destroyed on routine fecal flotation and require formalin-ethyl acetate sedimentation.
IV. Histopathologic examination of pancreatic tissue may show evidence of trematodes.

Differential Diagnosis

I. Chronic pancreatitis
II. Exocrine pancreatic insufficiency

Treatment and Monitoring

I. Treatment with fenbendazole 30 mg/kg/day PO for 6 days is effective for *E. procyonis*.

II. Praziquantel 40 mg/kg PO for 3 days is a reasonable alternative and has been recommended for *A. pseudofelinus* (Lewis et al., 1991).
III. Infected cats do not represent a zoonotic risk.

EXOCRINE PANCREATIC NEOPLASIA

Definition and Causes

I. Tumors of the exocrine pancreas are relatively rare in cats and dogs (approximately 0.6% of all neoplasms).
II. Benign pancreatic masses include nodular pancreatic hyperplasia and pancreatic adenomas.
III. Malignant tumors are usually adenocarcinomas.
  A. Typically arise from ductal cells
  B. Acinar cellular origin more common in cats
  C. Metastasis of other malignancies occasionally detected

Pathophysiology

I. Malignant pancreatic tumors are often very aggressive.
II. Metastasis to the duodenum, liver, regional lymph nodes, mesentry, stomach, and (less commonly) pulmonary tissues has usually occurred by the time of diagnosis.
III. Rapid, local growth of the neoplasm may cause gastric outflow, intestinal, obstruction or common bile duct obstruction.
IV. Abnormalities in liver enzyme activities and jaundice are common.

Clinical Signs

I. Pancreatic neoplasms are typically diagnosed in older dogs and cats.
II. Signs are often nonspecific and include obtundation, fever, weight loss, anorexia, abdominal pain, and dehydration.
  A. Vomiting is uncommon.
  B. A palpable mass may be detected in the right cranial abdomen.
  C. Jaundice may be present with bile duct involvement.
  D. Steatitis, panniculitis, and progressive alopecic dermatitis have occasionally been reported (Godfrey, 1998; Fabbrini et al., 2005).
III. Occasionally, concurrent signs of diabetes mellitus or EPI may be noted.
IV. Benign neoplasms of the pancreas typically do not cause clinical signs and are an incidental finding.

Diagnosis

I. Clinical signs and history are often vague.
II. Clinical biochemistry results may resemble acute pancreatitis and often indicate hepatic disease.
III. Serum lipase activity may be extremely elevated, but this finding is nonspecific.
IV. Ultrasonography of the abdomen may identify masses within the pancreas.
  A. Small pancreatic masses may be obscured by overlying gas-filled intestinal loops.
  B. Liver, duodenal, gastric, and mesenteric metastases may be detected.
  C. Ultrasound- or fluoroscopic-guided aspirates are useful in establishing a diagnosis (Bennett et al., 2001).
V. Thoracic radiography may detect pulmonary metastasis.
VI. Detection of neoplastic cells in abdominal effusions is uncommon.
VII. Exploratory laparotomy and histopathologic examination are required for definitive diagnosis.

Differential Diagnosis

I. Acute pancreatitis
II. Chronic pancreatitis
III. Cholangitis/cholangiohepatitis with jaundice
IV. Pancreatic paraneoplastic partial alopecia: see Table 73-1

Treatment and Monitoring

I. Surgical removal of isolated masses is indicated.
II. Palliative and salvage procedures may be performed in selected cases.
  A. Cholecystojejunostomy bypasses a common bile duct obstruction.
  B. Gastrojejunostomy bypasses a duodenal obstruction.
  C. These procedures have high morbidity and mortality rates, but may improve quality of life for short periods.
III. Successful chemotherapy for pancreatic carcinoma has not been reported in dogs and cats.
IV. The prognosis for most dogs and cats with pancreatic carcinomas is extremely poor.
V. Resolution of pancreatic paraneoplastic alopecia has been reported in a cat following resection of the associated mass (Tasker et al., 1999).

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CHAPTER 37

Diseases of the Hepatobiliary System

Kenneth Harkin

CONGENITAL/DEVELOPMENTAL DISEASES

Congenital Portosystemic Shunts

Definition and Causes

I. Congenital portosystemic shunt (PSS) is a vascular anomaly resulting in direct communication between the portal and systemic circulation.
II. Extrahepatic shunts are the most common type in small breeds of dogs and cats.
III. Intrahepatic shunts are the most common shunt in large breed dogs with a patent ductus venosus being the most frequent anomaly.
IV. Prevalence is unknown, but it is relatively common in the dog (0.5%) (Tobias and Rohrbach, 2002).
V. Commonly affected breeds include the Havanese, Yorkshire terrier, Maltese, Dandie Dinmont terrier, pug, miniature schnauzer, Irish wolfhound, and Cairn terrier.
VI. PSS is uncommon in cats.

Pathophysiology

I. Diversion of portal blood from the liver to the systemic circulation deprives the liver of trophic factors, resulting in hepatic atrophy.
II. Shunting of portal blood prevents normal clearance of toxins and bacteria by the liver.
III. Bacteremia is rarely significant, but toxins result in hepatic encephalopathy (see Hepatic Encephalopathy).

Clinical Signs

I. Hepatic encephalopathy
  A. Most commonly occurs after a meal
  B. Depression, stupor, or coma
  C. Circling, head pressing, amaurosis (blindness)
  D. Pica, personality changes, ptyalism (cats)
  E. Seizures (more common in cats)
II. Intermittent vomiting
III. Polyuria, polydipsia: may resolve with antibiotics
IV. Pollakiuria, stranguria, or hematuria associated with urate urolithiasis
V. Growth retardation

Diagnosis

I. Screening laboratory tests
  A. Complete blood count (CBC)
    1. Mild anemia: hypochromic, microcytic
    2. Poikilocytosis in cats
  B. Serum biochemistry profile
    1. Hypoalbuminemia, hypocholesterolemia, hypoglycemia
    2. Low blood urea nitrogen (BUN)
    3. Normal or mildly elevated serum alanine transaminase (ALT) and alkaline phosphatase (ALP)
    4. Often normal in cats
  C. Urinalysis
    1. Ammonium biurate crystalluria
    2. Hyposthenuria or isosthenuria
    3. Active sediment with urate cystic calculi
  D. Postprandial serum bile acids: significantly elevated
II. Imaging techniques
  A. Abdominal radiographs usually document microhepatica.
  B. Abdominal ultrasonography may reveal microhepatica with homogenous echogenicity.
    1. Visualization of the shunting vessel is often possible (d'Anjou et al., 2004).
    2. Renomegaly and urolithiasis may be identified.
  C. Rectal portal scintigraphy
    1. ^{99m}Technetium-pertechnetate placed in the rectum eventually enters the portal circulation.
    2. Radioactivity occurs in the liver before the heart in normal animals.
    3. Radioactivity is seen in the heart and lungs before the liver with PSS.
  D. Intraoperative portography
    1. Catheterization of mesenteric vein at laparotomy
    2. Radiographs or fluoroscopic images obtained during injection of contrast
    3. Often unnecessary, as the shunting vessel usually visible during laparotomy

Differential Diagnosis

I. Hypoglycemia in puppies (toy breeds)
II. Cobalamin deficiency in the border collie

III. Cirrhosis
IV. Intrahepatic arteriovenous fistula, acquired PSS
V. Hydrocephalus, idiopathic epilepsy, other causes of encephalopathy

Treatment

I. Medical management: see treatment of Hepatic Encephalopathy
II. Surgical correction of PSS
  A. The preferred treatment method
  B. Surgical options
    1. Silk ligation: partial or complete
    2. Ameroid constrictor
      a. Most popular technique
      b. Shorter surgery time than silk ligation (Hurn and Edwards, 2003)
    3. Cellophane banding
    4. Transvenous coil embolization
  C. Liver biopsy for histopathology
III. Surgical complications
  A. Portal hypertension occurs with a rapid onset of congestive enteropathy and ascites.
    1. Most common with complete silk ligation
    2. May require emergency surgery to remove the ligature
    3. Possible acquired shunts in some dogs
  B. Generalized motor seizures may develop 12 to 72 hours after ligation and are accompanied by a high mortality rate.
  C. Persistent clinical signs may be explained by the following:
    1. Concurrent presence of portal vein hypoplasia
    2. Development of acquired shunts from portal hypertension
    3. Incomplete ligation or failure to ligate additional PSSs
  D. Persistent signs may need long-term medical management or repeated ligation.

Monitoring of Animal

I. Monitoring after surgical ligation
  A. With partial ligation, rectal portal scintigraphy is repeated in 3 months to evaluate the need for additional ligation.
  B. With complete ligation or ameroid constrictor placement, follow-up is dependent on the presence of clinical signs.
    1. Asymptomatic animals are rechecked at 3 to 6 months, with evaluation of serum biochemistry profile and serum bile acids.
    2. In symptomatic animals, rectal portal scintigraphy, abdominal ultrasonography, biochemistries, and bile acids are repeated.
II. Monitoring during chronic medical therapy
  A. Serial serum bile acids are not very helpful, as the degree of dysfunction cannot be predicted by comparing levels from various times.
  B. Asymptomatic animals are reevaluated every 6 to 12 months.
  C. Animals that remain symptomatic require frequent evaluation to optimize therapy and monitor nutritional status.

Portal Vein Hypoplasia

Definition and Cause

I. It is abnormal microscopic circulation of the hepatic portal system that is poorly understood.
II. It is also termed *hepatic microvascular dysplasia,* although the term *portal vein hypoplasia* is preferred.
III. Despite the general acceptance of this condition as a disease, the histological changes identified can be seen in healthy dogs with normal serum bile acids.
IV. Although some liver disease is likely to be present in these dogs, portal vein hypoplasia has not been definitively proven.

Pathophysiology

I. Decreased portal vein circulation results in hepatic arterial overcirculation that maintains sinusoidal perfusion.
II. Sinusoidal pressure increases, resulting in dilation of portal lymphatics and hepatic venules.
III. Embryological sinusoidal vessels reopen from the hypertension, shunting blood away from sinusoids.
IV. These shunting vessels have a variable effect on the development of clinical signs.

Clinical Signs

I. No apparent clinical signs: most common
II. Signs of hepatic encephalopathy

Diagnosis

I. Screening laboratory tests
  A. CBC: usually normal in most cases; rarely, changes similar to PSS
  B. Serum biochemistry profile: usually normal; mild elevations in liver enzymes; changes similar to PSS (rare)
  C. Urinalysis: ammonium biurate crystals possible
  D. Serum bile acids: postprandial levels not as high as with PSS (median = 41 mmol/L) (Allen et al., 1999)
II. Imaging tests
  A. Liver size is usually normal on radiography.
  B. Ultrasonography and transcolonic scintigraphy are usually normal.
  C. Intraoperative contrast portography is usually normal.
III. Histopathologic findings
  A. Hepatic arteriolar tortuosity (duplication), portal venule hypoplasia
  B. Iron granuloma formation
  C. Also identified in dogs with PSS

Differential Diagnosis

I. Portosystemic shunt
II. Lysosomal storage diseases
III. Urea cycle enzyme deficiency

Treatment

I. Most dogs require no therapy.
II. Symptomatic dogs are treated with medical therapy as for PSS.

Urea Cycle Enzyme Defects

See Table 37-1.

INFECTIOUS DISEASES

Hepatic Abscess

Definition

I. Abscesses are variably sized, focal or multifocal, localized collections of purulent material that form from necrosis of hepatic tissue.
II. They may be infected (primary or secondary) or sterile.

Causes

I. Unknown in most cases
II. Hematogenous spread from infections of the skin, heart, gastrointestinal (GI) tract, etc.
III. Secondary to immunosuppressive conditions: diabetes mellitus, hyperadrenocorticism, exogenous corticosteroids
IV. Ascending biliary tract infection, pancreatitis
V. Hepatic neoplasia or infarcts

Pathophysiology

I. Inflammation from necrosis or infection results in fever and pain.
II. Release of toxins from bacteria cause systemic signs of sepsis.
III. Abscess rupture may result in peritonitis.

Clinical Signs

I. Lethargy, fever
II. Vomiting, diarrhea
III. Weight loss

Diagnosis

I. CBC
   A. Leukocytosis, often with a left shift
   B. Thrombocytopenia, possible evidence of disseminated intravascular coagulation (DIC)

TABLE 37-1

Miscellaneous Hepatobiliary Diseases

DISORDER	CAUSE(S)	CLINICAL FINDINGS	DIAGNOSIS	TREATMENT/PROGNOSIS
Urea cycle enzyme deficiency	Congenital defect	Hyperammonemia, HE	Biopsy and measurement of enzyme levels	Supportive therapy for HE Poor prognosis
Vacuolar hepatopathy	Cortisol excess Idiopathic Hyperlipidemia	Asymptomatic, polyuria/polydipsia, elevated ALP	Biopsy, tests for hyperadrenocorticism	Treat underlying disease Good prognosis
Idiopathic hepatic fibrosis	Unknown	Ascites, weight loss, polyuria/polydipsia, HE	Biopsy	Colchicine, diuretics, others as for chronic hepatitis Poor prognosis
Intrahepatic arteriovenous fistula	Congenital defect	Ascites, HE, GI signs, hypoalbuminemia	Ultrasonography, laparotomy, arteriography	Surgical resection of affected liver lobe Guarded prognosis
Granulomatous hepatitis	Bacterial and fungal infection Immune disorders Neoplasia Idiopathic forms	Anorexia, fever, hepatomegaly	Biopsy with special stains for fungi, culture, antinuclear antibody assay	Underlying etiology determines therapy and prognosis
Cholecystitis/cholangitis	Mucocele Cholelithiasis Pancreatitis Immune suppression	Abdominal pain, fever, vomiting, icterus, leukocytosis	Ultrasonography, bacterial culture of bile	Antibiotics, supportive care, ± cholecystectomy Good prognosis
Scottish terrier hepatopathy	Idiopathic	Asymptomatic, elevated ALP	Biopsy	No treatment needed Prognosis excellent
Biliary flukes (cat)	*Platynosomum* spp. *Amphimerus* spp.	GI signs, icterus	Fecal flotation	Praziquantel 20-40 mg/kg SC, PO SID for 3 days Variable prognosis

HE, Hepatic encephalopathy; *ALP,* alkaline phosphatase; *GI,* gastrointestinal.

C. Mild anemia
II. Serum biochemistry profile
A. Elevated ALP and ALT
B. Hypoalbuminemia
C. Hyperbilirubinemia (less common)
D. Hyperglobulinemia with chronicity
III. Coagulation profile: abnormal prothrombin time and partial thromboplastin time consistent with DIC
IV. Abdominal radiography
A. ± Hepatomegaly
B. ± Focal gas accumulation
C. ± Poor abdominal detail
V. Ultrasonography
A. Hyperechoic, mixed-echoic, or anechoic masses
B. ± Localized peritoneal effusion
VI. Definitive diagnosis
A. Laparotomy or laparoscopy with biopsy, aerobic and anaerobic bacterial culture
B. Ultrasound-guided aspiration with cytology and culture

Differential Diagnosis

I. Hepatic neoplasia: primary, metastatic
II. Nodular regeneration of the liver
III. Extramedullary hematopoiesis

Treatment

I. Antibiotic treatment is optimally guided by culture and sensitivity.
A. Good first choices in dogs pending culture results include the following:
1. Ampicillin 22 mg/kg IV, PO TID and enrofloxacin 5 mg/kg IV, PO BID
2. Cefoxitin 30 mg/kg IV TID to QID
3. Metronidazole 20 to 30 mg/kg IV, PO SID, cefazolin 22 mg/kg IV TID or cephalexin 22 mg/kg PO TID, and enrofloxacin or marbofloxacin 5 mg/kg PO BID
B. Long-term antibiotic therapy (4 to 6 months) is recommended.
II. Surgery is indicated for large abscesses, when the abscess has ruptured and septic peritonitis has occurred, and for abscesses localized to a single lobe.
III. Ultrasound-guided drainage and alcoholization is effective for confined lesions.

Monitoring of Animal

I. Underlying or predisposing conditions are identified and managed to prevent recurrence.
II. For animals that are managed medically, perform an ultrasound examination monthly until resolution or reduction in size is noted, and then every 3 months for 6 to 12 months after completing antibiotics.

Other Infectious Causes of Hepatitis

See Section 15.

Feline Acute Cholangiohepatitis

Definition and Causes

I. It is an acute bacterial infection of the liver and biliary tract.
II. It may result from an ascending infection with enteric bacteria.
III. The most common organisms isolated include *Escherichia coli*, *Enterobacter* spp., *Streptococcus* spp., *Klebsiella* spp., *Clostridia* spp., and *Bacteroides* spp.

Pathophysiology

I. The predominant finding on histopathology is a neutrophilic infiltration.
II. Although some degree of biliary stasis may be necessary for this to occur, diseases that cause biliary stasis (cholelithiasis, pancreatitis) are not often identified.

Clinical Signs

I. It typically affects young to middle-aged cats; males may be predisposed.
II. Duration of clinical signs is usually short (<5 days).
III. Jaundice, vomiting, diarrhea, and fever are common.

Diagnosis

I. Laboratory findings
A. Increased ALT: fivefold to tenfold increase
B. Increased ALP: twofold to fourfold increase
C. Elevated bilirubin (mean total bilirubin 5.0, range 0.1 to 20)
D. Leukocytosis with a left shift in 30% to 50% of cases
II. Imaging tests
A. Liver may be enlarged or normal in size on radiographs.
B. Liver may appear hypoechoic, and the biliary tree may appear thickened and dilated on ultrasonography.
C. Evidence of cholelithiasis may occasionally be found.
III. Definitive diagnosis by hepatic biopsy
A. Periductal and periportal suppurative inflammation and edema
B. Accumulation of suppurative exudate in intrahepatic bile ducts
C. Piecemeal necrosis with local extension of inflammation
D. Dilation of intrahepatic bile ducts

Differential Diagnosis

I. Acute pancreatitis
II. Feline infectious peritonitis (FIP)
III. Toxoplasmosis
IV. Tularemia
V. Cytauxzoonosis
VI. Salmonellosis

Treatment

I. Intravenous fluid therapy is usually required, with fluid deficits corrected over 8 to 12 hours and potassium supplemented as needed.

II. Antibiotic therapy is started pending the results of culture.
  A. Ampicillin 22 mg/kg IV, PO TID and enrofloxacin 5 mg/kg IV, PO SID
  B. Cefazolin 22 mg/kg IV TID and enrofloxacin
  C. Ticarcillin/clavulanic at acid 33 to 50 mg/kg of ticarcillin IV QID
  D. Amoxicillin/clavulanic acid 13.75 mg/kg PO BID
  E. Cefoxitin 30 mg/kg IV TID
III. Long-term, antibiotic therapy (3 to 6 months) is recommended.
IV. Cats rarely require surgery to relieve an extrahepatic bile duct obstruction or obstruction from inspissated bile.

Monitoring of Animal

I. Reevaluate liver enzymes every 1 to 2 weeks until antibiotic therapy is discontinued.
II. If liver enzymes are not normal after completing therapy, further evaluation (repeat biopsy) may be indicated.

INFLAMMATORY DISEASES

Canine Chronic Hepatitis and Cirrhosis

Definition

I. Chronic hepatitis is an inflammatory disease of the liver that is characterized by bridging fibrosis, hepatocellular necrosis, piecemeal necrosis, and predominantly nonsuppurative inflammation.
II. Most dogs are identified only when the disease is advanced.
III. Cirrhosis is the end result, with bridging fibrosis, nodular regeneration, and permanent distortion of the hepatic architecture.
IV. The term *chronic active hepatitis* has often been used previously for this disease.

Causes

I. In some cases the etiology may be identified; however, in most dogs the underlying cause is never defined.
II. Possible etiologies include canine adenovirus 1 (CAV-1), leptospirosis, and long-term administration of medications (e.g., phenobarbital, primidone, phenytoin, carprofen).
III. See also Copper Storage Hepatopathies.

Pathophysiology

I. The predominant inflammatory cells are lymphocytes and plasma cells.
II. Nonspecific, immunological response leads to chronic hepatic injury.
III. Antibodies are directed against liver-specific antigens and perpetuate hepatic injury.

Clinical Signs

I. Commonly affected breeds include the Doberman pinscher, American and English cocker spaniels, Labrador retriever, and German shepherd dog.
II. Typical age is 4 to 7 years.
III. Lethargy, anorexia, vomiting, and weight loss are common.
IV. Small bowel diarrhea, polyuria, and polydipsia are seen occasionally.
V. Ascites, icterus, and hepatic encephalopathy occur in severe cases.
VI. In some dogs the disease is subclinical and identified on routine laboratory testing.

Diagnosis

I. Serum biochemistry results
  A. Increased ALT and ALP occur in most affected dogs.
  B. Hypoalbuminemia is seen in many affected dogs.
  C. BUN is usually subnormal.
  D. Hyperbilirubinemia occurs early in the course of disease when the primary lesion is periportal.
    1. Clinical jaundice is not seen until bilirubin >2.0 mg/dL.
    2. Jaundice may not be apparent until bilirubin >4.0 mg/dL.
  E. Hyperglobulinemia is uncommon and occurs from chronic inflammation.
  F. Serum cholesterol may be increased, normal, or decreased.
  G. Hypoglycemia is rarely seen except in end-stage cirrhosis.
II. Coagulation profile results
  A. Variable, depending on the stage of chronic hepatitis
  B. Uncommonly associated with vitamin K deficiency
III. Bile acids concentrations: postprandial levels almost always abnormal
IV. Radiographic findings
  A. Survey radiography: small or normal sized liver
  B. Ultrasonography: normal or diffuse hyperechogenicity, microhepatica, irregular margins, cirrhotic nodules
V. Histopathologic examination of liver biopsy
  A. It provides the definitive diagnosis.
  B. Also submit samples for culture and mineral analysis.
  C. Samples obtained at laparotomy and laparoscopy are preferred.
    1. Tru-cut biopsies may not always provide the diagnosis.
    2. Fine-needle aspirate cytology often is not accurate enough to make the diagnosis.
VI. Recommendations for biopsy
  A. Persistently elevated liver enzymes without an obvious cause
  B. Not precluded by absence of clinical signs

Differential Diagnosis

I. Hepatic neoplasia
II. Protein-losing enteropathy
III. Systemic lupus erythematosus
IV. Right-sided congestive heart failure
V. Hypoadrenocorticism

Treatment

I. The goals of therapy are to control inflammation, arrest fibrosis, resolve infection, improve bile flow and decrease toxic bile acids, provide antioxidants, decrease absorption

of hepatic encephalopathic toxins, support hepatic regeneration, and manage or prevent GI complications.

II. Various drugs are used to control inflammation.
  A. Give prednisone at 1 mg/kg PO SID for 2 to 3 weeks, then taper.
    1. Do not give if cultures are positive.
    2. Dexamethasone (0.2 to 0.4 mg/kg PO SID) is an alternative in dogs with ascites, as it has less mineralocorticoid activity.
  B. Use azathioprine in combination with corticosteroids to reduce their dosage.
    1. Dose is 2 mg/kg PO SID for 10 to 14 days, then QOD for 3 to 6 months, then 1 mg/kg PO QOD indefinitely.
    2. Side effects include GI upset, myelosuppression, and pancreatitis.
  C. D-penicillamine is principally used as a copper chelator.
    1. Dose is 10 to 15 mg/kg PO BID.
    2. It may cause persistent vomiting.
  D. Metronidazole is given at 15 mg/kg PO SID or divided BID for its possible immunomodulatory and antioxidant effects.

III. Colchicine may be given to combat fibrosis.
  A. Recommended dose is 0.03 mg/kg PO SID (do not use the probenecid/colchicine combination).
  B. Side effects include hemorrhagic gastroenteritis, myelosuppression, nephrotoxicity, and neuromyopathies.

IV. Resolve or control infections.
  A. Antibiotics are recommended in the following situations:
    1. Positive culture results
    2. Significant suppurative component on biopsy
    3. To reduce any bacterial contribution to hepatic encephalopathy
    4. Prophylaxis after liver biopsy or episodes of gastroenteritis
  B. Antibiotic choices include the following:
    1. Ampicillin 22 mg/kg IV TID, amoxicillin 22 mg/kg PO TID, or amoxicillin-clavulanic acid 13.75 mg/kg PO BID
    2. Cephalexin 22 mg/kg PO TID or cefadroxil 22 mg/kg PO BID
    3. Enrofloxacin 5 mg/kg PO BID
    4. Metronidazole 15 mg/kg PO SID for anaerobic infections

V. Ursodeoxycholate 10 to 15 mg/kg PO SID is used to improve bile flow and reduce toxic bile acids.

VI. Antioxidant therapy helps protect against ischemic, hypoxic, oxidative, or free radical damage.
  A. Zinc acetate or gluconate
    1. Prescribed for copper hepatopathy
    2. May also have antifibrotic activity
  B. D-Alpha-tocopheryl-1000-polyethylene glycol succinate (*Liqui-E;* TwinLab, New York, N.Y.)
    1. It is a water-soluble form of vitamin E that accumulates in hepatocytes to a greater degree than does the acetate form.
    2. Dose is 25 IU/kg PO BID.
    3. The sweet taste may be objectionable to some dogs.
  C. S-adenosyl-L-methionine (SAMe)
    1. It is normally produced in the liver from dietary methionine, but in cirrhosis, SAMe synthetase is reduced.
    2. Administer SAMe on an empty stomach at a dose of 20 mg/kg PO SID.

VII. Decrease absorption of hepatic encephalopathic toxins.
  A. Give antibiotics to reduce production of toxins by enteric bacteria.
  B. Give lactulose at 0.5 mL/kg PO TID.

VIII. Institute dietary changes that support hepatic regeneration.
  A. Protein requirements are at least as high as those of healthy individuals.
  B. Protein is necessary to maintain a positive nitrogen balance and stimulate hepatic regeneration.
  C. In the animal without encephalopathy, give a diet that contains between 25% and 32% protein in a highly digestible source.
  D. Protein-restricted diets are given only to treat hepatic encephalopathy, which most commonly occurs in dogs with PSS and severe hepatic dysfunction.

IX. Prevent or treat GI complications.
  A. GI ulcers and subsequent hemorrhage can complicate hepatic encephalopathy, precipitate an encephalopathic crisis, and cause anorexia.
  B. Famotidine is given at 0.5 to 1.0 mg/kg PO SID to BID to decrease gastric acid production.
  C. Consider sucralfate as a GI protectant at 250 to 1000 mg PO TID.

X. Recommendations for managing ascites include the following:
  A. Furosemide is given at 1.0 mg/kg PO BID.
  B. Spironolactone may be tried at 1 to 2 mg/kg PO BID, alone or in combination with furosemide.
  C. Restricted exercise and decreased salt intake are rarely effective.
  D. Abdominocentesis is performed in dogs with significant ascites or compromised cardiac or respiratory functions or anorexia, and it is followed with diuretics.

Monitoring of Animal

I. Evaluate body weight, liver enzymes, serum albumin and bilirubin monthly until they are stable, then every 3 to 6 months.

II. Monitor serum bile acids every 6 to 12 months.
  A. Changes in degree of elevation do not correlate well with changes in hepatic function.
  B. Return to normal signals normalization of hepatic function (rare).

III. Any dog that suddenly decompensates with ascites, hepatic encephalopathy, or vomiting requires immediate reevaluation.

IV. Ascites is a poor prognostic sign.

V. For dogs that are receiving azathioprine, check a CBC at 2 and 4 weeks initially, then monthly while on 2 mg/kg QOD, and every 3 months when on the lowest dose.

Feline Chronic Cholangiohepatitis

Definition and Causes

I. It is also referred to as *nonsuppurative cholangitis*, *lymphoplasmacytic cholangitis,* or *cholangiohepatitis*.
II. It is presumed to be immune-mediated.
III. It often occurs as a component of other inflammatory diseases of the intestine or pancreas.

Pathophysiology

I. Predominant infiltrating cells are lymphocytes and plasma cells.
II. Nonspecific, immune-mediated destruction of the liver may arise from an unknown insult and be self perpetuating.
III. It may be a component of lymphoplasmacytic inflammatory diseases of the cat.
   A. In one study, 15 of 18 cats with chronic cholangiohepatitis had inflammatory bowel disease (IBD), 9 of 18 had pancreatitis, and 7 of 18 had both pancreatitis and IBD (Weiss et al., 1996).
   B. Other disorders associated with chronic cholangiohepatitis include toxoplasmosis, feline immunodeficiency virus (FIV) infection, and idiosyncratic reactions to chronic medications.

Clinical Signs

I. It is less severe than acute cholangiohepatitis, but cats are usually ill for longer periods.
II. Most are middle-aged cats.
III. Duration of illness is typically ≥3 weeks.
IV. No sex or breed predilection has been found.
V. Vomiting, diarrhea, and jaundice are common.
VI. Most cats have good appetites.

Diagnosis

I. ALT and bilirubin are mildly to moderately increased.
II. Abdominal radiography is usually unremarkable, but ultrasonography may reveal a diffuse to patchy hyperechogenicity of the hepatic parenchyma.
III. Definitive diagnosis is by biopsy.
   A. Mixed lymphoplasmacytic periportal inflammation
   B. Piecemeal necrosis and extension of lymphoplasmacytic inflammation into surrounding parenchyma
   C. Focal invasion of bile duct epithelium with lymphocytes
   D. Reduction in number of bile ducts
   E. Bridging portal fibrosis in later stages

Differential Diagnosis

I. Idiopathic hepatic lipidosis
II. Hepatobiliary neoplasia
III. Chronic pancreatitis
IV. Acute cholangiohepatitis
V. Toxoplasmosis
VI. Lymphocytic portal hepatitis
   A. It is a waxing and waning disease similar to chronic cholangiohepatitis.
   B. Affected cats are older (≥11 years) and have intermittent vomiting and jaundice for months to years.
   C. Hepatomegaly, marked leukocytosis, mild elevations in ALT and ALP, and hyperglobulinemia are common.
   D. A biopsy is required for diagnosis and demonstrates periportal lymphocytic infiltrates.
   E. Treatment is similar to chronic cholangiohepatitis, although some cats require no therapy if the disease is waning.

Treatment

I. Give prednisolone (which may be superior to prednisone in cats, as it needs no conversion to an active form) at 2 to 4 mg/kg PO SID for 4 to 8 weeks, and taper gradually to a dose that controls clinical signs.
II. Ursodeoxycholate acid may be tried at 10 to 15 mg/kg PO SID, but its efficacy is unproven.
III. Start antibiotics if there is evidence of infection based on culture of bile or hepatic tissue.
IV. Antioxidant therapy may be helpful.
   A. Give D-alpha-tocopheryl-1000-polyethylene glycol succinate *(Liqui-E)* at 25 IU/kg PO BID.
   B. Give SAMe at 20 mg/kg PO SID on an empty stomach.
V. Use cyclosporine at 5 mg/kg PO SID to BID in cats that have a poor response to prednisone or develop diabetes mellitus from chronic prednisone administration.

Monitoring of Animal

I. Monitor body weight and serum liver enzymes, bilirubin, and albumin every 2 to 4 weeks for several months.
II. If response to therapy is poor, perform a complete re-evaluation, including liver biopsy.
III. Prognosis is variable, although most affected cats have good long-term survival.

Copper Storage Hepatopathies

Definition

I. It is a chronic progressive hepatitis of dogs associated with the accumulation of copper in hepatocytes.
II. It is well characterized in the Bedlington terrier and West Highland white terrier.
III. It also occurs in the Dalmatian, Labrador retriever, Doberman pinscher, keeshond, and Skye terrier.

Causes

I. It is often a hereditary disease.
II. Cholestasis can also result in copper accumulation in hepatocytes.

Pathophysiology

I. In the Bedlington terrier, an autosomal trait leads to expression of an abnormal hepatic metallothionein, with resultant reduced biliary copper excretion.
II. As hepatic copper concentration increases progressively over time, hepatic injury increases.
III. Above a critical concentration, acute hepatic necrosis develops.

Clinical Signs

I. Many dogs are asymptomatic.
II. Acute episodes of anorexia, vomiting, weakness, lethargy, and dehydration may occur.
III. In chronic cases, anorexia or inappetence, poor body condition, and intermittent vomiting and diarrhea may occur weeks to months before onset of liver failure, and these dogs eventually develop jaundice, ascites, cachexia, and hepatic encephalopathy.
IV. Peracute episodes of hemolytic anemia and jaundice may occur.

Diagnosis

I. ALT is consistently elevated; ALP values are variable.
II. Bile acid assays indicate presence of liver disease.
III. Radiographic and ultrasonographic findings are variable.
IV. The measurement of serum or plasma copper or ceruloplasmin is not diagnostic.
V. Definitive diagnosis requires hepatic biopsy with quantitative measurement of hepatic copper.
   A. Dry matter copper >400 ppm is abnormal.
   B. Clinical disease usually occurs with copper levels >2000 ppm (dry matter).
VI. Affected Bedlington terriers accumulate copper as they age, so biopsies of the liver are performed at 6 months, and at 14 to 15 months of age.
   A. Normal dogs have normal liver copper content on both biopsies.
   B. Affected homozygotes have increased hepatic copper on both biopsies.
   C. Heterozygotes have elevated copper at 6 months but normal values at 14 to 15 months.
VII. In the West Highland white terrier, copper accumulation is not progressive with age.
   A. After 2 years, they do not appear to accumulate more copper.
   B. Maximum documented hepatic copper is much lower than in Bedlingtons.

Treatment

I. Zinc acetate or gluconate stimulates the production of intestinal metallothionein, which preferentially binds intestinal copper.
   A. Dose is 5 to 10 mg/kg PO SID of elemental zinc, or alternatively, give 50 to 100 mg SID to medium- and large-breed dogs.
   B. Some dietary constituents inhibit absorption, so zinc must be administered 1 hour before or 2 hours after a meal; however, it can be mixed with meat (tuna fish, ground beef) to prevent GI upset.
   C. The goal is to double baseline plasma zinc levels.
II. D-Penicillamine is a copper chelator that results in urinary excretion of copper.
   A. Dose is 10 to 15 mg/kg PO BID.
   B. Side effects include GI upset, renal disease, proteinuria, and cutaneous eruptions.
III. Trientine (2,2,2 tetramine, *Syprine*) is a copper chelator with no serious side effects.
   A. It is given at 10 to 15 mg/kg PO BID.
   B. It has substantially greater copper chelation ability than D-penicillamine.
   C. 2,3,2 Tetramine has greater than fourfold to ninefold potency compared to trientine, but is not commercially available.

Monitoring of Animal

I. Hepatic biopsy may be obtained every 1 to 6 months to monitor success of copper chelation.
II. Monitor serum liver enzymes, bilirubin, albumin, and cholesterol every 3 to 6 months.
III. The prognosis is good if the disease is identified before the onset of liver failure.

PARASITIC DISORDERS

See Table 37-1.

IDIOPATHIC DISEASES

Feline Idiopathic Hepatic Lipidosis

Definition

I. It is characterized by the accumulation of fat (triglycerides) in vacuoles within hepatocytes.
II. It is a syndrome of cyclic anorexia or inappetence that exacerbates the lipidosis, which in turn worsens the anorexia.

Causes

I. The exact etiology remains a mystery.
II. It usually occurs secondary to some stressful illness or event (e.g., upper respiratory infection, boarding, addition of new cats to the household, recent diet change), although an initiating event may not be identified.
III. It can occur secondary to other diseases.
   A. Examples include diabetes mellitus, other hepatic diseases, renal failure, hyperthyroidism, pancreatitis, neoplasia, small intestinal diseases, and starvation.
   B. Resolution of the primary disease may result in resolution of the lipidosis once the cat starts eating.
   C. Chronic pancreatitis is associated with a worse prognosis in cats with hepatic lipidosis.

Pathophysiology

I. Mechanisms for hepatic lipidosis include the following:
   A. Excess delivery of triglycerides to the liver during anorexia and insulin-deficient or insulin-resistant states
   B. Impaired formation and release of very low density lipoprotein
   C. Impaired oxidation of fatty acids
II. Acute hepatic failure is a consequence when treatment is delayed.
   A. Lipid vacuoles cause peripheral displacement of hepatocyte organelles and disruption of normal hepatocyte function.

B. The prognosis for recovery worsens with progressive hepatic failure, because hepatic encephalopathy may develop.
C. Coagulopathy may occur from decreased synthesis of clotting factors in the liver and decreased absorption of vitamin K.

Clinical Signs

I. No breed, age, or sex predilection
II. Indoor cats more often affected
III. Many cats initially obese
IV. Anorexia or decreased appetite for several days to weeks
V. Early signs: weight loss, dehydration, ptyalism, vomiting
VI. Late signs: severe wasting, icterus, hepatic encephalopathy (e.g., depression, head pressing, circling)

Diagnosis

I. CBC
  A. Mild, nonregenerative anemia
  B. Stress leukogram
II. Serum biochemistry profile
  A. ALP: often the most significantly elevated liver enzyme
  B. ALT also elevated
  C. Hyperbilirubinemia
  D. Evidence of liver failure: hypoalbuminemia, hypoglycemia, low BUN, hypocholesterolemia (bad prognostic indicator)
  E. Elevated creatine kinase: associated with anorexia, not muscle damage
III. Bilirubinuria: always abnormal in cats
IV. Serum bile acids: usually abnormal in both fasting and postprandial samples
V. Other tests to consider: feline leukemia virus (FeLV), FIV, toxoplasmosis, serum thyroxine
VI. Abdominal radiography
  A. It may reveal no significant findings.
  B. Many previously obese cats still have abundant falciform fat.
  C. The liver may be normal in size or slightly enlarged, with rounded edges.
VII. Abdominal ultrasonography: diffuse hyperechogenicity of liver parenchyma
VIII. Cytological and histopathologic examinations
  A. They are usually diagnostic.
  B. Fine-needle aspirate (FNA) reveals multiple hepatocytes packed with small and large vacuoles.
  C. Liver biopsy is superior to FNA, but may not be necessary.
    1. Obtaining a biopsy allows identification of other diseases (e.g., cholangiohepatitis).
    2. It may be obtained via ultrasound guidance, laparoscopy, or laparotomy.
    3. A coagulation profile is usually performed before biopsy.

Differential Diagnosis

I. Acute or chronic cholangiohepatitis
II. Hepatic neoplasia: lymphoma
III. Gastrointestinal diseases: IBD, lymphoma
IV. Pancreatitis

Treatment

I. Enteral feedings are the most critical component of therapy.
  A. Force feeding or appetite stimulants usually do not result in adequate food intake.
  B. Insert a feeding tube in all affected cats.
    1. Nasoesophageal tube
      a. A 5-French infant feeding tube is placed through the nose and into the esophagus.
      b. It allows for temporary nutritional support (2 to 4 days) and is a good option for initial stabilization of the cat in the hospital.
    2. Esophagostomy tube: preferred if there is no esophageal disease
    3. Gastrostomy tube options
      a. Percutaneous endoscopic gastrostomy (PEG) tube
      b. Many blind percutaneous gastrostomy tube techniques
      c. Major problems: splenic entrapment, pressure necrosis of the skin
  C. Provide a diet that has adequate calories and good quantities of protein, carbohydrates, and fat.
    1. Canned cat food can be blended and strained.
    2. On the first day, give $^1/_3$ the daily requirement, followed by $^2/_3$ on the second day, and then the full requirement thereafter.
    3. Divide food into 6 to 8 meals for the first 1 to 2 weeks, then gradually reduce the number of feedings to TID to QID.
    4. Some cats require nutritional support for ≥60 to 90 days, although most start eating on their own within 2 to 4 weeks.
    5. Let the cats eat on their own for 4 to 7 days (without nutritional supplementation) to evaluate whether they are eating enough before the tube is pulled.
II. Antiemetics may help reduce any associated vomiting, especially when tube feeding is started.
  A. Metoclopramide 0.2 to 0.4 mg/kg PO TID
  B. Cisapride 0.5 mg/kg PO BID
  C. Ondansetron 0.1 to 0.3 mg/kg IV BID to TID or dolasetron 0.5 mg/kg IV SID for refractory, severe vomiting
III. Give antacid therapy for GI hemorrhage (hematemesis, melena).
  A. Not routinely required
  B. Famotidine 0.5 mg/kg IV, PO SID to BID
  C. Sucralfate 250 mg PO BID to TID

Monitoring of Animal

I. Evaluate hepatic biochemistries and body weight every 1 to 2 weeks during therapy and recovery.
II. Do not discontinue tube feeding or remove tube too early.

Gallbladder Mucocele

Definition and Causes

I. It is a pathologic collection of mucus in the gallbladder.
II. It is one of the most common causes of extrahepatic biliary disease in the dog.
III. There is no known etiology.
IV. An infectious cause has been suggested, but cultures from bile or gallbladder wall are usually sterile.

Pathophysiology

I. Mucus accumulation admixed with bile can extend into the biliary tree, resulting in bile duct obstruction.
II. Progressive distension of the gallbladder may result in necrosis of the gallbladder wall.

Clinical Signs

I. Most dogs are older (≈10 years), although dogs as young as 3 years may be affected.
II. Dogs may be asymptomatic.
III. Acute to subacute onset of vomiting, anorexia, lethargy, and icterus may occur.
IV. Polyuria/polydipsia and abdominal discomfort may be noted.

Diagnosis

I. CBC
  A. Leukocytosis is common, often with a mature neutrophilia.
  B. Mild anemia may be present but is uncommon.
II. Serum biochemistry profile
  A. ALP is significantly elevated (as high as 11,100 U/L) (Pike et al., 2004).
  B. Moderate to significant elevations occur in ALT (as high as 4827 U/L).
  C. Hyperbilirubinemia (as high as 17.5 mg/dL) is common.
III. Abdominal radiography: normal, hepatomegaly
IV. Ultrasonography
  A. It is the definitive diagnostic test.
  B. Echogenic material in the gallbladder can appear striated, stellate, or amorphous.
  C. Dilated common bile ducts may be identified.
  D. Gallbladder wall rupture may appear as a loss of continuity in the wall.
  E. Echogenic peritoneal effusion is often seen but not diagnostic for rupture.

Differential Diagnosis

I. Acute pancreatitis
II. Leptospirosis
III. Gallbladder neoplasia
IV. Acute hepatitis
V. Cholelithiasis

Treatment

I. Asymptomatic animal
  A. Medical therapy may be attempted, but is not often successful.
    1. Antibiotics: amoxicillin-clavulanic acid, cephalosporins, fluoroquinolones, metronidazole
    2. Ursodeoxycholate 10 to 15 mg/kg PO SID
  B. Surgical therapy is often required.
II. Symptomatic animal
  A. Surgical treatment is required.
  B. Cholecystectomy is the treatment of choice.
  C. Obtain bile and gallbladder wall samples for aerobic and anaerobic bacterial culture.
  D. Adhesions to liver, omentum, stomach, and diaphragm may complicate removal.
  E. Gallbladder rupture requires copious lavage to remove contents from the abdomen.
  F. Assess patency of the common bile duct.
  G. Intraoperative hemorrhage from the hepatic fossa may occur after cholecystectomy, but is often readily controlled.
  H. Necrosis of the common bile duct may necessitate euthanasia.

Monitoring of Animal

I. Prognosis is dependent on the severity of signs, but is good for most dogs.
II. Ultrasonography and hepatic biochemistries are repeated every 2 to 4 weeks while on medical therapy.
III. Immediate postoperative therapy includes IV fluid therapy, IV antibiotics (e.g., ampicillin, cefazolin, cefoxitin), and pain control (e.g., buprenorphine, fentanyl, morphine).
IV. Complications after surgery include pancreatitis, bile peritonitis from bile duct leakage, pulmonary thromboembolism, and aspiration pneumonia.

Vacuolar Hepatopathies

See Table 37-1.

Idiopathic Hepatic Fibrosis in Young Dogs

See Table 37-1.

Hepatocutaneous Syndrome

Definition and Causes

I. It is also known as superficial necrolytic dermatitis and necrolytic migratory erythema.
II. Although a hepatopathy is recognized in most cases, the etiology is unknown except for those with a glucagonoma (rare).
III. A classic triad of findings occurs.
  A. Ulcerative and crusting lesions of foot pads, mucocutaneous junctions, ears, pressure points
  B. Vacuolar hepatopathy
  C. Late onset glucose intolerance: diabetes mellitus

Pathophysiology

I. There are two theories for the development of the cutaneous lesions.
  A. Increased portal glucagon with increased hepatic gluconeogenesis, decreased plasma amino acids, and protein depletion of the epidermis

B. Hyperglucagonemia with increased arachidonic acid synthesis in keratinocytes, inflammation, and necrosis
II. Dermatohistopathology reveals the following:
A. Epidermal parakeratotic hyperkeratosis
B. Severe intercellular and intracellular edema
C. Clefts and subcorneal vesicles
D. Foci of epidermal necrosis
E. Hyperplasia of the basal layers of the epidermis
III. Liver histopathology is characterized by the following:
A. Large, nodular areas of normal hepatic parenchyma are isolated by areas of parenchymal collapse.
B. Collapsed areas contain severely vacuolated hepatocytes (lipid), numerous small bile ductules, and a network of reticulin and fine collagen fibrils.
C. There is no evidence of cirrhosis.

Clinical Signs

I. Typically older dogs (6.5 to 16 years)
II. GI signs: diarrhea, vomiting, inappetence
III. Hyperkeratosis of footpads with severe crusting
IV. Reluctance to walk
V. Mucocutaneous ulcerations, ear crusting, pressure point ulcers, deformed nails
VI. Polyuria and polydipsia with diabetes mellitus

Diagnosis

I. Laboratory test results
A. ALP is elevated (often >1000 U/L) in all dogs.
B. ALT is mildly elevated in many dogs.
C. Low BUN and cholesterol are common.
D. Variable hyperglycemia is present.
E. Mild, normocytic, normochromic, nonregenerative anemia may be detected.
II. Abdominal ultrasonography
A. Liver can be small, normal (most common), or large in size.
B. Surface of liver is often slightly irregular.
C. A distinctive "honeycomb" pattern is present in the parenchyma, with variably sized hypoechoic regions surrounded by highly echogenic areas.
III. Specialized testing
A. Hypoaminoacidemia, especially low glutamine and proline (<10% of normal)
B. Serum glucagon levels
1. Normal in all dogs with vacuolar hepatopathy
2. Elevated with glucagonoma
IV. Histopathology of skin and liver: definitive

Differential Diagnosis

I. Diseases with similar gross cutaneous lesions
A. Pemphigus foliaceous
B. Lupus erythematosus
C. Zinc-responsive dermatosis
D. Generic dog-food dermatosis
II. Differentiated by skin biopsy

Treatment

I. Goals of treatment
A. Resolution of the cutaneous lesions
B. Prevention of deterioration of hepatic dysfunction
C. Effective management of diabetes mellitus
II. Short-term amino acid infusions for dogs with severe cutaneous lesions
III. Long-term treatment nutritional therapy
A. Do not feed a protein-restricted diet.
B. Attempt to correct hypoaminoacidemia.
C. Feed a high-quality, easily digestible protein.
1. Minimum of 28% to 35% protein (dry matter basis)
2. High-protein, low-fat diets (approximately 50% protein) preferred
D. Supplement diet to provide additional amino acids.
1. Egg yolks and cottage cheese
2. Amino acids (variety of products high in branched chain amino acids are available over the counter) at 1 to 2 g/5 to 10 kg body weight PO TID
3. Whey protein supplement at 1 to 2 g/kg/day PO (unflavored or vanilla preferred)
4. Powders mixed with yogurt or broth
IV. Zinc therapy is given as for copper hepatopathy.
V. Water-soluble vitamin E is given as for chronic hepatitis.
VI. Essential fatty acid therapy is also helpful
A. Dose: 30 to 90 mg/kg PO SID
B. Side effects: lethargy, vomiting, diarrhea
VII. Ursodeoxycholate is not a critical component of therapy, but is used as for chronic hepatitis.

Monitoring of Animal

I. Skin lesions
A. They improve within 4 to 6 weeks with successful therapy.
B. Monitor for secondary bacterial and fungal pododermatitis.
II. Hepatic lesions
A. Monitor liver enzymes, bilirubin, albumin, glucose, and cholesterol every 1 to 3 months.
B. Values improve within 2 to 4 months with successful therapy, but ALP may never normalize.
III. Diabetes mellitus
A. Develops in most dogs
B. Requires insulin therapy (see Chapter 44)

METABOLIC AND TOXIC DISEASES

Hepatic Encephalopathy

Definition and Causes

I. Hepatic encephalopathy (HE) is a complex neurological syndrome associated with acquired and congenital liver disease.
II. Causes include the following:
A. Portal vascular anomalies
B. Idiopathic feline hepatic lipidosis
C. Fulminant hepatic failure
D. End-stage chronic hepatitis/cirrhosis
E. Urea cycle enzyme deficiencies
III. Contributing factors include the following:
A. Anesthesia, surgery

B. High protein meal
C. GI bleeding: ulceration, intestinal parasites
D. Hypokalemia: enhances renal ammonia production
E. Bacterial infections or septicemia
F. Alkalosis: enhances transfer of ammonia into central nervous system (CNS)
G. Constipation, dehydration
H. Transfusions of stored blood
I. Diuretics

Pathophysiology

I. HE involves the accumulation of neurotoxins.
II. Ammonia is converted to glutamine in the brain, and this pathway can be rapidly overwhelmed.
  A. Serum glutamine levels are increased in dogs with HE.
  B. Blood ammonia is typically high in advanced liver failure.
    1. The level correlates poorly with severity of HE.
    2. Blood levels are not very useful in the diagnosis of HE.
  C. In the CNS, chronic hyperammonemia impairs the glutamate-nitric oxide-cGMP pathway (neurostimulatory pathway), which contributes to the neurological impairment.
III. False neurotransmitters are formed from excessive delivery of aromatic amino acids to the CNS.
  A. Tryptophan and phenylalanine are converted to false neurotransmitters, such as octopamine and phenylethanolamine.
  B. The false neurotransmitters are depressive in their action.
IV. Activation of central gamma-amino butyric acid (GABA)-benzodiazepine receptors also produces a depressive effect on the CNS.
V. Manganese intoxication produces clinical signs similar to HE (Schenker and Bay, 1997).
VI. Serum levels of tumor necrosis factor-α are increased in acute and chronic liver disease, and increase peripheral-type benzodiazepine receptors in the cerebral cortex.
VII. Other factors that may play a minor role include short-chain fatty acids, mercaptans, phenols, brain lactate, and zinc deficiency.

Clinical Signs

I. Grading scheme for HE
  A. Grade 0: normal
  B. Grade 1: irritability, restlessness, altered sleep, agitation
  C. Grade 2: lethargy, sluggishness, decreased inhibitions
  D. Grade 3: somnolent, but can be roused
  E. Grade 4: comatose
II. Common signs
  A. Depression, lethargy, stupor, coma
  B. Ataxia, circling, compulsive pacing
  C. Head pressing, disorientation, amaurosis
  D. Hysteria, aggression
  E. Excessive panting
  F. Ptyalism in cats
  G. Seizures (more common in cats)
  H. Polyuria, polydipsia
  I. Vomiting, diarrhea

Diagnosis

I. High index of suspicion in certain breeds
  A. Yorkshire terriers and other breeds known to have a high prevalence of PSS
  B. Doberman pinschers or other breeds with a high prevalence of chronic hepatitis
  C. Bedlington terrier or other breeds with a high prevalence of copper toxicosis
II. Compatible physical examination findings
  A. The presence of icterus
    1. Unexpected in dogs with PSS
    2. Common in dogs with acute hepatic failure
  B. Copper-colored irises in cats with PSS
  C. Hypersalivation in cats
  D. Microhepatica
III. Supportive laboratory results
  A. Hypoalbuminemia, hyperbilirubinemia, hypocholesterolemia, hypoglycemia, and elevated liver enzymes
  B. Abnormal serum bile acids
  C. Elevated blood ammonia levels
    1. Only accurate if assayed immediately and against a control sample
    2. Not elevated in every animal with HE
  D. Presence of PSS on ultrasonography

Differential Diagnosis

I. Hypoglycemia: see Chapter 46
II. Diabetic ketoacidosis
III. Azotemia
IV. Cerebral infarction
V. Meningitis or encephalitis: see Chapter 23
VI. Epilepsy
VII. Distemper encephalitis
VIII. Propane inhalation, carbon monoxide intoxication
IX. Inherited cobalamin deficiency: giant schnauzer, border collie

Treatment

I. Emergency therapy
  A. Lactulose can be given as an enema for grade 3 to 4 disease.
    1. Dose is 100 mL in 200 mL water, given at 5 to 15 mL/kg QID.
    2. The stool pH will be <6 if therapy is effective.
  B. Povidone iodine enema
    1. A 1:10 dilution of povidone iodine with water is given at 20 mL/kg QID.
    2. It acidifies the colon and decreases bacterial numbers.
  C. IV fluid therapy is started with crystalloid solutions that do not contain lactate.
  D. Give supplemental dextrose to animals with acute or fulminant hepatic failure.
II. Long-term management
  A. Surgically correct any PSS, if possible.

B. Institute therapy specific for any underlying, acquired liver disease.
C. Restrict dietary protein.
   1. Establish the protein tolerance of the animal and feed the highest amount tolerated.
   2. Supplementation of vegetable protein-based diets may allow a higher protein content to be fed.
   3. When restricting protein in cats, make sure the diet is high in arginine to prevent deficiency.
D. Lactulose is a nonabsorbable disaccharide that is metabolized in the colon by certain bacteria.
   1. Lactulose is converted to lactic acid, acetic acid, formic acid, and carbon dioxide, which decrease the breakdown of amino acids, protein, and blood, and minimize the formation of short-chain fatty acids.
   2. Acidification of the colon draws ammonia out of the blood into the gut, where it is trapped for excretion.
   3. Low pH decreases the survival of urease-producing bacteria and promotes growth of non–urease-producing bacteria.
   4. Cathartic action decreases the retention of nitrogenous waste.
   5. Give lactulose at 0.5 to 1.0 mL/kg PO TID and titrate to produce a soft stool.
E. Antibiotics kill the bacteria that produce ammonia and may have a synergistic effect with lactulose.
   1. Neomycin 20 mg/kg PO BID to TID for 10 to 14 days
   2. Metronidazole 15 mg/kg PO SID
   3. Ampicillin 20 mg/kg PO TID
F. Zinc may be given, as for Copper Hepatopathy.

Monitoring of Animal

I. See specific monitoring advice for the primary disease conditions.
II. Monitoring blood ammonia levels is not indicated because they correlate poorly with therapeutic success.
III. Regular evaluation of serum albumin is indicated for animals on low-protein diets.
IV. Avoidance of ulcerogenic medications (e.g., nonsteroidal antiinflammatory drugs) is warranted.

Hepatic Necrosis and Failure

Definition

I. Fulminant hepatic failure is characterized by hypoalbuminemia, hypoglycemia, hypocholesterolemia, decreased coagulation factors, and cholestasis of short (<2 weeks) duration, with the potential for complete recovery.
II. Not all forms of necrosis and failure are toxic in origin.

Causes

I. Blunt abdominal trauma with liver lobe rupture
II. Liver lobe torsion
   A. With or without diaphragmatic hernia
   B. Can lead to ischemic necrosis, endotoxic shock, and death
III. Postcaval syndromes: right-sided congestive heart failure (CHF), pericardial disease, Budd-Chiari-like syndrome from occlusion of the caudal vena cava between the heart and liver
IV. DIC with thromboembolic disease and infarction
V. Acute pancreatitis: shock, DIC, bacteremia, extrahepatic bile duct obstruction
VI. Gastric dilatation-volvulus: disrupted portal and vena caval blood flow
VII. Immune-mediated hemolytic anemia: hypoxia, damage from unconjugated bilirubin and hemoglobin, thromboembolism from autoagglutination
VIII. Vasculitis: infectious, noninfectious causes
IX. IBD: absorption of inflammatory mediators, endotoxin, and enteric bacteria
X. Hyperthermia: direct thermal injury, shock, DIC
XI. Neoplasia: tumor invasion (especially lymphoma), impaired perfusion, release of vasoactive substances
XII. Infections
   A. Viral: infectious canine hepatitis, canine herpesvirus
   B. Bacterial
      1. Bacteremia: *Staphylococcus* spp. or *Streptococcus* spp.
      2. Anaerobic bacteria of enteric origin
      3. *Bacillus piliformis* (Tyzzer's disease), salmonellosis
      4. Bacterial cholangiohepatitis
      5. Leptospirosis
      6. Tularemia
   C. Rickettsial
      1. *Ehrlichia canis*: liver disease uncommon, vasculitis-induced necrosis
      2. Rocky Mountain spotted fever: necrosis from vasculitis
   D. Protozoal
      1. Toxoplasmosis: hepatic necrosis from host response to tachyzoites
      2. Neosporosis: hepatic infiltration, necrosis
   E. Fungal: histoplasmosis, blastomycosis, coccidioidomycosis, aspergillosis
   F. Toxins
      1. Uncommon in dogs and cats
      2. Amanita mushroom poisoning: rare
      3. Drugs
         a. Thiacetarsamide, metofane, halothane, ketoconazole
         b. Cats: oral diazepam, griseofulvin
         c. Dogs: carprofen, trimethoprim-sulfa, amiodarone, methotrexate
      4. Blue-green algae

Pathophysiology

I. Distribution of necrosis
   A. Widespread: CAV-1, trimethoprim-sulfa, oral diazepam
   B. Focal: any insult, hypotension and local hypoxia during anesthesia, often seen in surgical biopsies
   C. Centrilobular: hypoxemia, hypoperfusion, chronic passive congestion, certain toxins (thiacetarsamide, aflatoxins, amanita mushrooms)

D. Midzonal: rare and usually associated with centrilobular necrosis
E. Periportal: uncommon; associated with some hepatotoxins, endotoxins, IBD, chronic pancreatitis
F. Paracentral: involves an entire hepatic acinus, occurs secondary to ischemia from thromboembolism

II. Consequences of fulminant hepatic failure
A. Hepatic encephalopathy
B. Cerebral edema
1. Major cause of death
2. Occurs from vasogenic edema, cytotoxic edema, cerebral ischemia
C. Coagulopathies
D. Hypotension: from endotoxemia, retention of vasogenic amines, etc.
E. Cardiac dysfunction and arrhythmias
F. Pulmonary edema
G. Acid-base and electrolyte disturbances: hyponatremia, hypokalemia, metabolic acidosis
H. Pancreatitis, renal failure
I. Hypoglycemia: develops rapidly
J. Secondary infections
K. Portal hypertension: grave prognostic sign
L. Cholestasis

Clinical Signs

I. Signs may be absent or vague.
II. Nonspecific signs occur in animals with focal, mild, or moderate hepatic necrosis.
III. Signs may relate to another organ system that is affected (e.g., CHF, pyometra, severe shock).
IV. With severe or massive acute hepatic necrosis, signs are often severe, but rarely specific.
A. Anorexia, depression, fever
B. Vomiting, possibly GI hemorrhage with melena, hematemesis
C. Jaundice, hepatic encephalopathy

Diagnosis

I. ALT and AST are consistently elevated within hours of the insult.
A. May reach levels 30 to 50 times the reference range
B. Often fall to lower levels with a few days
C. Poor correlation of elevation with severity of injury
II. Changes in ALP are dependent on the type of injury.
A. More severe elevations with cholestatic processes
B. Mild elevations typical in first days of hepatic necrosis
C. Often elevated longer than ALT
D. Persistent elevations from continued cholestasis, reactive biliary hyperplasia, or hepatic regeneration
III. Hyperbilirubinemia: more severe with periportal necrosis
IV. Hepatic biopsy to identify primary hepatic diseases

Treatment

I. Treat any primary disease.
II. The need for IV fluid therapy is dependent on the underlying condition and the severity of clinical signs and dehydration.
A. Crystalloid solutions that do not contain lactate are recommended.
B. Supplement with dextrose to provide a 2.5% or 5% solution, depending on serum glucose levels.
C. Potassium chloride supplementation is instituted.
1. Give 0.3 to 0.5 mEq/kg/hr in IV fluids to animals with severe hypokalemia.
2. Give 16 to 36 mEq/L in IV fluids to animals with normokalemia and on a maintenance rate of fluids (40 to 60 mL/kg/day).

III. Antioxidants may be beneficial.
A. D-Alpha-tocopheryl-1000-polyethylene glycol succinate (*Liqui-E;* TwinLab, New York N.Y.) is given at 25 IU/kg PO BID.
B. SAMe *(Denosyl)* is given at 20 mg/kg PO SID on an empty stomach.
C. Silymarin
1. Drug of choice for amanita mushroom poisoning
2. Dose: 25 to 50 mg/kg PO SID for dogs and cats

IV. Supportive care for complications of acute hepatic failure includes the following:
A. Treat hepatic encephalopathy, as discussed earlier.
B. Treat cerebral edema with mannitol (0.5 to 1 g/kg IV BID to TID) and with elevation of the head, but treatment is rarely successful.
C. Treat coagulopathies with fresh frozen plasma (5 to 10 mL/kg IV, repeated as needed to normalize coagulation profile) or fresh whole blood if anemic (10 to 20 mL/kg IV).
D. Treat hypotension initially with IV crystalloid fluid therapy, but severe hypotension that fails to respond may be treated with the following:
1. Hydroxyethyl starch 10 to 20 mL/kg IV bolus followed by 1 mL/kg/hr IV
2. Dopamine 2 to 10 µg/kg/min IV constant rate infusion (CRI)
3. Dobutamine 5 to 20 µg/kg/min IV as CRI (dog) or 0.5 to 2 µg/kg/min IV as CRI (cat)
E. Pulmonary edema is poorly responsive to therapy.
1. Furosemide 2 to 4 mg/kg IV TID to QID may be tried.
2. Supplement with oxygen via nasal cannula or oxygen cage.
F. Use antibiotics (e.g., ampicillin, ampicillin, enrofloxacin, cefoxitin) to prevent secondary infections.
G. Manage GI hemorrhage with famotidine.

V. Traumatic rupture rarely requires surgical intervention.
A. Stabilize the animal, providing blood products as needed.
B. Only intervene surgically if bleeding seems uncontrollable.

Monitoring of Animal

I. Prognosis is good with acute hepatic injury (e.g., toxin, trauma, brief hypoxia) if fulminant hepatic failure does not develop.
II. The development of cerebral edema, pulmonary edema, profound coagulopathy (prothrombin time and partial

thromboplastin time exceeding test limits), portal hypertension, and refractory hypotension are grave prognostic indicators.
III. The prognosis for survival is dependent on the primary disease condition or etiology.
1. Blue-green algae poisoning is routinely fatal.
2. Most infectious causes have a good prognosis with early treatment.

VASCULAR DISEASES

Acquired Portosystemic Shunt

Definition

I. Various vascular communications can develop near the kidneys that connect the portal and systemic circulation.
II. They may develop from preexisting but nonfunctional communications.
III. They are associated with any disease that causes portal hypertension.

Causes

I. Hepatic arteriovenous fistula
II. Noncirrhotic portal hypertension
III. Cirrhosis
IV. Hepatic fibrosis
V. Postligation of congenital PSS
VI. Any disease resulting in portal hypertension: cirrhosis, idiopathic hepatic fibrosis, portal vein thrombosis

Pathophysiology

I. Portal hypertension stimulates the opening of alternative vascular communications.
II. Development of HE is the same as for congenital PSS.

Clinical Signs

I. Dependent on underlying disease condition
II. Signs of HE

Diagnosis

I. Diagnostic tests are typically directed toward the primary hepatic disease.
II. Multiple tortuous vessels are identified near the kidney on ultrasonography.
III. Rectal portal scintigraphy confirms the presence of a shunt and is usually suggestive of acquired PSS.
IV. Direct visualization during laparotomy is needed in some cases.

Treatment

I. Treat the underlying disease condition.
II. Treat HE, if present.
III. Ligation of an acquired PSS is not recommended
A. An acquired PSS is a necessary adaptive process (in portal hypertension) to prevent congestive enteropathy and ascites.
B. Ligation results in immediate postoperative death.

NEOPLASIA

See Table 37-2.

TRAUMA

Extrahepatic Biliary Tract Rupture

Definition

It is a tear in the gallbladder, cystic duct, hepatic ducts, or common bile duct with secondary leakage of bile into the abdomen.

Causes

I. Blunt force trauma (e.g., automobile crash, cow kick)
II. Penetrating abdominal injury (e.g., gunshot)
III. Infectious cholecystitis
IV. Gallbladder mucocele
V. Cholelithiasis

Pathophysiology

I. Bile duct ruptures almost always arise from blunt force trauma.
A. Most common site of rupture is the common bile duct distal to the last hepatic duct.
B. Second most common site is at the junction of the common bile duct and duodenum.
C. The cystic duct is rarely ruptured by trauma.
II. Gallbladder rupture almost always occurs from nontraumatic causes.
III. Leakage of bile results in focal or diffuse peritonitis.

Clinical Signs

I. Abdominal pain
II. Abdominal distension
III. Vomiting, anorexia
IV. Icterus

Diagnosis

I. Hyperbilirubinemia and elevated liver enzymes occur.
II. Abdominal radiographs may show focal or diffuse loss of detail consistent with free abdominal fluid.
III. Abdominal ultrasonography may identify the etiology (e.g., mucocele), and the gallbladder may appear empty in cases of ductal rupture.
IV. Evaluation of fluid obtained on abdominocentesis or diagnostic peritoneal lavage documents the presence of bile.

Differential Diagnosis

I. Acute hepatitis
II. Ruptured splenic mass
III. Gastric perforation
IV. Pancreatitis
V. Peritonitis from other causes: see Chapter 38

Treatment and Monitoring

I. Surgical correction is required.
A. Ruptured common bile duct: duct repair, cholecystojejunostomy

TABLE 37-2

Hepatic Neoplasia

TUMOR TYPE	ULTRASONOGRAPHIC FEATURES	TREATMENT AND PROGNOSIS
Hepatocellular carcinoma or adenoma	Inhomogeneous echogenicity, either diffuse or circumscribed	Surgical resection if restricted to a single lobe Poor prognosis for carcinoma
Bile duct carcinoma	Multifocal with mixed echogenicity	Surgical resection if restricted to a single lobe Poor prognosis
Lymphoma	Generalized hyper- or hypoechogenicity Focal or multifocal nodules of varying echogenicity	Treatment same as for generalized lymphoma Fair prognosis for 1 year survival Grave prognosis if animal in liver failure Poor prognosis if cat is FeLV positive
Biliary cystadenoma (cats only)	Focal or multifocal cystic lesions within the liver	Excellent prognosis if surgically resectable Fair prognosis for 1-2 year survival if not resected
Hemangiosarcoma (primary and metastatic)	Solitary, circumscribed mass with cavitary lesions or multiple hypoechoic nodules	Surgical resection of solitary mass, followed by chemotherapy Poor prognosis for 6-month survival
Metastatic carcinoma	Multifocal hypoechoic nodules or diffuse inhomogeneity, target lesions	No therapy Grave prognosis
Insulinoma (metastatic)	Not routinely identified	Surgical removal of visible metastatic lesions Management of primary tumor Good prognosis for 1 year survival
Mast cell disease (metastatic)	Diffuse hyperechogenicity, hypoechoic nodules	Chemotherapy Fair prognosis for 1 year survival

FeLV, Feline leukemia virus.

B. Ligation of ruptured hepatic ducts
C. Cholecystectomy for gallbladder rupture

II. See treatment of peritonitis is Chapter 38.

III. Prognosis is dependent on the site of rupture.
A. Excellent for rupture of gallbladder and common bile duct distal to cystic duct
B. Variable depending on ease of repair for ruptures of common bile duct proximal to cystic duct
C. Fair to good when bile peritonitis is present

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CHAPTER 38

Diseases of the Peritoneum

Rhea V. Morgan

INFLAMMATORY DISORDERS

Peritonitis

Definition

I. Peritonitis is inflammation of the serous membranes of the abdomen and may involve the omentum.
II. Peritonitis can be categorized as primary or secondary, infectious or noninfectious, aseptic or septic, and focal or diffuse.
III. Secondary peritonitis is the most common form, and usually arises from some underlying abdominal disease or condition.

Causes and Classification

I. Primary peritonitis
  A. Feline infectious peritonitis (FIP) is the most common primary disease.
  B. Pansteatitis from vitamin E deficiency or excessive dietary polyunsaturated fats occurs rarely in the cat.
  C. Apparent spontaneous bacterial peritonitis has been reported rarely in immunocompromised animals (Kirby, 2003).
II. Septic peritonitis
  A. It is usually associated with compromise of the gastrointestinal (GI) tract and is bacterial in origin.
    1. GI necrosis, perforation, rupture, infarction, dehiscence, torsion, intussusception
    2. Pancreatic abcessation
    3. Hepatobiliary diseases
    4. Avulsion of the mesentery
  B. Contaminated or infected urogenital lesions may lead to septic peritonitis.
    1. Pyometra, uterine rupture or torsion
    2. Rupture of an infected bladder or an infected prostatic cyst
    3. Renal and prostatic abcessation
    4. Iatrogenic from cystocentesis of an infected bladder (rare) (Specht et al., 2002)
  C. Other causes include penetrating wounds, evisceration of the abdomen, contaminated peritoneal dialysis, splenic abscess, surgical contamination, umbilical abscess, among others.
  D. The most common bacterial pathogens are *Escherichia coli, Clostridium* spp., *Streptococcus faecalis,* and *Enterococcus* spp. (Swann and Hughes, 2000).
  E. *Actinomyces* and *Nocardia* spp. infections may occur, with and without known penetrating injuries.
  F. Viruses that may cause focal peritonitis in dogs include parvovirus and infectious hepatitis virus.
  G. Protozoal causes are rare, but include toxoplasmosis in cats and neosporosis in dogs (Holmberg et al., 2006).
III. Bile peritonitis develops from rupture of the gallbladder or bile duct(s) and leakage of bile into the abdomen.
  A. Causes include blunt trauma to the abdomen, necrotizing cholecystitis, bile duct obstruction (from calculi, parasites, neoplasia), and surgery (e.g., bile diversion procedures, gastric dilatation-volvulus correction).
  B. The peritonitis may be septic (most common agent is *E. coli)* or aseptic (Swann and Hughes, 2000).
  C. Bile causes a chemical peritonitis that may be lethal if untreated.
IV. Other causes of chemical peritonitis include aseptic pancreatitis, uroabdomen, and exposure to surgical glove powder, antibiotics, barium, povidone-iodine, or other agents.
  A. Urine does not usually cause serious peritonitis unless it is infected.
  B. Severe, sterile enzymatic peritonitis may accompany acute pancreatitis.
V. Parasitic peritonitis is uncommon, but may occur in dogs from abnormal nymphal pentastomiasis with *Porocephalus crotali* and infections with *Mesocestoides* spp. (Kirby, 2003).
VI. Mechanical peritonitis may arise from exposure of the abdomen to air (e.g., laparoscopy) or sterile foreign bodies (e.g., surgical gauze or other materials), rough handling of abdominal tissues, and other sources of trauma.
VII. Sclerosing encapsulating peritonitis is a rare disorder that results in encasement of the abdominal organs in a thick, collagenous connective tissue.
  A. It has been reported in dogs and one cat (Bellenger and Rothwell, 1991; Boothe et al., 1991; Hardie et al., 1994).
  B. Many of the dogs were young, large-breed dogs.
  C. In most cases the cause is unknown, but the cat had steatitis and, in three dogs, the condition was associated with ingestion of fiberglass, bacterial peritonitis

(Hardie et al., 1994), and leishmaniasis (Adamama-Moraitou et al., 2004).

Pathophysiology

I. Inflammation of peritoneal surfaces may lead to vasodilation, increased permeability, and loss of fluid and protein into the abdominal cavity (effusion).
II. Infection, necrosis, and decreased blood flow to abdominal organs generate inflammatory mediators and cytokines, with development of systemic inflammatory response syndrome (SIRS).
III. SIRS tends to be worse with septic, bacterial (especially bile) peritonitis and peritonitis associated with pancreatitis (Swann and Hughes, 2000).

Clinical Signs

I. History and clinical signs may be nonspecific (depression, anorexia, vomiting, diarrhea) or misleading in some animals.
   A. Onset of signs is acute in many cases of septic and traumatic peritonitis.
   B. Onset may be slower in animals with mesenteric avulsions (5 to 7 days) or aseptic, bile peritonitis (days to weeks) (Fossum, 2002a).
II. A history of recent abdominal surgery, abdominal trauma, and penetrating wounds is suggestive.
III. Abdominal enlargement, tachypnea, or dyspnea may occur with large volumes of abdominal effusion.
IV. Abdominal pain is variable in most animals, with septic or traumatic peritonitis being painful.
   A. Fewer cats (62%) than dogs with septic peritonitis exhibit abdominal pain (Costello et al., 2004).
   B. Most cats with FIP are not painful.
V. Signs of SIRS include injected mucous membranes, rapid capillary refill time, tachycardia, bounding pulses, and fever.
VI. Untreated SIRS may lead to dehydration, hypovolemia, cardiovascular collapse, and shock.
VII. Other signs relate to the underlying causes.
   A. Icterus: hepatobiliary disease
   B. Polyuria, polydipsia: pyometra, urinary tract disease
   C. Stranguria, dysuria: prostatic or other lower urinary tract diseases
   D. Fever, chorioretinitis, weight loss: FIP
   E. Abdominal bruising, puncture wounds, pelvic fractures: trauma

Diagnosis

I. Laboratory testing is indicated in all cases of suspected peritonitis.
   A. Significant leukocytosis and neutrophilia with a left shift are common in many cases of septic or chemical peritonitis.
   B. Anemia and evidence of dehydration may be detected.
   C. Biochemistry changes are variable and reflect the underlying cause or type of peritonitis.
      1. FIP: hyperglobulinemia from a polyclonal gammopathy, hyponatremia, hyperkalemia (Chastain and Panciera, 2002)
      2. Hepatobiliary disease, bile duct rupture: bilirubinemia, liver enzyme elevations, hyponatremia, hypoalbuminemia
      3. Uroabdomen: elevated blood urea nitrogen (BUN), creatinine, potassium
      4. Septic peritonitis: possible panhypoproteinemia, electrolyte abnormalities, hypoglycemia
      5. Pancreatitis: see Chapter 36
II. Abdominal radiography reveals a loss of abdominal detail that may be focal or generalized.
   A. Early signs of fluid accumulation are a patchy or mottled appearance to the abdominal organs and loss of discrete edges.
   B. With large amounts of effusion, the abdomen has a "ground-glass" appearance.
   C. The GI tract may contain excessive fluid, air, or both.
   D. Free abdominal air may be seen with penetrating wounds, rupture of hollow organs, gas-producing anaerobic bacterial infections, and after abdominal surgery, laparoscopy, or pneumoperitoneography.
   E. Other abnormalities may be detected (e.g., organomegaly, foreign body, emphysematous changes in the gallbladder or liver, distension of hollow organs, gallstones, pelvic or spinal fractures) depending on the underlying cause.
III. Ultrasonography may identify small volumes (<6 mL/kg) of effusion or localized effusions, and it often helps to determine the cause (Negrini et al., 2003).
   A. In early cases of peritonitis, little or no effusion may occur.
   B. Rupture of the GI tract may be difficult to identify with ultrasonography.
IV. Other imaging procedures to consider include thoracic radiography, positive-contrast radiography of the GI (using water-soluble iodinated contrast medium) or urinary tracts (see Chapter 4), and pneumoperitoneography.
V. Abdominocentesis and fluid analysis are indicated in cases with abdominal effusion.
   A. Contraindications are few (coagulopathies, gastric dilatation, uterine enlargement).
   B. It may be performed with or without ultrasound guidance.
   C. Techniques include a single paracentesis, four-quadrant paracentesis, or diagnostic peritoneal lavage.
   D. Submit samples for bacterial cultures, cytology, and fluid analysis.
VI. If abdominocentesis fails to yield a diagnostic sample, perform diagnostic peritoneal lavage.
   A. Insert a peritoneal lavage catheter into the abdomen via a 2-cm skin incision caudal to the umbilicus.
   B. If gentle suction yields no fluid, infuse 20 mL/kg of warm, sterile saline into the abdomen.
   C. Roll the animal from side to side, then collect fluid by gravity drainage.
   D. The volume retrieved is usually less than that infused, particularly in dehydrated animals.
VII. Results of fluid analysis may help determine the cause.

A. Normal fluid in abdomen: <1 mL/kg, <3000 nucleated cells/μL, <2.5 g/dL protein (mostly albumin) (Swann and Hughes, 2000)
B. Aseptic peritonitis (Kirby, 2003)
   1. Serosanguineous, turbid, cloudy fluid
   2. Nondegenerate neutrophils, absence of bacteria
   3. Protein > 3.0 g/dL, >5000 cells/μL
C. Septic peritonitis
   1. Serosanguineous, hemorrhagic, turbid, or cloudy fluid
   2. Toxic, degenerate neutrophils with intra- or extracellular bacteria
   3. Nucleated cell count 5000 to 100,000/μL, protein > 3.0 g/dL
   4. Low fluid glucose: <50 mg/dL or blood-to-fluid glucose difference >20 mg/dL
   5. Fluid-to-blood lactate difference >2 mmol/L (dogs)
D. Pancreatitis
   1. High numbers of degenerate neutrophils
   2. Possible fluid amylase and lipase concentrations higher than serum levels (Guija de Arespacochaga et al., 2006)
E. Uroabdomen
   1. Clear or slightly turbid fluid that may be yellow tinged
   2. Low cell counts early
   3. Transient fluid BUN concentration higher than serum levels, and persistent fluid creatinine and potassium concentrations higher than serum levels
F. Bile peritonitis (Moore and Andreasen, 2002; Fossum, 2002b)
   1. Dull green or purulent fluid, bile pigment in macrophages
   2. Fluid bilirubin concentration that is often >2 times greater than that of serum
   3. Fibrillar mucinous material occasionally identified in fluid (Owens et al., 2003)
G. FIP
   1. Clear, straw-colored fluid; rarely appears chylous (Savary et al., 2001)
   2. Viscous consistency, with possible clots
   3. Cell count 3000 to 15,000/μL, protein >3.5 g/dL
H. *Mesocestoides* spp. infection (Caruso et al., 2003; Bonfanti et al., 2004)
   1. Exudative, suppurative hemorrhagic fluid
   2. Calcareous corpuscles (remnants of cestodes), acephalic metacestodes visible on cytology

VIII. In some cases, peritonitis and its underlying cause are only diagnosed by laparoscopy or exploratory laparotomy, and histopathology (Figure 38-1).

Differential Diagnosis

I. Ascites
   A. Fluid is usually clear and colorless, but may be blood tinged after repeated paracenteses.
   B. Mononuclear cells and nondegenerate neutrophils are common.
   C. Fluid often contains <500 to 1500 cells/μL and <2.5 g/L protein (Kirby, 2003; Moore and Andreasen, 2002).
II. Chylous ascites or effusion
   A. Rare presence of chyle in the peritoneal cavity
   B. In cats, associated with intraabdominal neoplasia (hemangiosarcoma), biliary cirrhosis, extrahepatic portal shunts, cardiomyopathy (Gores et al., 1994; Nelson, 2001)
   C. In dogs, associated with rupture or thrombosis of mesenteric lymphatics, lymphatic obstruction, thoracic duct ligation, lymphangiectasia, chylothorax (Kirby, 2003; Moore and Andreasen, 2002)
   D. Characterized by a cloudy, white, or pinkish effusion that contains very high concentrations of triglyceride compared with serum triglyceride (Fossum et al., 1992) and stains positive with Sudan stain
III. Hemoabdomen: see Hemoabdomen
IV. Other causes of acute abdominal pain: see Chapter 39
V. Neoplastic effusions: see Neoplasia

Treatment

I. In critically ill animals, IV crystalloid and colloid fluids, and therapy for shock (see Chapter 132) are instituted.
   A. Provide glucose and potassium supplementation as needed.
   B. Consider sodium bicarbonate therapy.
   C. Low-dose heparin (50 to 100 U/kg SC BID) has been associated with higher survival rates in experimental septic peritonitis (Fossum, 2002a) and disseminated intravascular coagulopathy (DIC).
II. Administer parenteral antibiotics for septic peritonitis.
   A. Ampicillin 20 to 40 mg/kg IV TID to QID or cephazolin 20 mg/kg IV TID, possibly combined with amikacin 30 mg/kg IV SID (dogs) or 10 mg/kg IV SID (cats)
   B. Ampicillin or cefazolin combined with gentamicin 6 mg/kg SC SID
   C. Metronidazole 10 mg/kg IV BID added for anaerobic infections
   D. Third-generation cephalosporins
      1. Cefoxitin 30 mg/kg IV TID to QID
      2. Cefotaxime 30 to 40 mg/kg IV TID to QID (dogs)
      3. Ceftazidime 20 to 50 mg/kg IV TID (dogs)
   E. Imipenem 3 to 10 mg/kg IM TID to QID (dogs)
   F. Modified based on culture results
III. It is imperative to remove the underlying cause, which usually requires a celiotomy (see Figure 38-1).
   A. Perform corrective procedures (e.g., repair of bile ducts, gallbladder removal, biliary diversion, resuturing of dehiscences, intestinal anastomosis, repair of urinary tract ruptures, removal of ruptured uterus, omentalization of prostatic abscesses and cysts) and serosal patching of sutured sites.
      1. Serosal patching is used to decrease the incidence of dehiscence that is associated with peritonitis (Kirby, 2003).
      2. Use of suture materials that do not degrade quickly is also recommended.
   B. Obtain samples for culture and histopathology.

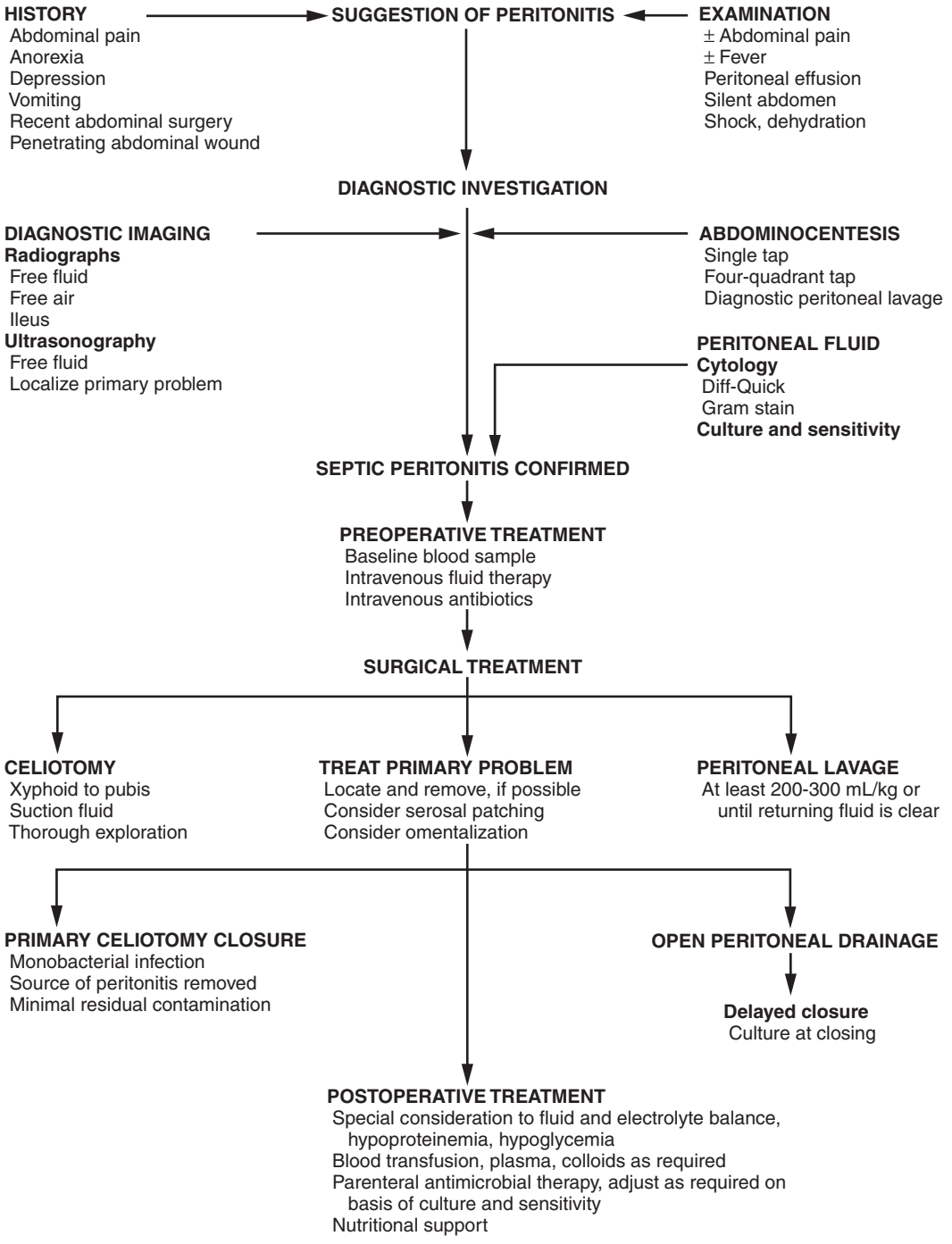

FIGURE 38-1 Algorithm for investigation and treatment of septic peritonitis. *Modified from Kirby BM. Peritoneum and peritoneal cavity. p. 414. In Slatter D (ed): Textbook of Small Animal Surgery. 3rd Ed. WB Saunders, Philadelphia, 2003, with permission.*

C. For diffuse peritonitis, the abdomen is usually lavaged with warm, sterile saline.
   1. A minimum of 200 to 300 mL is initially infused, and lavage with suction is continued until the abdominal fluid becomes clear.
   2. Addition of antibiotics to the fluid is not recommended because of the risk of chemical peritonitis.

D. After exploration, perform primary abdominal closure or leave the abdomen open for continued drainage.
   1. Closure may be done with or without drainage tubes and suction, and is usually performed for localized peritonitis.
   2. Open-abdominal drainage is often preferred for generalized or severe peritonitis (Kirby, 2003; Fossum, 2002a), although some cases may be managed with closed-suction drains (Mueller et al., 2001).

E. Open drainage involves removal of the falciform fat and partial closure of the abdominal wall (2- to 6-mm

gap, 8 to 10 cm in length) with monofilament nylon suture.
1. Cover the opening with a sterile bandage, changed BID initially.
2. The abdomen is usually closed in 3 to 5 days, once much of the drainage has subsided, and hematological and biochemistry parameters are improving or normal.

F. *Mesocestoides* spp. infections in dogs have been treated with fenbendazole 100 mg PO BID for 4 to 12 weeks, and abdominal drainage and lavage, with variable success (Caruso et al., 2003).
G. Specific therapies for sclerosing, encapsulating peritonitis have not been defined, although antibiotics and corticosteroids have been tried with mixed success.

Monitoring of Animal

I. Postoperatively, intensive monitoring is usually required (Lipowitz et al., 1996).
   A. Vital signs are monitored continuously for evidence of SIRS and sepsis.
   B. Electrolyte abnormalities are common and monitored SID to TID.
   C. Continuous electrocardiography is used to monitor for arrhythmias.
   D. Acid-base status and serum protein levels are monitored SID, as needed.
II. Postoperative treatment includes continued IV fluid therapy, plasma transfusions for hypoproteinemia, and blood transfusions for blood loss or anemia (see Chapter 71).
   A. Continue parenteral antibiotics until the animal is stable, then convert to oral forms.
   B. Change abdominal bandages using aseptic technique until the abdomen can be closed, taking special care to avoid contamination of the bandage with urine.
   C. Analgesia with oxymorphone, fentanyl, morphine, or butorphanol is recommended postoperatively (see Chapter 39).
   D. Consider low-dose heparin for animals with DIC (see Treatment under Peritonitis).
   E. Maintaining normal body temperature and providing adequate padding and nursing care are important in recumbent animals.
III. Prognosis is variable, depending on the severity and origin of the peritonitis.
   A. Mortality for animals with severe, generalized peritonitis that requires open abdominal drainage is 20% to 48% (Fossum, 2002a).
   B. Bile peritonitis is associated with an overall survival rate of 50%, but the prognosis for sterile bile peritonitis is much better (approaches 100%) than for septic bile peritonitis (27%) (Ludwig et al., 1997).
   C. Postoperative sepsis (complicated by hypoalbuminemia, hypo- or hyperglycemia), respiratory complications, or DIC are associated with higher mortality.
   D. Sclerosing, encapsulating peritonitis has a poor prognosis.

Hemoabdomen

Definition and Causes

I. Hemoabdomen or hemoperitoneum is free, nonclotting blood within the abdominal cavity.
II. Causes include ruptured neoplasia, trauma (blunt or penetrating), liver lobe torsion, splenic torsion, coagulopathies, and iatrogenic injury to abdominal organs (Figure 38-2).

Pathophysiology

I. Trauma to the abdomen is common following automobile injuries, with the spleen, liver, and kidneys being the most common sources of intraabdominal bleeding.
II. Hemangiosarcomas of the spleen and liver are the most common tumors associated with hemoabdomen.
III. Rapid loss of blood into the abdominal cavity causes circulatory compromise similar to external blood loss, with decreased blood pressure, tachycardia, pallor, weakness, and collapse (see Shock in Chapter 132).
IV. At least 40 mL/kg of blood must be present in the abdomen before abdominal distension can be detected (Vinayak and Krahwinkel, 2004).

Clinical Signs and Diagnosis

I. Signalment and history may be suggestive of hemoabdomen and its cause.
   A. Young, male, mixed-breed dogs are the most likely victims of abdominal trauma.
   B. Bleeding neoplasms occur most commonly in older, large-breed dogs.
   C. Recent abdominal surgery, ultrasound-guided or blind biopsies, or abdominocentesis may indicate iatrogenic injury.
   D. Hemoabdomen following minor trauma is suspicious of a coagulopathy.
II. Onset of signs is often acute and dramatic, but signs may be delayed for up to 3 hours after trauma (Vinayak and Krahwinkel, 2004) or originally be intermittent (e.g., recurrent mild bleeding from hemangiosarcomas).
III. Physical examination may reveal the following:
   A. Evidence of circulatory shock: pallor, weak and thready pulses, tachycardia, weakness, collapse
   B. Evidence of abdominal trauma: cutaneous bruising, lacerations, inability to walk from concurrent musculoskeletal injuries, hematuria
   C. Evidence of clotting problems: petechiae and/or ecchymoses elsewhere on the body, hematuria, pallor
   D. Abdominal distension, tenderness, and/or presence of a fluid wave with ballottement
   E. Palpable abdominal mass, especially in the spleen or liver
IV. Diagnostic imaging involves abdominal radiography and ultrasonography, and thoracic radiography.
   A. Abdominal radiography usually shows free fluid in the abdomen and loss of abdominal detail.
   B. Evidence of masses, abnormal organ contours, or peritonitis may also be detected.

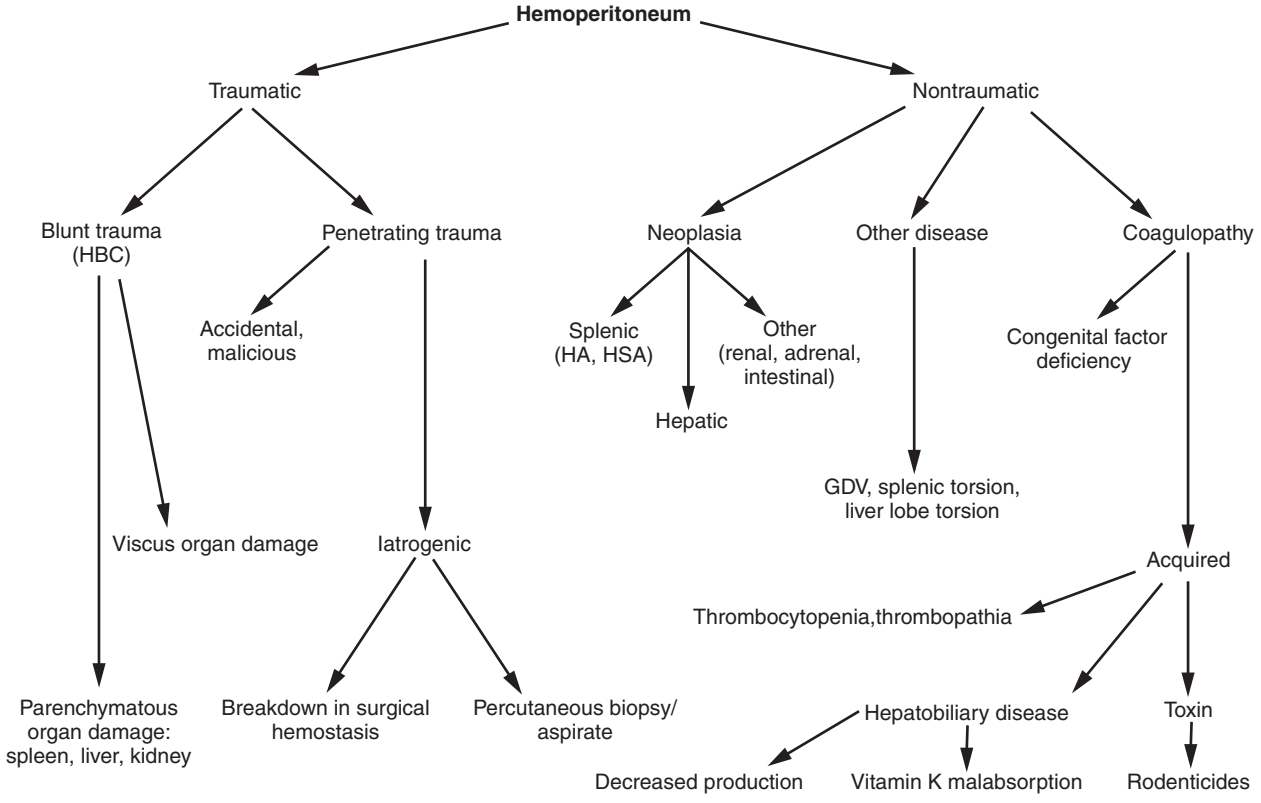

FIGURE 38-2 Causes of hemoabdomen. *HBC,* Hit by car; *HA*, hematoma; *HAS*, hemangiosarcoma; *GDV*, gastric dilatation-volvulus. *Modified from Brockman DJ, Mongil CM, Aronson LR et al: A practical approach to hemoperitoneum in the dog and cat. Vet Clin North Am Small Anim Pract 30:657, 2000, with permission.*

C. Ultrasonography is performed after the animal is stabilized to help identify the source of bleeding, any abdominal masses, sites of potential trauma, and torsion of the liver or spleen, as well as to guide paracentesis.
D. Thoracic radiographs are done to search for metastasis with suspected neoplasia and to rule out pulmonary trauma in cases of abdominal trauma.

V. Hemoabdomen is confirmed with abdominocentesis (50% to 62% accuracy) or diagnostic peritoneal lavage (~100% accuracy) (Mongil et al., 1995; Kirby, 2003).
A. Blood that has been present in the abdomen for >45 minutes and does not contain platelets will not clot (Crowe, 1980).
B. If the sample clots, then iatrogenic aspiration of the liver or spleen is likely.
C. The packed cell volume (PCV) and total solids (TS) of the fluid are measured and compared to peripheral blood.
1. PCV and TS >peripheral blood may occur with splenic aspiration.
2. PCV >2% to 5% in peritoneal lavage fluid indicates hemorrhage (Dye, 2003).
D. Cytology, biochemical assays, and cultures may also be performed on the fluid, especially if peritonitis is suspected.
1. Neoplastic cells are rarely seen and are a poor prognostic sign.
2. Red blood cells (RBCs) are the predominant cell with hemoabdomen.

VI. A complete blood count (CBC), biochemistry profile, and coagulation studies are indicated to help identify the underlying cause and evaluate the status of the animal before surgery.
A. Anemia (initially unresponsive) and hypoproteinemia are common if bleeding has been prolonged or profound.
B. The presence of nucleated RBCs in the CBC is suggestive of hemangiosarcoma.
C. Thrombocytopenia and other coagulation abnormalities may indicate primary bleeding problems or secondary changes (e.g., DIC).
D. Elevated liver enzymes may occur with hepatic contusion, torsion, or neoplasia.

VII. Cross-matching, blood typing, or both are indicated if transfusion therapy is anticipated.

Differential Diagnosis

I. Chronic or recurrent ascites
II. Hemorrhagic effusion associated with peritonitis

Treatment

I. Direct initial measures at stabilization of the animal, including rapid IV fluid therapy with crystalloids and/or colloids, oxygen supplementation, etc. (see Chapter 132).
II. Autotransfusion may be done in animals with traumatic hemoabdomen (Crowe, 1980) and transfusion of whole

blood may be considered in all cases with serious bleeding (see Chapter 71).

III. Replacement of clotting factors with cryoprecipitate, administration of platelet-rich plasma, and institution of vitamin K therapy may be indicated for certain coagulopathies (see Chapters 67 and 68).

IV. Once the animal is stable, further diagnostic tests are performed to better differentiate whether the source of the bleeding is neoplastic or nonneoplastic, and to stage (e.g., thoracic radiographs, abdominal ultrasonography, echocardiography with hemangiosarcomas) the animal with obvious neoplasia.

V. Mild cases of abdominal bleeding associated with trauma (blunt or iatrogenic) or bleeding from coagulopathies often subside with only medical therapy and strict rest.

VI. Exploratory laparotomy is indicated for suspected or confirmed neoplasia, persistent or uncontrolled bleeding (unassociated with coagulopathy), torsion of the spleen or liver, hemorrhage associated with rupture of the urinary tract or hollow organs, penetrating trauma, and if all other tests fail to reach a diagnosis.
   A. It is preferable to delay surgery until the animal is hemodynamically stable.
   B. Upon entering the abdomen, manually control hemorrhage and evacuate blood to allow thorough examination of the entire abdomen.
   C. Perform corrective surgical procedures and thoroughly lavage the abdomen before closure (see Peritonitis).

Monitoring of the Animal

I. Postoperative monitoring is similar to that for peritonitis.

II. Prognosis is variable, depending upon the underlying cause.
   A. Prognosis associated with nonneoplastic diseases is generally good.
   B. Most cases of mild external or iatrogenic trauma are self-limiting and cause no long-term consequences.
   C. Many (57%) cases of serious, traumatic hemoabdomen survive, and response improves (67% to 75%) with aggressive medical and/or surgical therapy (Mongil et al., 1995).
   D. Splenectomy and liver lobectomy are usually curative for torsions of the spleen and liver.
   E. Coagulopathies can vary in their severity and response to treatment (see Chapters 67 and 68).
   F. Hemangiosarcoma that has metastasized to the thorax, cardiac tissues, or multiple abdominal organs may warrant immediate euthanasia without further therapy.
   G. Hemangiosarcoma that has not metastasized at the time of surgery may be followed by chemotherapy in an attempt to prolong survival.

NEOPLASIA

Definition and Causes

I. The most common, primary neoplasm of the peritoneum is malignant mesothelioma, which can arise from the mesothelial cells of all coelomic cavities.

II. Secondary tumors often originate in adjacent abdominal organs and invade or metastasize to the peritoneum.

III. Examples of secondary tumors include hemangiosarcoma, visceral mast cell tumor, carcinomatosis of the omentum, and adenocarcinomas of the intestines and urogenital tract (Bertazzolo et al., 2003; de Souza et al., 2001).

IV. The following discussion pertains primarily to mesotheliomas (See Hemoabdomen for information on abdominal hemangiosarcomas).

Pathophysiology

I. Exposure to asbestos has been incriminated in the development of mesotheliomas in both people and dogs (Harbison and Godleski, 1983).

II. Mesothelioma is very rare in the cat and no predisposing factors have been identified.

III. Three histological types exist in cats and dogs: epithelioid, sarcomatoid, and biphasic (contains both epithelioid and sarcomatoid cells).

IV. A deciduoid form, which cytologically resembles endometrium of pregnancy, has been reported in one dog (Morini et al., 2006).

Clinical Signs

I. Most affected animals are middle-aged to older, but mesothelioma has been reported in dogs as young as 3 years (Geninet et al., 2003).

II. Weight loss, anorexia, lethargy, and abdominal distension are common signs, because most mesotheliomas cause peritoneal effusion.

III. Respiratory distress may be noted from abdominal effusion pressing on the diaphragm.

Diagnosis

I. Diagnostic work-up is similar to that described for peritonitis (see Figure 38-1).

II. Fluid retrieved by paracentesis may reveal malignant cells, but cells from mesotheliomas are difficult to differentiate from reactive mesothelial cells, which are common in many types of effusions.

III. Histopathology and immunohistochemistry are usually required to make a definitive diagnosis of mesothelioma and to determine the type (Geninet et al., 2003; Bacci et al., 2006; Morini et al., 2006).

Differential Diagnosis

I. Other causes of peritoneal effusion: see Peritonitis and Hemoabdomen

II. Causes of ascites and chylous effusions

Treatment and Monitoring

I. Because of its wide dissemination within the abdomen, surgical excision is usually impossible, but exploratory laparotomy may be needed to confirm the diagnosis.

II. The efficacy of chemotherapy for mesothelioma has not been well studied because of the relative rarity of the tumor.

III. Even with repeated abdominal drainage, most dogs are dead within 2 months, although one dog with a cystic form of the disease survived 3 years (DiPinto et al., 1995).

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CHAPTER 39

Acute Abdomen Syndrome

Daniel Z. Hume

Definition and Causes

I. Acute abdomen syndrome is the acute onset of abdominal pain.
II. Pain may arise from sites within or outside of the abdominal cavity.
III. General categories or types of acute abdomen syndrome include the following:
  A. Inflammatory
  B. Mechanical
  C. Neoplastic
  D. Vascular
  E. Associated with congenital defects
  F. Traumatic

Pathophysiology

I. Nociceptive pain is transient pain in response to a noxious stimulus.
II. A primary afferent nociceptor is a sensory neuron capable of reception and transmission of a stimulus following tissue damage.
  A. The peripheral terminals of the primary afferent neuron are located within the mesentery, within or on peritoneal surfaces, and within the mucosa and muscularis of hollow organs.
  B. Nociceptors have unmyelinated (C fibers) or thinly myelinated (Aδ fibers) axon fibers, and respond to various stimuli.
    1. Mechanical: stretch, distension, torsion, contraction
    2. Chemical: hydrogen ions, substance P, serotonin, prostaglandins, lipid metabolites, bradykinins
    3. Heat, cold
III. Three types of abdominal pain exist.
  A. Visceral pain
    1. Typically caused by mechanical stimulation of abdominal organs
    2. Transmitted by slow conducting C fibers
    3. Often described as a dull, achy, poor-localized pain
  B. Parietal pain
    1. Typically caused by inflammatory mediators and byproducts interacting with nociceptors within the parietal surface of the abdomen
    2. Transmitted by rapidly conducting Aδ fibers
    3. Often described as sharp, well-localized, shooting pain
  C. Referred pain
    1. Afferent signals from an extraabdominal region that enter the spinal cord at or near the same location as a visceral afferent neuron arising from an intra-abdominal region
    2. Shared nociceptive segment within a central pathway

Clinical Signs

I. Significant medical or historical information
  A. Previous medical problems
  B. Previous surgical procedures
  C. Last known estrus or breeding
  D. Access to toxins or garbage
  E. History of known foreign material ingestion
  F. Administration of prescribed, over-the-counter, or homeopathic medications
  G. Previous, similar episodes
II. Clinical signs
  A. Vomiting, diarrhea
  B. Abdominal pain, "prayer" position
  C. Anorexia, inappetence
  D. Lethargy, depression
  E. Vulvar or preputial discharge
  F. Abdominal distention
  G. Fever

Diagnosis

I. Physical examination
  A. Findings consistent with poor perfusion include increased capillary refill time, pale mucous membranes, weak to absent peripheral pulses, increased heart rate, decreased rectal temperature, and cool extremities.
  B. Findings consistent with dehydration include increased skin turgor, tacky mucous membranes, and recessed globes.
  C. The abdomen is palpated and evaluated for the following:
    1. Presence of abdominal pain
    2. Organomegaly, mass lesions
    3. Increased intestinal wall thickness, foreign bodies, intussusceptions, etc.
    4. Urogenital abnormalities
      a. Renal size, shape, architecture, presence of pain

b. Bladder size, compressibility, uroliths, presence of pain
5. Palpable fluid wave
6. External bruising, penetrating wounds, ulcerative lesions, petechiae, ecchymoses

D. Neurological status is accessed.
1. Mentation, level of alertness
2. Cranial nerve function
3. Movement, gait, postural reflexes, postural reactions

E. Assessment of respiration involves auscultation, with evaluation of respiratory rate, rhythm, effort, and synchrony.

F. Assessment of cardiovascular system includes the following:
1. Cardiac auscultation
2. Pulse quality and strength
3. Capillary refill time
4. Jugular pulse

G. Evaluate the vulva or penis and prepuce for discharge, bleeding, petechiae, etc.

H. Rectal examination is important.
1. Digital palpation for fractures or step defects of the pelvis
2. Digital palpation for prostate abnormalities
3. Fecal examination for digested or frank blood pigments, foreign material, mucous, etc.

II. Laboratory data

A. Initial tests
1. Packed cell volume (PCV) and total solids (TS)
a. Increased PCV and TS: hemoconcentration
b. Decreased PCV and normal to increased TS: hemolysis, decreased red blood cell production
c. Normal to increased PCV, decreased TS: decreased protein production or loss
d. Decreased PCV and TS: blood loss
2. Blood smear
a. Red blood cell morphology
b. Platelet estimate: 1 platelet per high power field (100 ×) = 10,000 to 15,000 platelets/μL
c. White blood cell (WBC) morphology and estimate
(1) Mean WBC in 10 fields (40 ×) × 1500 = leukocytes/μL
(2) Differential count
(3) Toxic or degenerative leukocyte changes
3. Serum color: icterus, hemolysis, lipemia
4. Urine: urine specific gravity, sediment examination
5. Electrolytes or venous blood gas analysis

B. Comprehensive database
1. Complete blood count
2. Serum chemistry
3. Urinalysis
4. Coagulation panel
5. Serum lactate
a. Indication of anaerobic metabolism
b. May be a measure of tissue perfusion

III. Survey abdominal radiography

A. Decreased abdominal serosal detail may be noted with abdominal effusion or peritonitis.

B. Moderate to severe enlargement of small intestines with gas or fluid may be seen with small intestinal mechanical obstruction.
1. In dogs, normal bowel diameter does not exceed the height of the central part of the body of a lumber vertebra and is not larger than twice the width of a rib.
2. In cats, diameter of the bowel is ≤12 mm.

C. A soft-tissue tubular structure may be seen in animals with intussusceptions, pyometra, and uterine enlargement.

D. Intestinal plication and teardrop-shaped luminal gas bubbles may be seen with a linear foreign body.

E. Compartmentalization of the stomach and pyloric displacement occur with a gastric dilation-volvulus (right lateral projection).

F. Animals with pancreatitis may have increased opacity, granularity, and decreased detail in the right cranial quadrant, along with an increase in the gastroduodenal angle.

G. Loss of distinct diaphragmatic borders or presence intrathoracic abdominal viscera may be seen with a diaphragmatic hernia.

H. Loss of retroperitoneal detail and increased size of retroperitoneal space may be seen with renal or ureteral urine leakage or hemorrhage.

I. The urinary bladder may be visualized when ruptured, and concomitant pelvic fractures may be seen.

J. Prostatic disease resulting in prostatic enlargement may cause cranial displacement of the bladder and increased soft-tissue density in the caudal abdomen.

K. Splenomegaly, displacement of adjacent abdominal organs, abnormal splenic location or shape, loss of abdominal detail, and intrasplenic gas may detected with a splenic torsion.

L. Increased renal size may occur with pyelonephritis, acute renal failure, neoplasia, feline infectious peritonitis, subcapsular cysts, compensatory hypertrophy, or ureteral obstruction with hydronephrosis.
1. In dogs, a normal kidney is approximately 2.5 to 3.5 times the length of the second lumbar (L2) vertebral body.
2. In cats, a normal kidney is approximately 1.9 to 2.4 times the length of the L2 vertebral body.

IV. Contrast radiography

A. Indications for upper gastrointestinal (GI) study (see Chapter 4)
1. Survey radiographs not definitive
2. A partial intestinal obstruction suspected
3. To evaluate GI transit time
4. Abdominal ultrasonography not definitive or available

B. Pneumocolonography
1. It may be used to discriminate between normal gas or feces-filled large intestine and a small intestine dilated with gas.
2. Survey radiographs are taken immediately before the procedure.

C. Peritoneography
1. It may be used in the diagnosis of a diaphragmatic or body wall hernia.
2. Barium is never used for this study.
3. Take survey radiographs immediately before the procedure.
4. Clip and aseptically prepare the abdomen, then insert a needle or over-the-needle catheter into the peritoneal cavity near the umbilicus.
5. Slowly inject an iodinated contrast agent (1.1 mL/kg or 2.2 mL/kg if ascites present) into the peritoneal cavity.
6. Elevate the pelvic area for 5 minutes to increase distribution to the cranial abdomen.
7. Orthogonal-view radiographs are obtained, focusing over the area of interest.

V. Abdominal ultrasonography
A. A complete or partial abdominal ultrasound may be used to evaluate the architecture and size of the abdominal viscera, identify and procure samples of abdominal effusate, and aid in the diagnosis of many abdominal diseases.
B. Focused assessment with sonography for trauma (FAST screening) involves the following (Boysen et al., 2004):
1. Uses standardized technique to assess free abdominal fluid
2. Involves transverse and longitudinal views of four abdominal quadrants (cranial abdomen, caudal abdomen, dependent flank, and nondependent flank)

VI. Simple abdominal paracentesis
A. Indicated in any animal with an abdominal effusion of unknown etiology
B. May be contraindicated with a suspected bleeding problem
C. Successful procedure: >5 mL/kg retrieved using a single-hole needle or catheter
D. Increased yield with ultrasound guidance
E. Procedure
1. Place animal in lateral recumbency; clip and aseptically prepare area.
2. Use a 20- to 22-gauge needle or catheter.
3. Gently insert the needle or catheter near the umbilicus.
4. Allow fluid to drip into sample tubes or evacuate via gentle aspiration.
5. Increase yield with side-hole or a peritoneal dialysis.

VII. Four-quadrant paracentesis
A. Four quadrants are sampled, as described previously, for simple abdominocentesis.
B. Samples are taken from an imaginary square centered over the umbilicus, with the corners of the square being approximately 4 to 6 cm from the umbilicus.
1. Right cranial and caudal quadrants
2. Left cranial and caudal quadrants

VIII. Diagnostic peritoneal lavage
A. Indications
1. Indicated in animals with suspected abdominal disease in which simple abdominal or four-quadrant paracentesis has been unsuccessful
2. More sensitive than paracentesis
B. Procedure
1. Local and systemic analgesia are indicated.
2. Clip and aseptically prepare an area approximately 10×10 cm that is centered around the umbilicus.
3. Place animal in lateral recumbency.
4. Gently insert an 18- to 22-gauge IV or peritoneal dialysis catheter into the abdominal cavity near the umbilicus and direct the catheter caudally.
5. If no fluid is detected after removal of the stylet, infuse sterile, warmed crystalloid fluid (20 to 22 mL/kg) over approximately 5 minutes and remove the catheter.
6. Roll the animal from side to side and massage the abdomen to help distribute the fluids.
7. Repeat a simple or four-quadrant paracentesis.

IX Abdominal fluid analysis
A. Assess PCV, total protein (TP), and total nucleated cell count (TNCC).
1. Transudate: TNCC <1500 cells/μL, TP < 2.5 g/dL
2. Modified transudate: TNCC 1000 to 7000 cells/μL, TP 2.5 to 5.5 g/dL
3. Exudate: TNCC >5000 cells/μL, TP > 3.0 g/dL
B. Cytological evaluation involves a subjective description of the fluid.
1. Determination of the type of inflammatory infiltrate
2. Presence and degree of nuclear degeneration, microorganisms, plant or food material, or bile
3. Evidence of malignancy.
C. Perform aerobic and anaerobic bacterial culture.
D. Supportive evidence of a septic effusion includes the following:
1. Glucose levels < 50 mg/dL
2. Blood-to-peritoneal glucose difference >20 mg/dL
3. Peritoneal-to-blood lactate difference >2 mmol/L
4. Effusion lactate levels >2.5mmol/L
5. Effusion pH <7.2
E. Changes supportive of uroabdomen include the following:
1. Abdominal fluid creatinine >2 times serum creatinine
2. In dogs: potassium in the fluid >1.4 times serum potassium
3. In cats: potassium in the fluid >1.9 times serum potassium
F. Bilirubin is also assessed.
1. Fluid bilirubin concentration >2.0 times serum bilirubin is supportive of bile peritonitis.
2. Bile pigment may also be seen on cytological evaluation.

Differential Diagnosis

I. Hepatobiliary system lesions
A. Acute hepatitis

B. Liver lobe torsion
C. Gall bladder rupture
D. Biliary mucocele
E. Extrahepatic bile duct obstruction
F. Cholecystitis
G. Hepatic abscess
H. Neoplasia
I. Cholangiohepatitis
J. Cholelithiasis

II. GI disorders
A. GI erosion and/or ulceration
B. Mechanical obstruction or intussusception
C. Neoplasia
D. Mesenteric volvulus or torsion
E. Gastric dilation, with or without volvulus
F. Mesenteric infarction
G. Severe gastritis, enteritis, and/or colitis
H. Gastroesophageal intussusception

III. Pancreatic lesions
A. Pancreatitis
B. Pancreatic abscess
C. Neoplasia
D. Necrosis

IV. Reproductive tract disorders
A. Pyometra, metritis, uterine torsion
B. Prostatic infection, abscess, neoplasia, cyst
C. Testicular infection, torsion, abscess, neoplasia
D. Dystocia

V. Urinary tract diseases
A. Pyelonephritis, nephroliths, infarction, swelling, acute nephritis, renal failure
B. Ureteral obstruction, avulsion
C. Urinary bladder infection, inflammation, rupture, cystoliths
D. Urethral obstruction
E. Neoplasia

VI. Peritoneal cavity disorders
A. Peritonitis
1. Septic or bile peritonitis
2. Pneumoperitoneum, uroperitoneum, hemoperitoneum
B. Steatitis
C. Hernias: abdominal wall, inguinal hernia, umbilical hernia, diaphragmatic hernia
D. Myositis of abdominal musculature

VII. Spleen: splenic torsion, neoplasia, splenitis

VIII. Other causes of periabdominal pain
A. Intervertebral disk disease
B. Diskospondylitis
C. Fractures, luxations, subluxations

Treatment

I. Every attempt is made to aggressively enhance and maintain peripheral tissue perfusion in animals with poor perfusion.

II. Results of thorough physical examination, minimum laboratory tests, and blood pressure measurements are considered before initiation of fluid therapy.

III. Fluids therapy involves the following:
A. Crystalloid fluid therapy: see Chapter 132
B. Hypertonic (7%) saline: 4 to 5 mL/kg IV over 10 to 15 minutes
C. Colloid fluid therapy: see Chapter 132
D. Plasma and blood product therapy: see Chapter 71

IV. Careful attention is paid to making the animal as comfortable as possible during hospitalization or until definitive therapy can be attempted.
A. Opioids are preferred, with the following being typical dosages in dogs:
1. Morphine 0.5 to 1.0 mg/kg IM, IV every 4 to 6 hours
2. Fentanyl 3 to 10 μg/kg IV initial bolus, followed by a constant rate infusion (CRI) of 0.5 to 1.0 μg/kg/min IV
3. Hydromorphone: 0.1 to 0.2 mg/kg IM, IV every 4 to 6 hours
4. Buprenorphine: 6 to 15 μg/kg SC, IM, IV TID to QID
5. Butorphanol: 0.1 to 0.5 mg/kg SC, IM, IV every 4 to 6 hours or as a CRI of 0.1 to 0.4 mg/kg/hr IV
B. Nonsteroidal anti inflammatory drugs (NSAIDs) are avoided until a definitive diagnosis is established and the animal is stabilized.

V. A significant number of the cases of acute abdomen require exploratory laparotomy for definitive diagnosis and treatment, and surgical indications include the following:
A. Lack of positive response to appropriate medical therapy
B. Intracellular bacteria visualized on cytology of the peritoneal effusion
C. Free peritoneal gas or penetrating wound(s)
D. Intestinal obstruction
E. Evidence of pyometra
F. Hemoabdomen
G. Suspected abscessation of an abdominal organ
H. Torsion, volvulus, rupture of an abdominal organ
I. Procurement of a biopsy
J. Evidence of intraabdominal leakage or urine, bile, GI contents

VI. Adjunctive medical therapy is usually required.
A. Antiemetics (dosages for dogs)
1. Metoclopramide 0.2 to 0.4 mg/kg IM, IV, PO, SC TID to QID or CRI of 1 to 2 mg/kg/day IV
2. Dolasetron 0.5 to 1.0 mg/kg IV SID
3. Ondansetron 0.1 to 0.2 mg/kg IV, PO BID to QID
4. Prochlorperazine 0.1 to 0.5 mg/kg IM, SC TID to QID; may cause hypotension
5. Chlorpromazine 0.1 to 0.5 mg/kg IM, SC TID; may cause hypotension
B. Gastrointestinal protectants (dosages for dogs)
1. Famotidine 0.5 mg/kg IV SID to BID
2. Ranitidine
a. May not be effective at acid suppression in the dog (Bersenas et al., 2005)
b. Dose: 0.5 to 2.0 mg/kg PO, IV BID to TID
3. Cimetidine 5 to 10 mg/kg IV, PO TID to QID

TABLE 39-1

Antimicrobials Useful for Acute Abdominal Syndrome

ANTIMICROBIAL	DOSE IN DOGS	DOSE IN CATS
Ampicillin sodium	22 mg/kg IV TID	22 mg/kg IV TID
Enrofloxacin	5-20 mg/kg IV SID	5 mg/kg IV SID
Amikacin sulfate	15 mg/kg IV SID	15 mg/kg IV SID
Metronidazole	10-15 mg/kg IV BID	10-15 mg/kg IV BID
Clindamycin	10 mg/kg IV TID	10 mg/kg IV TID
Ticarcillin/ clavulanate	50 mg/kg IV QID	50 mg/kg IV QID
Cefoxitin sodium	15-30 mg/kg IV QID	15-30 mg/kg IV QID

4. Omeprazole 1 mg/kg PO SID to BID
5. Esomeprazole 0.5 to 1 mg/kg PO SID to BID
6. Pantoprazole: 1 mg/kg PO SID to BID
7. Sucralfate: 250 mg/15kg PO TID to QID
8. Misoprostol: 2 to 5 μg/kg PO TID to QID

C. Antimicrobial therapy (Table 39-1)
1. Broad-spectrum antimicrobials are considered in all animals with septic foci (identified or suspected).
2. Critically ill animals may be at increased risk for bacterial translocation and secondary sepsis.
3. Ideally, appropriate samples for aerobic and anaerobic cultures are procured before the commencement of therapy.

D. Glycemic control
1. Blood or serum glucose is monitored frequently.
2. Ideal range is 80 to 140 mg/dL.
3. For blood glucose concentrations <80 mg/dL, consider a CRI of dextrose 2.5% to 5.0% in isotonic fluids.
4. If blood glucose is <50 mg/dL, consider a bolus of dextrose 0.25 to 0.5 g/kg IV, diluted to a 10% solution if given via a peripheral catheter.
5. If blood glucose is persistently >250 mg/dL, consider regular insulin 0.1 U/kg IM.

VII. Early implementation of nutrition may improve outcome (see Chapter 122).

Monitoring of Animal

I. Animals with an acute abdomen are often critically ill and very dynamic.
II. Diligent and frequent monitoring is paramount.
III. Monitoring parameters include the following:
A. Vital parameters (temperature, heart rate, pulse quality, respiratory rate and effort, capillary refill time) every 2 to 4 hours
B. Systemic blood pressure every 2 to 4 hours
C. Blood glucose every 2 to 6 hours
D. Pulse oximetry every 4 to 6 hours
E. Mentation every 4 to 6 hours
F. Pain scoring (see Chapter 1) every 4 to 6 hours
G. PCV/TS and electrolytes every 4 to 6 hours

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CHAPTER 40

Introduction

Rita H. Miller

GENERAL CONSIDERATIONS

I. Hormones are chemical messengers that are secreted from endocrine glands and interact with specific receptors of target cells to regulate cellular activity in the body.
   A. Hormones are transported in blood as free hormone or bound to specific carrier proteins.
   B. The free hormone is the biologically active form.

II. Hormones can be classified according to their biochemical structure.
   A. Peptides
   B. Steroids
   C. Amines
   D. Fatty acids

III. Hormones interact with specific receptors located on a membrane surface or within the nucleus of a cell.
   A. The hormone-receptor interaction leads to activation of second messengers, such as cyclic adenosine monophosphate (AMP) and cyclic guanosine monophosphate (GMP), which subsequently initiate cellular events.
   B. The message transmitted by the hormone generates a specific biological response.

IV. Hormone production is regulated by homeostatic mechanisms to maintain concentrations within a narrow range according to a physiological "set-point."
   A. Most hormones are secreted continuously throughout the day.
      1. Basal secretion is minimal in the absence of stimulatory signals.
      2. Concentrations of some hormones fluctuate in a rhythmic fashion throughout the day.
   B. Hormone production is influenced by biological needs.
   C. Feedback loops exist that sense the circulating concentration of a hormone, and subsequently down-regulate or up-regulate hormone production.
      1. Feedback control of hormonal secretion is determined by the concentration of free hormone.
      2. Feedback loops may involve the central nervous system and hypothalamus via electrical and chemical signals.
      3. A direct feedback may exist whereby the response generated by the hormone directly affects the gland of origin.
   D. Feedback loops are dysfunctional in endocrine diseases, leading to loss of regulation of hormone production.

V. Hormones are rapidly inactivated to prevent a continuous cellular response.
   A. Hormone degradation takes place in target tissues or nontarget tissues, such as the liver and kidney.
   B. Hormones may be degraded into metabolically active or inactive metabolites.
   C. Some hormones are excreted unchanged into the urine or bile.

VI. Secretory tissues and their associated endocrine hormones are as follows:
   A. Hypothalamus
      1. Corticotropin-releasing hormone
      2. Thyrotropin-releasing hormone
      3. Growth hormone-releasing hormone
      4. Somatostatin
      5. Antidiuretic hormone
   B. Pituitary gland
      1. Thyroid-stimulating hormone
      2. Adrenocorticotropic hormone
      3. Growth hormone
   C. Thyroid gland
      1. Thyroxine
      2. Triiodothyronine
      3. Calcitonin
   D. Adrenal gland
      1. Cortisol
      2. Aldosterone
      3. Epinephrine
      4. Norepinephrine

E. Pancreas
   1. Insulin
   2. Glucagon
   3. Somatostatin
F. Parathyroid gland: parathyroid hormone
G. Skin, liver: vitamin D_3
H. Kidney
   1. Vitamin D_3
   2. Erythropoietin
I. Heart: atrial natriuretic factor

DISORDERS OF THE ENDOCRINE GLANDS

I. Primary injury to an endocrine gland leads to a decrease in function.
   A. Immune-mediated disease
   B. Neoplasia
   C. Surgical manipulation
   D. Drug-induced damage
II. Secondary or tertiary disease causes inappropriate stimulation of the gland.
III. Excessive hormone production results from several mechanisms.
   A. Primary hypersecretion of the hormone can develop in a diseased endocrine gland.
      1. Hyperplasia of endocrine gland
      2. Neoplasia of endocrine gland
   B. Hyperstimulation of the endocrine gland may result from secondary or tertiary disease.
   C. Ectopic hormone production can result from tumors of nonendocrine glands.
   D. Iatrogenic disease arises from drug administration, leading to excessive systemic hormone concentrations.
IV. A hormone defect may be present, which is often of genetic origin.
V. Hormone resistance can develop when the sensitivity of the target tissue to the hormone is reduced.
   A. Antibody production against a hormone or hormone receptor
   B. Defect in hormone receptor or postreceptor mechanisms
VI. Abnormal hormone transport is possible.
   A. Decrease in plasma concentration of carrier protein
   B. Competition for carrier proteins by certain medications

DIAGNOSTIC APPROACH TO ENDOCRINE DISEASES

I. Breed predilection is present in several endocrine diseases.
II. Sex predilection is noted for most endocrine diseases.
III. Most endocrine diseases develop in middle-aged adult and geriatric patients.
IV. Diagnostic evaluation often provides early clues to the diagnosis.
   A. Collect baseline laboratory data, including a complete blood count, serum biochemistry profile, and urinalysis.
   B. Hormone concentration is measured using radioimmunoassay, enzyme assay, or dialysis techniques.
      1. Total hormone concentration in serum
      2. Free hormone concentration in serum
      3. Total hormone concentration in urine
   C. Dynamic tests measure the response of a hormone to a stimulatory or suppressive agent.
      1. Stimulation test to assess response to a normal stimulatory hormone
      2. Suppression test to diagnose disorders of hypersecretion
   D. Measurement of the primary stimulatory or suppressive hormone in serum is possible for some diseases.
   E. Measurement of antibodies against the hormone supports an immune-mediated pathogenesis in endocrine disease.
   F. Radioisotope studies are used to study physiological and biochemical responses of a gland.
   G. Diagnosis is best made when the signalment, history, clinical signs, and test results are consistent with the disease condition.
V. Dilemmas exist in the diagnosis of endocrine diseases.
   A. A normal or abnormal hormone concentration or dynamic test result does not always rule in or rule out the endocrine disease.
   B. Hormone secretions are often pulsatile in nature, so concentrations vary throughout the day.
   C. Antibodies produced against a particular hormone may interfere with the radioimmunoassay test.
   D. Blood concentrations of some hormones, such as catecholamines, cannot be accurately measured.
   E. Hormone concentrations are affected by multiple factors.
      1. Age of the animal
      2. Overall health of the animal
      3. Sexual cycle
      4. Serum protein concentration, which influences the plasma concentrations of protein-bound hormones
      5. Drug administration, which can alter the affinity of carrier proteins to bind hormone, resulting in changes in total hormone concentration
      6. Instability of hormone during transport and processing, leading to inaccurate test results

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CHAPTER 41

Diseases of the Pituitary Gland

Kate E. Hill | Clinton D. Lothrop, Jr.

PITUITARY HYPOFUNCTION: PITUITARY DWARFISM

Definition

I. Hypopituitarism is a deficiency of one, several, or all pituitary hormones.
II. In young dogs, the term *hypopituitarism* is used to describe growth hormone (GH) deficiency, with or without loss of other pituitary hormones (pituitary or endocrine dwarfism).

Causes

I. Certain factors contribute to the development of congenital hypopituitarism.
   A. Failure of oropharyngeal ectoderm of Rathke's pouch to differentiate into trophic hormone-secreting cells of the anterior pituitary gland
   B. Progressive formation of enlarging pituitary cysts that exert pressure on adjacent structures
   C. Benign tumor of Rathke's pouch (craniopharyngioma): uncommon
II. Pituitary or endocrine dwarfism is an inherited autosomal recessive disease.
III. Adult-onset hypopituitarism is frequently associated with primary pituitary neoplasia or head trauma.

Pathophysiology

I. Deficiency of pituitary hormones arises.
   A. Growth hormone
   B. Adrenocorticotropic hormone (ACTH)
   C. Luteinizing hormone
   D. Follicle-stimulating hormone
   E. Thyroid-stimulating hormone (TSH)
II. Synthesis and secretion of target organ hormones, including cortisol, thyroid hormone, and/or insulin-like growth factors (IGFs) are decreased.
III. Normal growth requires the presence of IGFs and other factors, as well as the ability of target tissues to respond to them.
   A. IGFs (somatomedins)
      1. Somatomedins have marked growth-promoting effects on bone, cartilage, connective tissue, and skeletal and cardiac muscle.
      2. Their production is GH dependent.
   B. Fibroblast growth factor, nerve growth factor, epidermal growth factor
IV. Normal body maturation and growth also depend on normal concentrations of thyroid hormone.
V. The absence of GH, IGFs, or thyroid hormone results in dwarfism.

Clinical Signs

I. Short stature compared to litter mates
II. Hair coat abnormalities
   A. Retention of puppy hair coat
   B. Gradual bilateral alopecia sparing the head and extremities
III. Progressive hyperpigmentation of skin
IV. Delayed or absent permanent dentition
V. Infantile external genitalia, variable reproductive function
VI. With advancing age
   A. Obesity, weakness, lethargy
   B. Thickening and peeling of skin
VII. Water consumption and urination usually normal
VIII. German shepherd and carnelian bear dogs overrepresented

Diagnosis

I. Presumptive diagnosis of pituitary dwarfism: typical breed, history, and clinical signs
II. Laboratory evaluation
   A. Complete blood count: occasional decreased packed cell volume
   B. Biochemistry profile
      1. Slightly decreased phosphorus, albumin
      2. Possibly increased blood urea nitrogen (BUN)
   C. Urinalysis: to rule out kidney disease
III. Definitive diagnosis: GH stimulation test or measurement of serum IGFs
   A. Insulin response test (Nichols et al., 1997)
      1. In animals with GH deficiency, insulin-induced hypoglycemia is more severe than in normal animals.
      2. Problems with the test include serious hypoglycemia and difficulty in the interpretation of results.
      3. The test is rarely performed.
   B. GH stimulation test with clonidine or xylazine: GH analysis currently unavailable

C. Serum IGF-I (somatomedin C) assay from Michigan State University Animal Health Diagnostic Laboratory, East Lansing, Mich.
1. Indirect measurement of pituitary function
2. Decreased serum concentrations diagnostic of GH deficiency (normal IGF-I = 5 to 45 nmol/L)

IV. Assessment of thyroid and adrenal function (see Chapters 42 and 45)
A. Uncomplicated hypopituitarism: results usually normal
B. Secondary hypothyroidism, hypoadrenocorticism possible
1. Low thyroxine (T_4), free T_4, cortisol concentrations
2. Low resting ACTH, TSH values
3. Poor response to stimulation with TSH or ACTH

Differential Diagnosis

I. Malnutrition-induced short stature
A. Decreased caloric intake
B. Maldigestion and/or malabsorption syndromes
II. Hypothyroidism of thyroid origin
III. Congenital heart disease
IV. Congenital gastrointestinal, liver, or kidney diseases
V. Chondrodystrophic dwarfism
VI. Mucopolysaccharidosis
VII. Hydrocephalus

Treatment

I. Growth hormone replacement
A. Give dogs porcine GH 0.1 IU/kg SC three times per week for 1 to 2 months.
B. Human GH may cause antibody formation.
II. Progesterone therapy
A. Successful in a small number of cases
B. Medroxyprogesterone acetate 2.5 to 5.0 mg/kg PO initially every 3 weeks and then every 6 weeks (Kooistra et al., 1998)
C. Proligestone 10 mg/kg SC every 3 weeks (Knottenbelt and Herrtage, 2002)
III. Thyroid replacement therapy
A. Most pituitary dwarfs have secondary hypothyroidism.
B. Give L-thyroxine 20 µg/kg PO SID for life.
IV. Glucocorticoid replacement therapy
A. Glucocorticoid replacement is not clinically beneficial in cases of pituitary dwarfism, despite low-normal baseline cortisol levels and sluggish responses to ACTH stimulation.
B. In animals with grossly abnormal ACTH response tests, administer prednisone or prednisolone 0.2 to 0.4 mg/kg/day PO.

Monitoring of Animal

I. Most pituitary dwarfs are presented for hair coat abnormalities (alopecia) that improve with replacement therapy.
A. Monitor the animal every 60 to 90 days after initial GH administration for signs of recurrent alopecia.
B. The goal of therapy is to have a plasma IGF-1 concentration within the reference range.
C. If hair coat abnormalities recur, resume GH therapy for an additional 1 to 2 months.
II. Some dogs become refractory to GH replacement therapy.
A. They develop antibodies to GH, thereby diminishing the biological activity of GH.
B. Consider changing to a different species-type of GH.
C. Porcine GH has the same antigenicity as canine GH, so antibody formation is not usually a problem.
III. Instruct owners to monitor urine glucose concentrations on a daily basis, and to measure blood glucose weekly during GH treatment.
A. Stop GH administration if hyperglycemia occurs.
B. Transient and even permanent diabetes mellitus is a potential side effect, especially with older dogs.
IV. Because most pituitary dwarfs receive a diagnosis when their long bone growth plates are near or past closure, a significant increase in stature is not expected.

Acromegaly

Definition

I. Acromegaly is a disease characterized by an overgrowth of connective tissue, increased appositional bone growth, coarsening of facial features, and enlargement of viscera.
II. It arises from excessive secretion of GH.

Causes and Pathophysiology

I. In the dog, acromegaly is primarily associated with administration of progestational agents or with increased endogenous progesterone levels (diestrus).
A. Canine acromegaly: progesterone stimulation of GH production in ductular epithelia cells in the mammary gland (diestrus)
B. Rarely from pituitary neoplasia
II. Feline acromegaly is commonly associated with pituitary neoplasia.
III. GH has both anabolic and catabolic effects.
A. Anabolic effects are mediated by IGFs.
B. GH has antiinsulin effects, so excessive levels may induce diabetes mellitus.

Clinical Signs

I. Prominent skinfolds of face and neck
II. Blunt, broad facial features
III. Enlarged interdental spaces from increased connective tissue growth
IV. Inspiratory stridor from enlargement of orolingual, oropharyngeal, and orolaryngeal tissues
V. Abdominal enlargement
VI. Panting, fatigue
VII. Diabetes mellitus
A. Diabetes is often difficult to control or regulate.
B. Weight gain occurs in an insulin-resistant, diabetic animal.
VIII. Central nervous system (CNS) signs in animals with pituitary tumors

A. Head pressing, dull behavior
B. Inappetence in older dogs and cats

IX. Cats: cardiomyopathy, arthropathy, renal failure

Diagnosis

I. History of progesterone use for estrus or behavioral control in dogs
II. Common laboratory abnormalities
  A. Elevated serum alkaline phosphatase
  B. Increased blood glucose
  C. Persistent hyperphosphatemia without azotemia
  D. Renal failure: late stages of feline acromegaly
III. Radiographic abnormalities
  A. Diffuse increase in soft-tissue structures of the lingual, oropharyngeal, and laryngeal regions
  B. Degenerative arthropathy with periosteal reactions
IV. High circulating somatomedin C: IGF-I >100 nmol/L
  A. Serum IGF-1 concentrations between 70 and 100 nmol/L are considered nondiagnostic and should be repeated in 3 months.
  B. Some insulin-resistant, diabetic cats can have IGF-1 concentrations in the nondiagnostic range.
  C. Cats with acromegaly show an increase in the IGF-1 concentration over this 3-month period.
V. Computed tomography or magnetic resonance imaging of the brain
  A. For suspected pituitary tumor
  B. A consideration for diabetics with high insulin requirements not associated with other diseases
    1. Rule out hyperadrenocorticism and corticosteroid overdose.
    2. Rule out systemic infections.
  C. Often normal in dogs
  D. May identify a pituitary mass in cats
VI. GH suppression test
  A. GH analysis has limited availability in the United States; the University of Florida veterinary endocrinology laboratory can perform the assay.
  B. GH analysis is available at Utrecht University, The Netherlands.

Differential Diagnosis

I. Inspiratory stridor: other causes of upper airway obstruction
  A. Elongated soft palate
  B. Laryngeal paralysis
  C. Foreign body
  D. Neoplasia: thyroid adenocarcinoma, intratracheal ring carcinoma
II. Other causes of insulin-resistant diabetes mellitus
III. Hyperadrenocorticism

Treatment

I. Following exogenous progesterone withdrawal, GH levels dramatically decline, soft-tissue abnormalities reverse, and glucose intolerance improves.
II. Perform ovariohysterectomy to eliminate the estrous cycle.
III. Spontaneous acromegaly in cats associated with neoplasia of the pituitary gland may respond to external-beam cobalt therapy.
IV. Somatostatin therapy has been ineffective.
V. Dogs with acromegaly induced by medroxyprogesterone acetate injections have been successfully treated with aglépristone, a progesterone receptor blocker.

Monitoring of Animal

I. Reversal of soft-tissue abnormalities occurs in about 6 to 8 weeks.
II. GH-induced diabetes mellitus may be permanent or reversible.
  A. Prognostic factors for reversibility of GH-induced diabetes include the following:
    1. High-fasting serum insulin concentrations: pancreatic beta cell reserves present with adequate chance for recovery
    2. Low or undetectable serum insulin concentrations: pancreatic beta cell reserves exhausted, so poor chance for recovery
    3. Dose or duration of progestational agents or progesterone phase of estrous: higher dose and duration decrease reversibility
  B. Carefully monitor blood glucose after progesterone withdrawal, because insulin requirements usually diminish.
III. Prognosis for feline acromegalics is guarded because most develop serious renal, cardiac, and other complications.

Diabetes Insipidus

Definition

I. Central diabetes insipidus (CDI) is a partial or absolute deficiency of antidiuretic hormone (ADH) or vasopressin.
II. Nephrogenic diabetes insipidus (NDI) is a congenital or acquired disease in which the kidneys are unresponsive to ADH.
III. Acquired NDI is the most common form of diabetes insipidus (DI).

Causes

I. Causes of CDI
  A. Congenital defects
  B. Infection, inflammation
  C. Trauma: accidental or surgical
  D. Neoplasia
II. Causes of NDI (Nichols, 2004; Feldman and Nelson, 2004b)
  A. Congenital, end-organ unresponsiveness to ADH: rare
  B. Acquired defects of distal tubules and collecting ducts following infections: pyelonephritis, chronic renal failure, pyometra
  C. Secondary to metabolic disorders: hypokalemia, hypercalcemia, hyperadrenocorticism, pyometra, hyperthyroidism, hypoadrenocorticism
  D. Secondary to drugs: lithium, demeclocycline, methoxyflurane

Pathophysiology

I. ADH is produced by the hypothalamus.
II. Production and release of ADH are controlled by a variety of factors.
  A. Elevations in serum osmolality, primarily sodium
  B. Elevated blood volume or blood pressure
  C. Fear, body temperature
  D. Pharmacologic agents: barbiturates, nicotine, morphine
III. ADH primarily acts on the distal convoluted tubules and collecting ducts of the kidney.
  A. ADH attachment to receptor sites increases permeability of the renal tubular epithelial cells.
  B. Water moves across the epithelial cells from the tubular lumen to the interstitium (gradient present in renal medulla).
  C. The final concentration (urine specific gravity [USG], osmolality) of the urine is dependent on ADH action and the renal medullary concentration gradient.
IV. Absent ADH activity or renal medullary washout results in an extremely dilute urine (USG <1.008).
V. Partial ADH deficiency results in urine with a specific gravity of 1.00 to 1.016.

Clinical Signs

I. Profound polyuria and polydipsia (PU/PD) are present, often with an acute onset.
II. Although the frequency of urination may decrease with time from stretching of the urinary bladder, the volume of urine remains the same.
III. Severe, rapid dehydration may occur in animals with complete DI if water is unavailable for as little as 4 to 6 hours.
IV. Occasionally anorexia, weight loss, and CNS signs occur.

Diagnosis

I. Physical examination: often unremarkable
II. Complete blood count and serum biochemistry profile
  A. Occasional hypernatremia
  B. Important in ruling out other causes of PU/PD
III. Urine specific gravity
  A. It is usually 1.001 to 1.007 in complete DI.
  B. With severe dehydration in partial DI, USG may approach isotonicity or be slightly hypertonic (rare).
IV. Specific testing for diagnosis and definition of DI requires thorough assessment of urine concentrating capacity before and after exposure to exogenous vasopressin.
  A. Modified water deprivation test
  B. Exogenous vasopressin test
  C. Repositol vasopressin test, ADH trial
  D. 1-Deamino-8-D-arginine vasopressin (DDAVP) trial
V. Modified water deprivation test
  A. Cautions
    1. Perform only after ruling out other causes of PU/PD.
    2. Allow gradual water restriction to 100 mL/kg/day for 3 to 4 days before the test to restore the renal medullary interstitial gradient and correct concentration abnormalities from medullary washout.
  B. Test protocol
    1. Obtain baseline data, including body weight, USG, BUN, estimated skin elasticity, and urine and serum osmolality.
    2. Urine osmolarity can be roughly calculated by multiplying the last two digits of the USG by 36 (NOTE: not accurate with severe proteinuria or glycosuria).
    3. Remove all water and food.
    4. Empty the urinary bladder every 60 to 120 minutes either by catheterization or walking the dog; cats require an indwelling urinary catheter.
    5. Monitor USG, urine osmolarity, body weight, hydration, BUN, serum electrolytes, and serum osmolarity every 60 to 120 minutes.
    6. Stop test when any of the following occurs:
      a. USG = 1.025 (900 mOsm/L)
      b. Increased BUN
      c. Loss in body weight >3% to 5%
      d. Dehydration: decreased skin elasticity, significant increases in hematocrit or total solids
  C. Interpretation
    1. USG ≤ 1.008: complete central DI or NDI
    2. USG of 1.010 to 1.020: partial central DI
    3. USG >1.025: psychogenic DI
VI. Response to exogenous vasopressin
  A. Indications
    1. If the water deprivation test suggests nonpsychogenic DI (USG <1.025)
    2. Characterization of the disorder as central or nephrogenic in origin (CDI versus NDI)
    3. As a continuation of the modified water deprivation test
  B. Test protocol
    1. Administer aqueous vasopressin 2 to 5 U IM.
    2. Empty the bladder at 30, 60, and 90 minutes; check urine osmolarity, USG, BUN, serum electrolytes, hydration, and CNS status.
    3. Alternatively, give desmopressin acetate (DDAVP) 4 drops into the conjunctival sac or 10 to 20 μg/kg of the intranasal preparation IV, SC.
      a. Use a bacteriostatic filter if administering IV.
      b. Collect urine samples every 1 to 2 hours for 8 hours and possibly at 12 and 24 hours.
    4. End the test and introduce small amounts of water (10 to 20 mL/kg PO every 30 minutes for 1 to 2 hours).
  C. Interpretation
    1. USG increases <10% (USG <1.015): nephrogenic DI or medullary washout
    2. USG increases 10% to 50%: partial CDI
    3. USG increases 50% to 800%: CDI
VII. Response to desmopressin as a diagnostic trial
  A. Use
    1. Demopressin helps to diagnose CDI when the differential considerations are CDI, NDI, or psychogenic polydipsia.
    2. It can overcome medullary washout within 2 to 4 days.

B. Test protocol
   1. Owner monitors water intake for 2 to 3 days before and throughout the trial.
   2. Owner administers DDAVP nasal spray into conjunctival sac, 4 drops BID for 5 to 7 days.
   3. Owner collects a urine sample for urine osmolarity and USG at the predetermined times each day, with urine samples collected between days 5 and 7.

C. Interpretation
   1. A dramatic reduction in water intake and an increase in USG >50% is consistent with central DI.
   2. Dogs with NDI are not helped by DDAVP.
   3. Dogs with psychogenic polydipsia may have a slight decrease in water intake and urine output; however, some dogs have increased urine output.
   4. Dogs with early hyperadrenocorticism (PU/PD, but no other signs) may have a mild to moderate increase in urine concentration, but DDAVP eventually becomes ineffective as hyperadrenocorticism continues to suppress vasopressin activity.

Differential Diagnosis

I. Most disease processes causing PU/PD are characterized by other systemic signs, which help differentiate them from DI.
II. Rule out other causes of PU/PD.
   A. Diabetes mellitus
   B. Renal disease, pyelonephritis
   C. Liver disease, portosystemic shunt
   D. Pyometra
   E. Hyperadrenocorticism, hypoadrenocorticism
   F. Defect in renal glucose resorption (Fanconi's syndrome)
   G. Hyperviscosity syndrome
   H. Psychogenic polydipsia
   I. Hyperthyroidism (cats)
   J. Hypercalcemia, potassium depletion

Treatment

I. Treatment of CDI involves the use of exogenous ADH.
   A. Repositol vasopressin (pitressin tannate) has been discontinued.
   B. Desmopressin acetate (DDAVP) is commercially available.
      1. Intranasal form: 0.1 mL (2 to 4 drops) in each nostril or conjunctival sac SID to BID, with frequency titrated to control PU/PD
      2. Alternate route of intranasal form: 2 to 5 μg SC
         a. Administered through a bacteriostatic filter (Nichols, 2004).
         b. Intranasal form is significantly cheaper than parenteral form.
      3. Oral tablets (0.1 or 0.2 mg size)
         a. Give 0.1 mg PO TID, then increase to effect.
         b. Some dogs can have the dose decreased to BID.
      4. Parenteral DDAVP (4 μg/mL): 0.5 to 2 μg SC SID to BID
   C. Lysine-8-vasopressin (*Diapid* nasal spray)
      1. Dose to effect: often 1 to 2 sprays in a nostril SID to TID
      2. Less expensive, also less effective in some animals
      3. Administration not as well tolerated
II. Ancillary therapy may be tried in certain cases.
   A. Thiazide diuretics
      1. Probably work by decreasing resorption of sodium, consequently decreasing urine volume
      2. Useful in CDI, especially in association with low-sodium diets
   B. Chlorpropamide *(Diabinese)* 125 to 250 mg/day PO to decrease PU/PD (Nichols, 2000; Nichols, 2004)
III. Partial forms of CDI may require no specific therapy other than unlimited access to water.
IV. NDI is usually difficult to treat.
   A. Treat any underlying cause of acquired NDI.
   B. No specific therapy exists for primary NDI, but palliative measures include the following:
      1. Hydrochlorothiazide 0.5 to 1.0 mg/kg PO BID
      2. Chlorothiazide 10 to 40 mg/kg PO BID (Nichols, 2004)
      3. Avoidance of excessive salt (rawhide toys, salty foods)
   C. Allow unlimited access to water.

Monitoring of Animal

I. During the initial course of therapy, monitor for overhydration and, if it occurs, reduce the availability of water until the animal acclimates.
II. Long term, the owner can be taught to judge the optimal dosage and frequency of medication to be administered based on water intake and behavior.
III. DI is generally irreversible, except when caused by head trauma or hypophysectomy.
IV. Prognosis is variable.
   A. Prognosis is generally good with treatment, depending on the underlying disorder.
   B. If not treated, affected animals are prone to severe dehydration during illness or with water restriction.

Adult-Onset Growth Hormone Deficiency

Definition

I. Selective GH deficiency in the adult dog, with normal concentrations of other pituitary hormones, results in dermatological manifestations (see Chapter 87).
II. This disease is also called *hair cycle arrest* (previously known as *Alopecia X*), and the pathogenesis is poorly understood (Frank, 2005).

Clinical Signs

I. Normal stature
II. Bilateral, symmetrical hair loss with secondary hyperpigmentation that spares the head and distal extremities
III. No systemic clinical signs
IV. Breeds affected: chow chow, samoyed, poodle, Pomeranian (primarily males)

Diagnosis

I. Low GH levels, no response to provocative stimulation
   A. Normal GH response test in 30% of affected animals

   B. Thyroid and adrenal function tests normal
II. Possibly normal somatomedin C serum concentrations

Differential Diagnosis

I. Rule out other causes of endocrine dermatoses, including hyperadrenocorticism, hypothyroidism, and sex hormone abnormalities.
II. See Differential Diagnoses for Symmetrical Alopecia in Chapter 87.

Treatment and Monitoring

I. GH replacement therapy may be tried (see Pituitary Hypofunction, above).
II. Mitotane therapy is controversial (see Chapter 87).
   A. For adrenal hyperplasia-like syndrome
   B. Requires monitoring with ACTH stimulation testing to avoid secondary adrenal insufficiency
   C. Variable regrowth of hair
III. Intact male dogs are usually castrated before GH or mitotane treatment.
IV. Melatonin (3 to 6 mg PO BID) may help hair growth.
V. Trilostane has resulted in regrowth of hair.
   A. Dogs <2.5 kg: 20 mg PO SID
   B. Dogs 2.5 to 5.0 kg: 30 mg PO SID
   C. Dogs 5 to 10 kg: 60 mg PO SID

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CHAPTER 42

Diseases of the Thyroid

Cynthia R. Ward

HYPOTHYROID DISEASES

Canine Hypothyroidism

Definition

I. Clinical hypothyroidism results from lack of circulating thyroid hormone.
II. It is the most commonly diagnosed endocrinopathy in the dog owing to a significant incidence of false-positive diagnoses.

Causes

I. The most common cause is destruction of both thyroid glands, resulting in lack of production of thyroid hormone.
II. The initiating insult is unknown.
III. A genetic component is suggested, with a polygenic mode of inheritance in colony-raised beagles and an autosomal recessive mode of inheritance in borzois.
IV. It is associated with a rare major histocompatibility complex class II haplotype (Kennedy et al., 2006).

Pathophysiology

I. Primary disease (most common)
  A. Lymphocytic thyroiditis
    1. Probably immune-mediated
    2. Antibodies (Abs) against triiodothyronine (T_3), thyroxine (T_4), and thyroglobulin found in hypothyroid dogs
    3. Thyroid gland infiltrate: lymphocytes, plasma cells, and macrophages
    4. Slowly progressive follicle destruction over years
    5. Clinical signs when 75% of gland destroyed
    6. Increased prevalence of antithyroid hormone Abs in certain breeds, females, and larger dogs (Nachreiner et al., 2002)
    7. Association between recent vaccination and increased anticanine thyroglobulin antibodies (Scott-Moncrieff et al., 2002)
  B. Thyroid atrophy
    1. Adipose tissue replaces thyroid parenchyma.
    2. No inflammatory cells are seen, and the cause is unknown.
    3. It may reflect end-stage lymphocytic thyroiditis.
  C. Neoplastic destruction
    1. Bilateral primary thyroid neoplasia
    2. Metastatic thyroid neoplasia
    3. Most animals euthyroid, but may be hypothyroid with significant thyroid gland destruction
  D. Parasitic destruction: *Leishmania* spp.
II. Secondary disease
  A. Lack of thyroid-stimulating hormone (TSH) synthesis or secretion
  B. Rare in dogs
  C. Pituitary malformations and neoplasia
III. Congenital
  A. Also known as cretinism, congenital hypothyroidism is rare in dogs.
  B. Thyrotropin-releasing hormone (TRH) or TSH deficiency has been identified in giant schnauzers and boxers (Greco et al., 1991).
  C. Thyroid peroxidase deficiency and goiter occur as an autosomal recessive disease in toy fox terriers (Fyfe et al., 2003).
IV. Iatrogenic disease
  A. Following surgery, radiation, or ^{131}I treatment for thyroid adenocarcinoma
  B. Trimethoprim-sulfa antibacterials: trimethoprim-sulfadiazine, trimethoprim-sulfamethoxazole (Gookin et al., 1999)
    1. Dose and duration dependent: high end of dosage range for >4 weeks
    2. Resolution of clinical signs and normalization of thyroid function after treatment cessation
    3. Postulated interference with thyroid peroxidase activity and inhibition of thyroid hormone synthesis

Clinical Signs

I. Signalment
  A. Middle-aged dogs: range = 0.5 to 15 years
  B. Golden retrievers and Doberman pinschers overrepresented
  C. Spayed females and castrated male dogs may be at increased risk
II. Signs often subtle with gradual onset
III. Metabolic signs from decreased cellular metabolism
  A. Lethargy, exercise intolerance
  B. Heat seeking
  C. Weight gain, obesity
  D. Mental dullness

E. Decreased appetite, constipation
F. Bradycardia, hypothermia

IV. Dermatological signs (see Chapter 87)
V. Neuromuscular signs
A. Muscle weakness, muscle atrophy
B. Ataxia, tetraparesis, decreased spinal reflexes
C. Cranial nerve paralysis
D. Lameness: one or more limbs
E. Peripheral vestibular disease
F. Subclinical myopathy
G. Myasthenia gravis (Dewey et al., 1995)
H. Possibly laryngeal paralysis
1. No causal relationship established
2. Minimal or no resolution following thyroxine supplementation (Jaggy et al., 1994)
I. Rare cerebral disorders
1. Myxedema coma with severe mental dullness, facial myxedema, bradycardia, and hypothermia
2. Atherosclerosis and severe lipidemia with seizures, disorientation, and circling
J. Cricopharyngeal achalasia (Bruchim et al., 2005)

VI. Reproductive signs
A. Prolonged interestrous intervals
B. Failure to cycle
C. Lack of libido in the bitch
D. Hyperprolactinemia and inappropriate galactorrhea
E. Normal fertility in male dogs (Johnson et al., 1999)

VII. Cardiovascular signs
A. Sinus bradycardia
B. Low-voltage R waves on electrocardiography
C. Thromboembolic disease from atherosclerosis
D. Possible association with dilated cardiomyopathy (Phillips and Harkin, 2003)

VIII. Congenital hypothyroidism (cretinism)
A. Growth, mental retardation
B. Disproportionately large heads
C. Retention of puppy coat
D. Disproportionate dwarfism: retarded epiphyseal growth

IX. Concurrent endocrine diseases
A. Immune-mediated, polyglandular endocrine gland destruction
B. Possible concurrent hypoadrenocorticism, diabetes mellitus, and hypoparathyroidism

X. Behavioral changes
A. Aggression (Fatjo et al., 2002)
B. Cognitive dysfunction

Diagnosis

I. Hematological abnormalities: mild to moderate normocytic, normochromic, nonregenerative anemia
II. Serum chemistry abnormalities
A. Fasting hypercholesterolemia: possibly severe
B. Fasting hypertriglyceridemia
C. Possible mild elevations in liver enzymes
D. Increased creatine kinase (rare)

III. Baseline thyroid hormone assays
A. T_4 and free thyroxine (fT_4) are commonly measured.
B. Basal T_4 is a useful screening assay.
1. Values in the mid to high end of the reference range usually signify euthyroidism.
2. Values in the low-normal or below-normal range are not diagnostic of hypothyroidism.
3. Antibodies against T_4 may cause spurious results (low or high).
4. Measurement is affected by many physiological and pharmacologic factors.
5. Greyhounds and Scottish deerhounds have lower T_4 levels (Gaughan and Bruyette, 2001).
6. Conditions that may decrease T_4 in euthyroid animals include concurrent illnesses and certain drugs.
a. Any critical illness
b. Hypoadrenocorticism or hyperadrenocorticism
c. Diabetes mellitus
d. Heart and renal failure
e. Liver disease
f. Weight loss
g. Infections
h. Endurance conditioning (Evason et al., 2004; Panciera et al., 2003)
7. Common drugs that may decrease T_4 in euthyroid animals include the following:
a. Phenobarbital
b. Glucocorticoids
c. Trimethoprim-sulfa antibiotics
d. Clomipramine

C. Basal T_3 measurement is less accurate than T_4 for diagnosing hypothyroidism and is also affected by serum anti-T_3 Abs.
D. The fT_4 assay involves separating serum T_4 from its binding proteins.
1. Effects of drugs or illness on serum T_4 transport protein concentration or affinity are eliminated.
2. The free hormone (separated by equilibrium dialysis) offers several diagnostic advantages over T_4 measurement alone.
a. Unaffected by anti-T_4 Abs
b. Superior sensitivity, specificity, and accuracy
c. Recommended test when nonthyroidal illness present
3. Results must be interpreted with caution in animals on phenobarbital therapy because a falsely lowered fT_4 may occur, even though the animal is euthyroid (Kantrowitz et al., 1999).

E. Basal thyrotropin or canine thyroid-stimulating hormone (cTSH) concentrations are usually elevated in hypothyroid dogs.
1. Measurement of TSH in dogs has been hampered by lack of a readily available sensitive assay for cTSH.
2. Sensitivity and specificity are less than that of the T_4 or fT_4 measurement, so cTSH is not recommended as a single test.
3. Between 13% and 38% of hypothyroid dogs have a cTSH value within the reference range (Peterson et al., 1997; Scott-Moncrieff et al., 1998).

4. Approximately 8% to 18% of euthyroid dogs with concurrent illness have elevated cTSH concentrations (Scott-Moncrief et al., 1998; Dixon and Mooney, 1999).
5. When combined with low T_4 or fT_4, cTSH measurement is very specific.
6. Animals on treatment with phenobarbital may have a falsely increased cTSH (and lowered fT_4), even though they are euthyroid.

IV. Circulating Abs to T_3, T_4, and thyroglobulin can be measured with a specific enzyme-linked immunosorbent assay.
   A. Elevations of these Ab concentrations, especially antithyroglobulin Ab, may indicate early immune-mediated destruction of the gland.
      1. Approximately 50% of hypothyroid dogs have Abs against thyroglobulin, which indicates the presence of lymphocytic thyroiditis (Young et al., 1991; Refsal and Nachreiner, 1997; Vajner, 1997).
      2. Anti-T_3 and -T_4 antibodies are much less prevalent (6% and 2% of samples, respectively), and are not well correlated with hypothyroidism.
      3. Anti-T_3 and -T_4 antibodies are measured to determine if spurious interference has occurred in basal T_3 and T_4 measurements.
   B. Euthyroid dogs also may have positive antithyroglobulin Ab titers (Nachreiner et al., 1998).
   C. Measurement of antithyroglobulin Ab may be useful in breeding animals to help identify potential carriers of hypothyroidism.

V. Scintigraphy with ^{99m}technetium pertechnetate (TcO_4^-) is used to assess thyroid function.
   A. TcO_4^- is taken up by the thyroid gland in proportion to thyroid activity.
   B. Though useful when thyroid function testing is equivocal, expense and lack of availability limits its usefulness in the diagnosis of hypothyroidism.

VI. Thyroid glands may be imaged with ultrasonography; in hypothyroid dogs, they are usually smaller and have decreased volume compared with glands in euthyroid dogs (Bromel et al., 2005; Reese et al., 2005).

VII. TSH response test assesses thyroid gland reserve, but it is limited by expense and inconsistent availability of medical-grade bovine TSH.

VIII. Therapeutic trials (response to treatment) are used as a last resort when no other means of testing is diagnostic.
   A. Results are evaluated with caution because euthyroid animals may show clinical improvement with thyroid supplementation.
   B. Challenge by withdrawal of thyroid supplementation and observation of recurrence of clinical signs is desirable when diagnosis is made by a therapeutic trial.

Differential Diagnosis

I. Hyperadrenocorticism
II. Sex hormone abnormalities
III. Other causes of obesity and lethargy
IV. Other causes of cranial and peripheral neuropathies
V. Other causes of infertility in the bitch

Treatment

I. Emergency therapy of myxedema stupor or coma
   A. Administer sodium levothyroxine (L-thyroxine) 1 to 5 μg/kg IV BID.
   B. Maintain hydration with IV crystalloid fluid therapy.
   C. Combat hypothermia.

II. Thyroid supplementation with sodium L-thyroxine
   A. Brand-name products are recommended because generic replacements may have limited or variable bioavailability.
   B. Dosages are adjusted for each individual animal and can be very variable.
      1. The initial dose is 0.02 mg/kg PO BID.
      2. Increase to 0.04 mg/kg PO BID if necessary.
      3. Use BID initially, then possibly reduce to SID when clinical signs improve (Greco et al., 1998).
   C. Use lower initial dosages in dogs with cardiac illness or severe debilitation or in geriatric animals.

Monitoring of Animal

I. Improvement in clinical signs
   A. Improvement in activity and appetite usually occurs in 1 to 3 weeks.
   B. Improvement in skin and hair coat generally takes 4 to 6 weeks.
   C. Neurological abnormalities may take several months to improve.

II. Thyroid hormone measurements
   A. Begin monitoring serum hormone concentrations 2 to 4 weeks after instituting therapy.
   B. T_4 levels measured 4 to 6 hours post pill should be in the high-normal or slightly above the reference range.
   C. T_4 levels measured just before the next dose are ideally in the normal range.
   D. fT_4 is measured in animals with T_4 autoantibodies and should be in the middle-upper normal range 6 hours post-pill.
   E. Continue monitoring every 4 to 8 weeks for the first 8 to 10 months because, as metabolism changes, thyroid hormone replacement requirements vary.

Feline Hypothyroidism

Definition and Causes

I. It is a rare disease in cats.
II. It can be congenital or acquired.
III. The most common cause is iatrogenic disease following treatment of hyperthyroidism.

Clinical Signs

I. Severe lethargy
II. Constipation
III. Inappetence
IV. Obesity

V. Seborrhea sicca
VI. Stunted growth

Diagnosis

I. Appropriate history and clinical signs
II. Baseline serum T_4 measurement usually diagnostic
III. Measurement of feline TSH
  A. Canine assay is validated for cats.
  B. High TSH along with a low T_4 supports a diagnosis of hypothyroidism.
IV. TRH stimulation test
  A. TRH 0.1 mg/kg IV (Relefact by Ferring; Thypinone by Abbott) is administered.
  B. Serum samples are submitted before and 6 hours after TRH injection.
  C. Normal cats demonstrate a 50% increase in T_4, whereas hypothyroid cats do not show an appropriate increase.
  D. Transient side effects of TRH administration in cats include salivation, vomiting, tachypnea, and defecation.

Differential Diagnosis

I. Other causes of obesity, poor hair coat quality, and constipation
II. Other causes of severe lethargy
III. Other endocrinopathies: acromegaly, hyperadrenocorticism
IV. Unrelated illnesses arising after treatment of hyperthyroidism

Treatment and Monitoring

I. L-thyroxine is started at 0.05 to 0.1 mg (per cat) PO SID to BID.
II. Dosage is adjusted based on resolution of clinical signs and serum T_4 measurements, as in dogs.
III. Clinical signs and T_4 measurements usually improve within 4 to 6 weeks.

HYPERTHYROID DISEASES AND NEOPLASIA

Feline Hyperthyroidism

Definition

I. Hyperthyroidism results from an excess of circulating thyroid hormone.
II. The disease first appeared in the United States in the late 1970s.
III. It is now the most common endocrinopathy diagnosed in cats.

Causes

I. Hyperplastic or neoplastic thyroid cells overproduce thyroid hormone independent of any negative regulatory signals from the hypothalamic-pituitary-thyroid axis.
II. Etiology is unknown, but may be related to environmental (cat litter), nutritional (canned food), or abnormal cellular factors (Kass et al., 1999, Edinboro et al., 2004, Ward et al., 2005).

Pathophysiology

I. Adenomatous hyperplasia
  A. Small, multifocal functional nodules throughout the thyroid gland or generalized hyperplasia
  B. Most common cause
  C. Bilateral in approximately 70% of affected cats (Holzworth et al., 1980)
II. Solitary adenoma
  A. Circumscribed adenoma involving much of the gland
  B. Much less common: approximately 10% of hyperthyroid cats
  C. Bilateral or unilateral
III. Carcinoma
  A. Accounts for 1% to 2% of cases (Turrel et al., 1988)
  B. May be functional or nonfunctional

Clinical Signs

I. Signalment
  A. Middle-aged to older cats: average age at time of onset, 12 to 13 years; range, 4 to 21 years
  B. No reported breed or gender predilection
  C. Siamese and Himalayan cats potentially at decreased risk
II. Clinical signs (Broussard et al., 1995)
  A. Often less severe when diagnosed early
  B. Weight loss
    1. Most common clinical sign: 87% of affected cats
    2. From increased metabolic rate
  C. Polyphagia (49%)
  D. Vomiting (44%)
    1. Undigested food, often following rapid ingestion
    2. Acute gastric distention
    3. Worsened by overgrooming and hairball formation
  E. Polyuria/polydipsia (36%)
    1. Increased medullary blood flow and solute washout, decreased urine concentration
    2. Potential psychogenic polydipsia
  F. Behavioral changes (31%)
    1. Nervousness, hyperactivity, aggression
    2. Increased vocalization
    3. Shivering, tremors
  G. Diarrhea (15%)
    1. Loose and bulky stools, increased fecal volume
    2. Malabsorption and increased fecal fat content
  H. Weakness, lethargy: less common, variable
  I. Heat or stress intolerance: seeks cool places
  J. Panting, respiratory distress: sometimes attributable to cardiac disease
  K. Sudden-onset blindness from hypertension-induced retinal detachment
  L. Anorexia (7%) interspersed with polyphagia
III. Physical examination findings (Broussard et al., 1995)
  A. Enlarged palpable thyroid gland (83%)
    1. Discovery dependent on palpation skill
    2. Unilateral or bilateral enlargement
    3. Possible extension into the thoracic inlet
  B. Thin or cachectic (65%)

C. Cardiovascular signs
   1. Cardiac murmurs (54%)
   2. Tachycardia (42%)
   3. Gallop rhythm
   4. Atrial and ventricular arrhythmias
   5. Congestive heart failure
   6. Pleural effusion with muffled heart sounds
   7. Systemic hypertension
D. Dermatological signs
   1. Excessive shedding, matting of hair coat
   2. Greasy or dry skin, seborrhea
   3. Increased rate of claw growth
   4. Truncal alopecia from hair pulling, thin skin
E. Neuromuscular signs
   1. Muscle weakness, ventriflexion of the neck
   2. Muscle tremors, gait abnormalities
   3. Collapse, seizures
   4. Inability to jump to high places
F. Respiratory signs: tachypnea, dyspnea
G. Ocular abnormalities
   1. Retinal hemorrhages, dilated retinal vessels
   2. Detached retina
H. Dehydration
I. Apathetic hyperthyroidism
   1. Occurs infrequently: approximately 10% of hyperthyroid cats
   2. Severely ill
   3. Lethargy, anorexia

Diagnosis

I. Complete blood count (CBC)
   A. Mild elevation in packed cell volume
   B. Increased mean cell volume
   C. Stress leukogram: mature neutrophilia, lymphopenia, eosinopenia
   D. Increased platelet size
   E. Possible anemia
II. Serum biochemistry results
   A. Mild to moderate elevation of serum liver enzyme concentrations
   B. Mild hyperphosphatemia, hypokalemia
   C. Hyperglycemia from stress or concurrent diabetes mellitus
   D. Increased urea nitrogen and creatinine with concurrent renal disease or dehydration
   E. Decreased ionized calcium
III. Urinalysis
   A. Possible isosthenuria if renal insufficiency or polyuria present
   B. Possible glucosuria from stress hyperglycemia or concurrent diabetes mellitus
IV. Thoracic radiography
   A. Mild to severe cardiomegaly
   B. Signs of heart failure: pleural effusion and/or pulmonary edema
V. Basal serum total T_4 concentration
   A. It is increased in >95% of hyperthyroid cats (Broussard et al., 1995).
   B. It is the primary test used to diagnose hyperthyroidism.
   C. If T_4 is normal in a cat suspected to be hyperthyroid, repeat the test in 1 to 2 weeks, because hormone levels are known to fluctuate.
   D. It is affected by nonthyroidal illnesses (McLoughlin et al., 1993).
      1. Nonthyroidal illness artificially decreases serum T_4 to low-normal or below the reference range in euthyroid cats.
      2. Hyperthyroid cats with concurrent nonthyroid disease may have T_4 concentrations within or even below the normal range, making the diagnosis of hyperthyroidism difficult.
VI. Serum fT_4 concentration measured by equilibrium dialysis
   A. It is increased in hyperthyroid cats.
   B. It is useful in early hyperthyroidism when T_4 is normal.
   C. It may be misleading as a sole diagnostic test because 6% to 12% of euthyroid cats with nonthyroidal illness have elevated fT_4 (Mooney et al., 1996; Peterson et al., 2001).
   D. It is evaluated concurrently with a T_4.
   E. It is less accurate as a single test than a serum T_4.
VII. Serum T_3 or free T_3 measurements
   A. More baseline fluctuation than T_4 measurements
   B. No increased benefit over T_4 and fT_4
VIII. T_3 suppression test (Refsal et al., 1991)
   A. T_3 inhibits TSH secretion from the pituitary gland, so T_4 secretion decreases in a normal animal (T_4 half-life = 6 to 8 hours).
   B. Protocol is as follows:
      1. Day 1: obtain serum for basal T_3 and T_4 levels, and freeze or refrigerate separated serum.
      2. Day 2 to 3: give 25 μg T_3 (liothyronine) PO TID for seven treatments.
      3. Day 4: 2 to 4 hours after the seventh treatment, obtain samples for T_3 and T_4 measurement.
   C. Interpretation is as follows:
      1. Normal animal: T_4 values <1.5 μg/dL (20 nmol/L) or suppression of T_4 to ≤50% of pretreatment values
      2. Hyperthyroid animal: T_4 >1.5 μg/dL (20 nmol/L)
      3. Serum T_3 values
         a. Not useful in the diagnosis of hyperthyroidism
         b. Helpful to determine whether the owner gave the medication as instructed and that it was properly absorbed from the gastrointestinal (GI) tract
         c. Should increase after liothyronine treatment
   D. It is an excellent test to diagnose hyperthyroidism, especially in animals with nonthyroidal illness.
   E. Problems with the test include owner compliance with pill administration, low GI absorption, and the need to return the cat at the proper sampling times.
IX. TSH stimulation test
   A. TSH stimulates T_3 and T_4 release in normal animals.

B. In hyperthyroid cats, TSH administration should result in decreased release of T_4 and T_3.
C. T_4 levels following TSH are often normal in hyperthyroid cats, so the test is difficult to interpret and not useful.

X. TRH stimulation test (Peterson et al., 1994)
A. TRH stimulates TSH, T_3, and T_4 release in normal cats.
B. In hyperthyroid cats, TRH should induce no changes in T_4 and T_3.
C. The test involves obtaining blood for basal T_3 and T_4 levels, then giving TRH (*Relefact* or *Thypinone*) 0.1 mg/kg IV and collecting samples for T_3 and T_4 4 hours post-TRH.
D. Immediate side effects of TRH administration include salivation, vomiting, tachypnea, and defecation, but these are transient.
E. Interpretation is difficult and the test has limited diagnostic utility.

XI. Thyroid imaging with ^{131}I, ^{125}I, or pertechnetate ($^{99m}TCO_4^-$)
A. Identifies functional thyroid tissue
B. Determines extent of thyroid gland involvement and localizes ectopic thyroid tissue
C. Identifies metastatic tissue in cats with functional thyroid carcinoma
D. Pertechnetate faster, and comparison with salivary gland uptake helps quantify functional activity (Daniel et al., 2002)
E. Expensive, with limited availability

Differential Diagnosis

I. Diabetes mellitus
II. Chronic renal failure
III. Intestinal malabsorptive disease
A. Inflammatory bowel disease
B. Intestinal lymphosarcoma
C. Exocrine pancreatic insufficiency
D. Other GI diseases resulting in malabsorption and/or maldigestion

Treatment

I. Medical therapy with antithyroid thiourelene compounds
A. Mechanism of action
1. Prevention of iodine incorporation into tyrosyl groups
2. Prevention of coupling of monoiodotyrosine and diiodotyrosine into T_3 and T_4
3. Direct interaction with the thyroglobulin molecule
B. Examples
1. Methimazole *(Tapazole):* medical treatment of choice
2. Propylthiouracil: not recommended owing to side effects
C. Advantages of methimazole therapy
1. Less initial financial outlay
2. Allows for partial control of disease in animals with renal compromise
3. Stabilization of animals for surgery or ^{131}I treatment
4. Trial use to determine presence of renal compromise (i.e., worsening of renal function tests as hyperthyroidism is controlled)
D. Disadvantages of methimazole therapy
1. Daily pilling
2. Side effects common within the first 3 months or as dosages increase
a. Transient anorexia, vomiting, lethargy
b. Facial excoriations
c. Hepatic toxicity
d. Hemolytic anemia
e. Leukopenia, thrombocytopenia
f. Positive antinuclear antibody titers
g. Bleeding tendencies: increased proteins induced by vitamin K absence or antagonists
h. Usually resolve with discontinuation of the drug
E. Methimazole treatment regimen
1. Should be given BID for maximal control (Trepanier et al., 2003)
2. If renal function is normal, give 2.5 to 5 mg PO BID, depending on severity of clinical signs and thyroid hormone serum levels.
3. If renal insufficiency or failure is present, give 1.25 to 2.5 mg PO BID.
4. Transdermal gel forms can be compounded and are used on the ear pinna at the same dose and frequency as oral methimazole (Sartor et al., 2004); owners must wear gloves during application.

II. Medical therapy with oral cholecystographic contrast agents
A. Mechanism of action is via inhibition of outer-ring 5′ deiodination of T_4 to T_3, and direct inhibition of thyroid hormone secretion.
B. They are used in methimazole-intolerant cats to stabilize them for surgery or ^{131}I therapy.
C. Optimal results are obtained in cats with mild or moderate disease, and most cats become refractory to the drug after approximately 3 months.
D. Ipodate is administered at 100 mg PO SID or divided BID, but has limited availability.
E. Telepaque, iopanoic acid, another cholecystographic agent may be used at similar doses, although there are no direct studies in cats.

III. Stable iodine therapy
A. Large doses of iodine decrease thyroid hormone synthesis by an unknown mechanism.
B. Effects are usually transient, so iodine is only used to stabilize animals before surgery.
C. It is used in combination with a β-adrenergic blocking agent 10 to 14 days before surgery (Foster and Thoday, 1999).
D. Dose is 30 to 100 mg PO SID or divided BID.
E. Available preparations include the following:
1. Potassium iodide (*Thyroshield;* Fleming Laboratories, Mumbai, India) is available as a 65-mg/mL solution of potassium iodide.

2. Lugol's solution (5 g iodine with 10 g potassium iodide per 100 mL solution) yields 6 mg iodine/drop.
3. Taste is unpleasant, but the drug can be placed in a gelatin capsule immediately before administration.

IV. Surgical therapy: thyroidectomy
- A. Optimal to remove both glands; can operate one side at a time
- B. Presurgical methimazole administered through the morning of surgery
- C. Beta-blocking agents possibly administered before and after surgery
- D. Curative in most cases
- E. Postsurgical hypoparathyroidism and hypocalcemia: common, often resolves in several days
- F. May unmask renal failure

V. Iodine-131 treatment
- A. Treatment of choice in cats with normal renal function
- B. Mechanism of action
  1. Iodine-131 is concentrated in the hyperfunctioning follicles of the thyroid glands.
  2. Iodine-131 is primarily a beta radiation emitter that causes local tissue damage and kills hyperfunctional follicle cells.
  3. Radioactive half-life is 8 days.
- C. Advantages
  1. One subcutaneous injection is curative in 95% of cats, and a second treatment is necessary in only 2.5% of cases (Peterson and Becker, 1995).
  2. Side effects are negligible, with hypothyroidism occurring in 2.5% of treated cases (Peterson and Becker, 1995).
  3. It is not invasive.
  4. Destruction of ectopic thyroid tissue is accomplished.
  5. Destruction of malignant cells is possible at high doses.
- D. Disadvantages
  1. Hospitalized throughout the time of radioactive clearance, usually for 3 to 10 days
  2. Expensive
  3. May precipitate onset of renal failure

VI. Percutaneous ethanol injection
- A. It involves ultrasound-guided injection of ethanol into the thyroid gland.
- B. Its major complication is laryngeal paralysis, and large-scale studies are lacking in cats.

VII. β-Adrenoreceptor blocking agents
- A. Used to control tachycardia, hypertension, hyperexcitability, and arrhythmias associated with hyperthyroidism
- B. Used in cats awaiting surgery or ^{131}I therapy, or during initial therapy with methimazole
- C. Used during methimazole withdrawal to prevent signs of acute thyrotoxicosis (thyroid storm)
- D. Atenolol 6.25 mg PO SID to BID; contraindicated if congestive heart failure present

VIII. Therapy of combined hyperthyroidism and renal failure
- A. These diseases often coexist.
- B. Thyroid hormone increases cardiac output, decreases peripheral vascular resistance, increases renal plasma flow, and increases glomerular filtration rate (GFR) (Graves et al., 1994).
- C. With successful treatment of hyperthyroidism and subsequent GFR reduction, renal disease may become apparent.
- D. Careful management is required of cats with overt renal failure at the time of diagnosis.
  1. Methimazole is the treatment of choice, because serum T_4 concentrations can be kept slightly above the normal range if renal parameters worsen.
  2. Methimazole is instituted at a lower dose (see earlier discussion).
  3. Beta-blockers, such as propranolol or atenolol, are used for tachycardia and arrhythmias in those animals with renal failure in which serum T_4 normalization is contraindicated.

Monitoring of Animal

I. Methimazole therapy
- A. Monitor CBC, platelet count, blood urea nitrogen, creatinine, and serum T_4 2 to 3 weeks after starting therapy.
  1. Decrease dosage or discontinue if T_4 is low, hematological abnormalities are noted, or renal function has deteriorated.
  2. Institute beta-blockade therapy if methimazole is severely reduced or withdrawn to prevent acute thyrotoxicosis (thyroid storm).
  3. Increase dosage if T_4 remains elevated and other parameters are normal.
- B. Recheck every 2 to 3 weeks for first 3 months; then every 3 to 6 months, as necessary.

II. Iopanoic acid therapy
- A. Monitor for resolution of clinical signs.
- B. T_3 levels usually return to normal.
- C. T_4 levels usually not helpful for monitoring.

III. Surgical therapy
- A. Monitor serum calcium for 4 to 5 days after bilateral thyroidectomy because hypoparathyroidism may develop with damage or inadvertent removal of the parathyroid glands at the time of surgery.
- B. See treatment of Hypocalcemia in Chapter 43.
- C. Following surgery, hypothyroidism may develop and become clinically significant in some cats, requiring supplementation with L-thyroxine (see Feline Hypothyroidism).

IV. Radioactive iodine therapy
- A. Measure serum T_4 and renal parameters 2 weeks after ^{131}I treatment.
- B. Repeat measurements monthly until T_4 levels are normal or stabilize.
- C. Transient hypothyroidism is possible, but T_4 values usually normalize within 6 to 8 weeks, and these cats

usually show no clinical signs and do not require thyroid supplementation.
D. Cats may take 6 months before T_4 levels normalize.
E. Cats with low serum T_4 levels do not require treatment unless clinical signs of hypothyroidism are present.

Thyroid Tumors in Dogs

Definition and Cause

I. Relatively common tumors: 1% to 4% of all canine neoplasms (Harari et al., 1986)
II. Usually large, nonfunctional masses in the neck
III. Most malignant (>90%), with metastasis by the time of detection
IV. Cause unknown

Pathophysiology

I. Malignant carcinoma
  A. Most common (>70%) of all canine thyroid tumors
  B. Most unilateral; bilateral possible
  C. Develop in normal thyroid area or ectopic locations
  D. Locally invasive to esophagus, cervical musculature, surrounding vasculature and nerves, and trachea
  E. Possible metastasis to local lymph nodes at time of diagnosis
  F. Variable thyroid function
    1. Most animals are euthyroid because the tumor is nonfunctional.
    2. Rarely (<5%) tumors are functional and hyperthyroidism occurs.
    3. Some animals (possibly up to 30%) become hypothyroid when normal thyroid tissue is destroyed by the tumor.
II. Benign adenomas
  A. Much less common
  B. Usually small and found incidentally on necropsy
  C. Usually nonfunctional

Clinical Signs

I. Signalment
  A. Middle-aged or older (>5 years) dogs
  B. No sex predilection
  C. Boxers, beagles, and golden retrievers at increased risk
II. Clinical signs
  A. Large palpable cervical mass
  B. Signs related to local tissue compression and invasion by the mass
    1. Dyspnea, cough
    2. Dysphagia, hoarseness of bark
    3. Anorexia, weight loss
  C. Signs associated with functional thyroid tumors
    1. Signs of overproduction of thyroid hormone include polyuria/polydipsia, polyphagia, weight loss, restlessness, nervousness, and frequent defecation.
    2. Fewer signs of local tissue compression are noted, because the mass is often detected earlier, while it is still small.

Diagnosis

I. Palpable mass in ventral cervical region
II. Possibly enlarged regional lymph nodes
III. Imaging studies
  A. Plain cervical radiography identifies a soft tissue mass.
  B. Computed tomography or magnetic resonance imaging determines extent of invasion.
  C. Pertechnetate ($^{99m}TCO_4^-$) imaging identifies both metastatic disease and local invasion (Marks et al., 1994).
  D. Chest radiography is used to detect metastatic disease.
IV. Fine-needle aspirate
  A. Samples are often nondiagnostic and diluted with blood.
  B. Thyroid tumors do not exfoliate well.
  C. Malignant thyroid tumors may appear benign on cytological examination.
V. Biopsy
  A. Surgical wedge biopsies are often necessary.
  B. Percutaneous Tru-Cut biopsies are difficult to obtain, and significant bleeding may occur after the biopsy.
VI. Thyroid function testing
  A. Baseline hormone assays reveal increased serum T_4 or fT_4 with functional thyroid tumors.
  B. Endogenous TSH concentrations are low or low-normal with functional thyroid tumors.
  C. Rule out the presence of T_3 and T_4 autoantibodies that artificially elevate baseline T_4 concentrations (see Canine Hypothyroidism).

Differential Diagnosis

I. Nonthyroid neoplasia: lymphoma, regional soft tissue sarcoma, chemodectoma (carotid body tumors), metastatic oral tumors
II. Infectious or inflammatory conditions: abscess, granuloma
III. Salivary mucocele

Treatment

I. Thyroid tumors in dogs are highly malignant and have often metastasized by the time of diagnosis, so treatment is often palliative.
II. Surgical excision is the treatment of choice (Klein et al., 1995; Brearley et al., 1999).
  A. Excision is possible with small, encapsulated tumors.
  B. Many tumors are large and invasive, rendering them difficult to completely remove.
  C. If complete removal is impossible, debulking facilitates further treatment or is palliative.
  D. Tumors are very vascular, and intraoperative hemorrhage is common.
III. Chemotherapy produces variable results.
  A. Doxorubicin may reduce tumor size, but remission is not usually achieved.
  B. Cisplatin may be tried.
  C. Combination chemotherapy with cyclophosphamide and vincristine can also be attempted.
  D. Combination therapy with surgical debulking may be more effective.

IV. Different types of radiation therapy are available (Theon et al., 2000).
   A. External beam (cobalt) irradiation
      1. Important modality for control of invasive thyroid carcinoma
      2. Also used for large, nonresectable tumors as adjunctive therapy postsurgery
      3. Potential side effects: pharyngitis, laryngitis, esophagitis
      4. Considered even if metastatic disease is present, because the disease is often slowly progressive
      5. Median survival time: 2 years (Pack et al., 2001)
   B. Iodine-131 therapy
      1. Used most successfully in dogs with functional tumors
      2. High doses necessary
      3. Reversal of clinical signs possible, but treatment not curative (Adams et al., 1995)
      4. Adjunctive therapy to surgery (Worth et al., 2005)
      5. Shown to reduce size of mediastinal metastases
      6. Methimazole and beta-blocker agents to control signs of hyperthyroidism

Monitoring of Animal

I. Histologically evaluate all surgical margins.
II. Assess the animal every month for return of clinical signs, tumor regrowth, lymph node metastasis, and pulmonary metastasis.
III. If a functional tumor was present, measure thyroid function (T_4, fT_4, and/or endogenous TSH concentrations) every 1 to 3 months.

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CHAPTER 43

Disorders of the Parathyroid Gland

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PRIMARY HYPOPARATHYROIDISM

Definition and Causes

I. Diffuse lymphocytic parathyroiditis (immune-mediated origin suspected) is the most common histological finding.
II. Parathyroid agenesis is rare.
III. Iatrogenic hypoparathyroidism is possible following surgical manipulation, removal of the parathyroid glands, or trauma.
IV. Both hypomagnesemia and hypermagnesemia can reduce secretion of parathormone (PTH) and impair PTH action on its receptors.
V. Signalment is as follows:
   A. Dogs from 6 weeks to 13 years of age
   B. Cats ranging in age from 5 months to 6.7 years
   C. Females more common than males
   D. Most common breeds: toy poodle, miniature schnauzer, Labrador retriever, German shepherd dog, terriers

Pathophysiology

I. The normal response of the body to decreased ionized calcium is increased production of PTH.
II. The lack of PTH secretion leads to hypocalcemia as a result of the following mechanisms:
   A. Inability to mobilize calcium and phosphorus from bone
   B. Failure to reabsorb calcium in the urine and to increase 1,25-dihydroxyvitamin D_3 (calcitriol) synthesis in the kidney
   C. Decrease in urinary phosphorus excretion, which can result in mild hyperphosphatemia
   D. Failure to reabsorb calcium and phosphorus from the intestine

Clinical Signs

I. Common clinical signs of hypocalcemia include the following:
   A. Seizures and/or tetany
   B. Twitching, muscle tremors, and fasciculations
   C. Stiff gait, ataxia
   D. Disorientation, abnormal behavior
   E. Weakness
II. Other clinical signs are possible in dogs.
   A. Facial rubbing, pruritus
   B. Anorexia
   C. Panting
   D. Fever
   E. Weakness
   F. Polyuria/polydipsia (PU/PD)
III. Signs are often intermittent and most obvious after exercise or stress, possibly owing to blood pH changes and a shift of ionized calcium to bound fractions.
IV. Cats exhibit facial rubbing, ptyalism, dysphagia, and sometimes prolapse of the third eyelid.
V. Physical examination reveals other possible abnormalities, such as cataracts, bradycardia in cats, hyperthermia, and hypothermia.
VI. Electrocardiographic abnormalities include sinus bradycardia, prolonged ST segment duration, and prolonged Q-T interval.

Diagnosis

I. Serum biochemistry profile reveals hypocalcemia (<6.5 mg/dL) and hyperphosphatemia (>6 mg/dL).
II. Serum PTH concentration is evaluated concurrently with serum calcium concentration.
   A. Serum PTH is often undetectable.
   B. Low or low-normal PTH in the face of ionized hypocalcemia is abnormal.
   C. Normal parathyroid glands synthesize and secrete high levels of PTH when challenged by ionized hypocalcemia.

Differential Diagnosis

I. Other common causes of hypocalcemia
   A. Hypoalbuminemia, which leads to decreased binding stores for calcium
      1. Ionized calcium (Ca^{2+}) may be normal or low.
      2. So-called calcium-correction formulas that use serum albumin cannot accurately predict ionized Ca^{2+}.
   B. Chronic renal failure
   C. Eclampsia
   D. Acute renal failure
   E. Acute pancreatitis
II. Occasional causes of hypocalcemia
   A. Ethylene glycol toxicity
   B. Phosphate enema
   C. Sodium bicarbonate administration
III. Rare causes of hypocalcemia

A. Acute tumor lysis syndrome
B. Vitamin D deficiency
C. Laboratory error
D. Intestinal malabsorption
E. Transfusion of citrate anticoagulant-containing blood
F. Nutritional secondary hyperparathyroidism

IV. Prioritization and elimination of most differential diagnoses
A. History and physical examination findings
B. Laboratory database

Treatment

I. Intravenous calcium administration
A. Infuse 5 to 15 mg elemental calcium/kg (0.5 to 1.5 mL/kg of 10% calcium gluconate) slowly IV to effect over 10 to 15 minutes.
B. Monitor heart rate and electrocardiogram (ECG) during calcium infusion.
C. Stop calcium infusion if signs of cardiotoxicity occur, including bradycardia, elevated ST segment, or short Q-T interval.

II. Parenteral calcium administration following cessation of seizures/tetany
A. Constant-rate infusion of calcium is provided in fluids free of lactate, bicarbonate, phosphates, or acetates.
B. Subcutaneous administration of diluted calcium salts is no longer recommended because of the possible development of calcinosis cutis and sterile abscesses in the region of injection sites.

III. Maintenance therapy
A. Oral vitamin D
1. Ergocalciferol (vitamin D_2; *Drisdol*)
a. Low cost
b. High doses required: 1000 to 2000 U/kg PO SID, tapered to once a week
c. Maximum effect not achieved for several weeks
d. Chronic problems with hypercalcemia associated with the drug's long half-life
2. Dihydrotachysterol USP (DHT tablets)
a. Long half-life
b. Dosage extremely variable: 0.01 to 0.02 mg/kg PO SID to QOD
c. Recently removed from the market in North America
3. Calcitriol *(Rocaltrol):* the vitamin D metabolite of choice
a. Rapid onset of action
b. Short half-life, allowing frequent dosing adjustments
c. Induction dose: 20 to 30 ng/kg/day PO for 3 to 4 days
d. Maintenance dose: 5 to 15 ng/kg/day PO
B. Oral calcium therapy
1. Necessary acutely to ensure gastrointestinal (GI) calcium absorption
2. Tapered and usually discontinued over time because dietary calcium intake is adequate
3. Calcium carbonate: preferred form
4. Dosage: 25 to 50 mg/kg/day PO of elemental calcium in divided doses

Monitoring of Animal

I. Goal of chronic therapy is to maintain serum calcium in the low-normal range.
II. Monitor for hypercalcemia or hypocalcemia via serum calcium concentration.
A. Monitor daily while animal is hospitalized.
B. Monitor weekly until it has stabilized in low-normal range.
C. Recheck every 3 months thereafter.

HYPERPARATHYROIDISM

Definition and Causes

I. The most common cause is a solitary adenoma of one of the four parathyroid glands.
II. Malignant parathyroid tumors are rare.
III. Benign hyperplasia of the parathyroid glands has been reported.
IV. Typical signalment is as follows:
A. Older animal with a mean age of 11.2 years (range 6 to 17 years) in dogs and 12.9 years (range 8 to 15 years) in cats (Feldman et al., 2005)
B. No sex predilection in either species
C. Keeshonds and Siamese cats overrepresented

Pathophysiology

I. The normal parathyroid gland synthesizes and secretes PTH at a rate that is inversely proportional to the concentration of extracellular ionized Ca^{2+}.
II. The function of PTH is to increase serum calcium concentration; major sites of action are the kidneys, bones, and intestines.
A. PTH increases calcium reabsorption from the renal tubules and increases urinary phosphorus excretion.
B. PTH increases the release of calcium from bone.
C. PTH stimulates the absorption of calcium in the intestines indirectly via increased synthesis of calcitriol.
III. PTH synthesis is inhibited by hypercalcemia, hypophosphatemia, and by calcitriol (in the face of normal serum calcium concentration) through a negative feedback loop.
IV. The normal, negative feedback control of serum calcium concentration is lost in cases of primary hyperparathyroidism, with increased production of PTH and subsequent hypercalcemia.

Clinical Signs

I. The clinical signs in dogs are often insidious in onset, and hypercalcemia is sometimes an incidental finding on routine or preanesthetic laboratory tests.
A. Urinary effects
1. PU/PD is most common and is sometimes accompanied by urinary incontinence with increased volume of urine production.
2. Urolithiasis is present in one third of canine cases.

B. Gastrointestinal signs
   1. Anorexia
   2. Vomiting
   3. Constipation
C. Neuromuscular signs
   1. Lethargy, exercise intolerance
   2. Muscle weakness or wasting in dogs
   3. Shivering and muscle twitching, seizures with severe hypercalcemia
D. Stiffness, apparent limb pain

II. Clinical signs in cats are nonspecific.
A. Anorexia, vomiting, weight loss
B. Weakness
C. Polyuria/polydipsia

III. Physical examination is often unremarkable or may reveal the following:
A. Muscle atrophy, weakness, or tremor occurs in dogs.
B. Pain may be elicited on orthopedic examination.
C. Parathyroid gland adenomas are usually too small to palpate in dogs.
D. Most cats have a palpable cervical mass, usually from adenoma-associated cystic changes.

Diagnosis

I. Hemogram is usually unremarkable.

II. Biochemistry profile demonstrates several abnormalities.
A. Persistent hypercalcemia, and low or low-normal serum phosphorus concentration occur in dogs with normal renal function.
   1. Serum phosphorus increases with renal failure.
   2. Mean total calcium concentration in dogs is 14.5 mg/dL (range 12.1 to 23.0 mg/dL) (Feldman et al., 2005).
   3. Mean plasma ionized Ca^{2+} concentrations in dogs is 1.71 mg/dL (range 1.22 to 2.41 mg/dL) (Feldman et al., 2005).
   4. Hypercalcemia is the only consistent finding in cats and usually ranges from 11 to 22.8 mg/dL (Kallet et al., 1991).
B. Prerenal or renal azotemia is uncommon.
C. Serum alkaline phosphatase is sometimes mildly increased in dogs.
D. Ca^{2+} concentration is increased, often before total serum calcium exceeds the normal range.
E. Urinalysis in both species may reveal dilute urine (urine specific gravity <1.030), with or without red blood cells, white blood cells, bacteria, or crystals.

III. Serum intact PTH concentration is increased or mid- to high-normal.
A. There is no correlation between PTH and serum calcium concentrations.
B. The "two-site" PTH immunoradiometric assay is validated for dogs and cats.
   1. Reference ranges at the Endocrine Diagnostic Section, Animal Health Diagnostic Laboratory, East Lansing, Mich., are as follows:
      a. Normal canine serum PTH: 2 to 13 pmol/L
      b. Normal feline serum PTH: 0 to 4 pmol/L
   2. Proper sample handling is very important.
      a. PTH degrades during transit to a commercial laboratory, especially with high prevailing temperatures.
      b. Serum proteases, responsible for much of PTH degradation, are inhibited by submitting ethylenediamine tetraacetic acid (EDTA)-treated plasma rather than serum, or by using special tubes containing aprotinin.
      c. Chilled samples retard degradation of PTH.
      d. EDTA-treated plasma samples arriving at refrigerated temperatures (4° C) are preferred.
C. Evaluate elevated serum PTH in light of serum total or ionized Ca^{2+} concentration.
   1. Hypercalcemia reduces PTH concentrations in animals with normal parathyroid glands.
   2. A normal PTH may be inappropriately high in hypercalcemic dogs, especially if it is in the upper half of the normal range.
   3. Very low PTH values in cats are expected; it is not possible to inhibit PTH to below-normal range.
D. Serum parathyroid hormone-related peptide (PTHrP) is undetectable in dogs with primary hyperparathyroidism.

IV. Radiography and ultrasonography are recommended.
A. Thoracic and abdominal radiographs may be normal.
   1. Calcium-containing cystic calculi are possible in dogs and cats.
   2. A generalized decrease in long bone cortical density is noted with long-standing hyperparathyroidism.
B. Ultrasonography of the neck using a high-frequency transducer may identify parathyroid gland masses.
   1. Parathyroid glands are <3 mm in diameter in normal dogs (Wisner, 1998).
   2. The median greatest diameter was 6 mm (range 3 to 23 mm) in hyperparathyroid dogs, and almost all parathyroid masses were >4 mm in diameter (Feldman et al., 2005).
   3. False negative scans can occur in hyperparathyroid dogs.

Differential Diagnosis

I. Hypercalcemia of malignancy
A. Physical examination findings: lymphadenopathy, organomegaly, bone pain, or an anal gland mass (dogs)
B. Radiography (chest, abdomen, and bone) and abdominal ultrasonography: possible identification of masses
C. Lymph node and/or bone marrow aspirate: possible detection of lymphosarcoma
D. PTH: low or undetectable
E. PTHrP increased in some malignancies, especially carcinomas
F. Serum phosphorus concentration: normal to low in the absence of azotemia

II. Renal failure
A. Serum phosphorus increased
B. Serum PTH normal or increased
C. Ca^{2+} decreased or normal

III. Vitamin D toxicosis: serum phosphorus possibly increased
IV. Hypoadrenocorticism
V. Osteolytic disease
VI. Nonpathologic causes
  A. Laboratory error
  B. Lipemia
  C. Young, growing animal
  D. Postprandial sample
VII. Idiopathic hypercalcemia (cats): the most common cause of hypercalcemia in cats
VIII. Other causes of cranial cervical masses, especially in cats

Treatment

I. Each hyperparathyroid case must be evaluated individually to determine preoperative therapy.
  A. Those with the greatest degree of presurgical hypercalcemia need the most supportive care before and after surgery.
  B. Animals with a calcium × phosphorus (Ca × Phos) of >60 require aggressive therapy to prevent soft-tissue mineralization.
    1. Most hyperparathyroid animals have low serum phosphorus and a Ca × Phos of <60.
    2. Animals with primary hyperparathyroidism usually do not need emergency therapy.
II. Medical therapy for hypercalcemia is instituted.
  A. Correct fluid deficits with IV fluids.
  B. Give diuretics with 0.9% saline at 100 to 125 mL/kg/day IV to promote calciuresis.
  C. Diuretics are sometimes given to reduce serum calcium concentration following rehydration.
    1. Furosemide 2 mg/kg IV, SC, or PO BID to TID
    2. Thiazide diuretics: contraindicated as they increase renal tubular reabsorption of calcium
  D. Sodium bicarbonate infusion (1 mEq/kg IV slow bolus) is used only for a hypercalcemic crisis to transiently lower ionized Ca^{2+} and total calcium.
  E. Prednisone 1 to 2.2 mg/kg PO BID or dexamethasone 0.1 to 0.22 mg/kg IV, SC BID is given to promote calciuresis and for other nonspecific effects on the GI tract and bone.
    1. Give only if a diagnosis has been confirmed.
    2. Lymphosarcoma is difficult or impossible to diagnose once glucocorticoids have been administered.
  F. Other options to reduce hypercalcemia are as follows:
    1. Bisphosphonates may be tried in dogs.
      a. Etidronate *(Didronel)* 10 to 40 mg/kg/day PO divided BID
      b. Pamidronate *(Aredia)* 1 to 2 mg/kg diluted in 0.9% NaCl and infused IV over 2 to 4 hours
        (1) Effects last 2 to 4 weeks.
        (2) Repeat treatment if needed.
    2. Calcitonin provides quick-acting adjunctive treatment to further decrease ionized Ca^{2+} in those with severe hypercalcemia.
      a. It can be tried while waiting for other treatment to become effective.
      b. Its effects are short-lived, and dogs may develop anorexia and vomiting during treatment.
III. Surgical removal of all enlarged or grossly abnormal parathyroid tissue is recommended.
IV. Ultrasound-guided ethanol chemical ablation or radiofrequency heat ablation is the treatment of choice at select institutions if concurrent surgery for cystic calculi is not necessary.

Monitoring of Animal

I. Hypocalcemia is possible within 2 to 6 days of surgery as a result of atrophy of the remaining parathyroid glands.
  A. It is most likely to develop in animals with the highest presurgical hypercalcemia.
  B. Hospitalize animals with severe presurgical hypercalcemia for at least 5 to 7 days postoperatively.
  C. Monitor calcium concentrations once or twice daily.
  D. Cats infrequently develop hypocalcemia postoperatively.
II. Prophylactic vitamin D metabolite therapy is started before surgery to prevent hypocalcemia, especially in dogs with severe hypercalcemia.
  A. Dihydrotachysterol (DHT) is prescribed at 0.02 mg/kg/day PO for 3 days, followed by 0.01 mg/kg/day PO for 1 week, but the product is currently not available in North America.
  B. Calcitriol *(Rocaltrol)* 5 to 10 ng/kg PO BID is the preferred fast-acting vitamin D metabolite; it also has a short half-life.
  C. The dose of vitamin D metabolite is gradually reduced weekly by 25% to 50%, as long as serum calcium concentration remains >8 mg/dL.
  D. Vitamin D metabolite therapy is usually discontinued by weeks 12 to 16.
  E. The goal of vitamin D and calcium therapy is to maintain serum calcium in the low-normal range to allow continued stimulation of the remaining parathyroid glands so they may recover from atrophy.
III. Vitamin D metabolite therapy can cause hypercalcemia and subsequent renal toxicity.
  A. If hypercalcemia develops, discontinue vitamin D therapy.
  B. Reinstitute vitamin D only if hypocalcemia recurs.
IV. Prognosis for dogs and cats is excellent if surgery is successfully performed and animals are monitored closely postoperatively.
  A. Hypercalcemia may recur if an adenoma develops in one of the remaining parathyroid glands.
  B. If hypercalcemia persists following the removal of one gland, consider that either an adenomatous gland has been missed or multiple endocrine neoplasia exists.
  C. Renal failure can develop before or after surgery.

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CHAPTER 44

Diseases of the Endocrine Pancreas (Islet Cells)

Rebecka S. Hess

DIABETES MELLITUS

Definition

I. Derivation of name: diabetes = polyuria; mellitus = sweet
II. Type I diabetes mellitus (DM)
  A. Most common form of DM in dogs and cats
  B. Develops from beta cell destruction and impaired insulin secretion, (hypoinsulinemia)
  C. Usually insulin-dependent diabetes mellitus (IDDM)
  D. Possible progression from non–insulin-dependent diabetes mellitus (NIDDM) to IDDM
III. Type II DM
  A. Uncommon in cats and rare in dogs
  B. Characterized by insulin resistance and impaired insulin secretion, with or without beta cell destruction
  C. Serum insulin concentration normal, high, or low
IV. Secondary DM
  A. Secondary to diestrus or pregnancy in the dog
  B. Secondary to megestrol acetate treatment in the cat
V. Transient DM
  A. Occurs mainly in cats
  B. Theorized to develop in animals with subclinical DM and a concurrent disorder or exposure to an insulin-antagonistic drug

Causes

I. Type I DM
  A. Genetic: autosomal recessive inheritance in Keeshonds
  B. Immune-mediated following precipitating events: infections, toxins, unknown causes
II. Type II DM
  A. Obesity
  B. Islet-specific amyloid deposition
  C. Genetic
  D. Unknown

Pathophysiology

I. The Islets of Langerhans represent the endocrine pancreas and contain four types of cells.
  A. Alpha cells contain glucagon.
  B. Beta cells contain insulin.
  C. Delta cells contain somatostatin.
  D. F cells contain pancreatic polypeptide.
II. Insulin affects carbohydrate, protein, and fat metabolism.
  A. Insulin is anabolic, and its principal effects on carbohydrate metabolism are as follows:
    1. Increase glucose entry to muscle and adipose tissue
    2. Increase glycogen synthesis in the liver
    3. Decrease gluconeogenesis in the liver
  B. Insulin's principal anabolic effects on protein metabolism are the following:
    1. Increase amino acid uptake in muscle
    2. Increase protein synthesis in muscle and liver
    3. Decrease protein catabolism in muscle
  C. Insulin's principal anabolic effects on fat metabolism include the following:
    1. Increase lipid synthesis in adipose tissue and liver
    2. Decrease ketogenesis
    3. Activate lipoprotein lipase
    4. Inhibit hormone-sensitive lipase
  D. Lack of insulin or decreased action of insulin leads to the following:
    1. Hyperglycemia
    2. Catabolism of glycogen, protein, and fat stores
    3. Ketogenesis
    4. Lipemia
III. Other actions of insulin include increasing cell growth and increasing intracellular uptake of potassium and phosphorous.
IV. Insulin secretion is stimulated by various agents.
  A. Glucose
  B. Mannose, fructose
  C. Amino acids
  D. Glucagon
  E. Intestinal hormones: gastrin, secretin, cholecystokinin
V. Insulin-induced hypoglycemia can be reversed by four counterregulatory or diabetogenic hormones.
  A. Glucagon
  B. Catecholamines
  C. Glucocorticoids
  D. Growth hormone

Clinical Signs

I. Signalment
  A. Dogs
    1. Mean age of onset is 7 to 9 years.
    2. Samoyeds, miniature schnauzers, miniature and toy poodles, and pugs are at increased risk.

3. German shepherd dogs, golden retrievers, and American pit bull terriers are at decreased risk.
4. Intact and neutered females may have an increased risk of developing DM.

B. Cats
1. Mean age of onset is 10 years.
2. Burmese cats are at increased risk in Australia.
3. Neutered males may be at increased risk.

II. History and clinical signs
A. Polyuria and polydipsia (PU/PD)
B. Weight loss
C. Polyphagia
D. Blindness (dogs)
E. Plantigrade stance (cats)

III. Physical examination findings
A. Animals may be normal to severely compromised.
B. Signs are often nonspecific.
1. Underweight, normal, or obese body condition
2. Variable hydration status: normal or dehydrated
3. Hepatomegaly
4. Cataracts (dogs)
5. Plantigrade stance (cats)
6. Lethargy, weakness

Diagnosis

I. Appropriate history, clinical signs, and physical examination findings along with persistent hyperglycemia and glucosuria are sufficient for a diagnosis of DM.

II. Affected animals frequently have concurrent diseases that may influence clinical signs and physical exam findings.
A. Hyperadrenocorticism (dogs)
B. Urinary tract infection (UTI; dogs)
C. Hypothyroidism (dogs)
D. Acute pancreatitis (dogs and cats)
E. Neoplasia (dogs and cats)
F. Hepatic lipidosis (cats)
G. Chronic renal failure (cats)
H. Bacterial and viral infection (cats)

III. Because diabetics are usually middle-aged to older animals with concurrent disorders, further diagnostics are warranted.
A. Complete blood count (CBC)
1. The CBC is often normal.
2. Hematocrit may be normal, low, or high.
3. "Stress leukogram" may be present and is characterized by mature neutrophilia, monocytosis, lymphopenia, and eosinopenia.
4. Neutrophilia with a left shift may occur with infection.

B. Serum biochemistry profile
1. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (SAP) activity may be increased.
2. Lipemia and hypercholesterolemia are common.
3. Total bilirubin concentration may be increased.
4. Azotemia may be present.

C. Urinalysis (UA)
1. Specific gravity is variable, although it is usually >1.025.
2. Glucosuria is present.
3. Proteinuria, bacteruria, or ketonuria may be present.

D. Urine culture and sensitivity (C & S)
1. They are always performed in diabetic animals even if white blood cells (WBCs) are not apparent in the urine sediment.
2. Animals with DM are often immunocompromised; therefore, they may have a UTI with few or no WBCs in the urine sediment.
3. Glucosuria also increases the risk of UTIs.

E. Serum insulin or C-peptide concentration
1. Expected to be low in type I DM
2. Variable in type II DM

Differential Diagnosis

I. PU/PD
A. Renal disease
B. Liver disease
C. Hyperadrenocorticism
D. Hypoadrenocorticism
E. Hyperthyroidism
F. Hypercalcemia
G. Hypokalemia
H. Drugs, iatrogenic: glucocorticoids, diuretics, anticonvulsants, fluid overload
I. Pyometra
J. Diabetes insipidus
K. Psychogenic
L. Polycythemia

II. Weight loss despite polyphagia
A. Hyperthyroidism
B. Gastrointestinal parasites
C. Exocrine pancreatic insufficiency
D. Protein-losing enteropathy or nephropathy

III. Hyperglycemia
A. Stress
B. Hyperadrenocorticism
C. Drugs: glucocorticoids, progesterone, megestrol acetate
D. Total parenteral nutrition or other intravenous fluids
E. Postprandial
F. Diestrus
G. Pheochromocytoma
H. Acromegaly
I. Acute pancreatitis
J. Factitious measurement

IV. Glucosuria: primary renal glucosuria

Treatment

I. Insulin (Table 44-1)
A. Sources of insulins
1. Human insulin or human insulin analogue produced in bacteria by recombinant DNA techniques
2. Porcine or porcine–bovine mixture insulin

B. Types of insulin and durations of action
1. Short-acting insulins
a. Regular insulin
b. Identical to human insulin

TABLE 44-1

Insulin Products Used in Dogs or Cats

BRAND NAME	GENERIC NAME	SPECIES SOURCE	DURATION	MANUFACTURER	CONCENTRATION*	VOLUME, CONCENTRATION, APPROXIMATE COST
Humulin R, Novolin R	Regular insulin	HA[†]	Short	Eli Lilly[‡] Novo Nordisk[§]	U-100	10 mL, 1 vial = 1000 units, $25-$35
Humulin N, Novolin N	Neutral protamine Hagedon (NPH)	HA[†]	Intermediate	Eli Lilly Novo Nordisk	U-100	10 mL, 1 vial = 1000 units, $20-$30
Vetsulin (United States), *Caninsulin* (Europe, Australia)	Lente	Porcine	Intermediate	Intervet[‖]	U-40	10 mL, 1 vial = 400 units, $16-$30
PZI Vet	Protamine zinc insulin (PZI)	90% beef, 10% pork	Intermediate	Idexx[¶]	U-40	10 mL, 1 vial = 400 units, $86-$100
Lantus	Glargine	HA[†]	Intermediate to long	Aventis[#]	U-100	10 mL, 1 vial = 1000 units, $60-$74

*U-100 = 100 U/mL; U-40 = 40 U/mL.

[†]Human insulin analogue produced in bacteria by recombinant DNA techniques.

[‡]Indianapolis, Ind.

[§]Princeton, N.J.

[‖]Hillsboro, Del.

[¶]Westbrook, Me.

[#]Bridgewater, N.J.

c. Currently the only short-acting insulin that has been well characterized in dogs and cats

2. Intermediate acting insulins
   a. Neutral protamine Hagedorn (NPH) isophane insulin suspension: identical to human insulin
   b. Purified porcine lente insulin
   c. Protamine zinc insulin (PZI): mixture of 90% beef and 10% pork insulin
3. Long-acting insulin
   a. Glargine insulin
   b. Human insulin analogue
   c. Currently the only long-acting insulin characterized in dogs and cats

C. Frequency of insulin therapy
1. Twice-daily insulin is usually required in dogs and cats.
2. Occasionally, once-daily insulin treatment is sufficient.
3. Successful, once-daily treatment is observed more commonly with glargine insulin and in cats

D. Initial dosage
1. A safe initial dose for all insulin products in both dogs and cats is 0.5 U/kg subcutaneously.
2. The dose is adjusted based on clinical signs and glucose curves (see Monitoring of Animal).

II. Diet
A. Dog
1. Diet components: high insoluble fiber, complex carbohydrates, fixed protein, restricted fat
2. Examples: Canine w/d by Hill's (Topeka, Kan.), Glucose-Control by IAMS (Dayton, Ohio)

B. Cat
1. Diet components: high protein, low carbohydrate
2. Examples: Feline m/d by Hill's, Feline DM by Purina (St. Louis, Mo.)

C. Feeding schedule
1. Twice daily, at a fixed time
2. Before insulin administration to ensure dietary intake before onset of insulin action

III. Exercise
A. Promotes weight loss
B. May increase glucose transport and glycogen synthesis in dogs and cats

IV. Oral hypoglycemics
A. Sulfonylureas (glipizide)
1. Mode of action
   a. Stimulates insulin secretion from pancreatic beta cells
   b. Increases peripheral glucose uptake
2. Adverse effects in cats
   a. Vomiting shortly after drug administration
   b. Increased hepatic enzyme activities, icterus
   c. Hypoglycemia
3. Candidates for glipizide therapy
   a. Cats with type II DM are more likely to respond than cats with type I DM.
   b. Treat only clinically stable, uncomplicated diabetics.

c. Do not use in cats with profound hyperglycemia or diabetic ketoacidosis.

4. Dosage
   a. Give 2.5 mg/cat PO BID for first 2 weeks.
   b. If no adverse effects occur and the cat is still hyperglycemic, increase to 5 mg PO BID after 2 weeks.
   c. If the cat is still hyperglycemic at 4 weeks, discontinue glipizide and begin insulin treatment.

B. Vanadium
1. Mode of action is to increase insulin sensitivity in skeletal tissue and liver.
2. Candidates for treatment are the same as for glipizide.
3. Cats treated with insulin and vanadium may require less insulin and have better resolution of clinical signs than cats treated with insulin alone.
4. Dose is 45 mg/cat PO SID.
5. Adverse effects include vomiting, diarrhea, and anorexia.

C. Chromium
1. Proposed mode of action in rodents and humans is to increase insulin sensitivity.
2. Currently there are no studies to suggest that chromium improves glycemic control in cats or dogs with naturally occurring diabetes mellitus.
3. Chromium supplementation in cats does not affect glucose tolerance in obese and nonobese cats.

D. Acarbose
1. Mode of action is to competitively inhibit alpha glucosidase enzymes, resulting in reduced postprandial hyperglycemia.
2. Candidates for treatment are diabetics on appropriate insulin and dietary therapy that exhibit postprandial hyperglycemia.
3. Acarbose is administered at the time of a meal.
4. Acarbose is used in conjunction with insulin.
5. Doses in dogs are as follows:
   a. Dogs weighing <10 kg: 25 mg PO BID for 2 weeks, then 50 mg PO BID
   b. Dogs weighing ≥10 kg: 50 mg PO BID for 2 weeks, then 100 mg PO BID
6. Dose in cats is 12.5 mg PO BID
7. Adverse effects (observed more commonly with higher dosages) include diarrhea and flatulence, and usually subside with time.

V. Suspected insulin resistance
A. Insulin resistance is suspected when clinical signs and hyperglycemia persist with insulin dosages >1.5 U/kg per dose.
B. Reasons for perceived insulin resistance are as follows:
1. Improper handling or administration of insulin
2. Outdated, inactive insulin
3. Improper dosage or frequency of insulin injection
4. Poor absorption of insulin
5. Antiinsulin antibodies
6. Somogyi effect

C. Presence of concurrent disorders listed in the preceding Diagnosis section can cause true insulin resistance.

Monitoring of Animal

I. Owners must monitor the following parameters.
A. Changes in clinical signs: PU/PD, polyphagia, body weight
B. Urine glucose BID: before feeding
C. Ketonuria BID: emergency situation if present
D. Appetite BID

II. Adjust the insulin dose and seek veterinary advice in the following instances:
A. If vomiting or anorexia occur, administer half the insulin dose.
B. If the animal does not eat its meal, administer half the insulin dose.
C. If seizures, weakness, or signs of insulin-induced hypoglycemia are observed, rub corn syrup onto gums and seek emergency veterinary care.

III. Monitoring of cats is similar to dogs, but can be more difficult.
A. Cats often reject fixed BID meals and require free-choice food.
B. Cats may refuse appropriate diets.
C. Sampling urine at fixed times can be difficult.

IV. Veterinary monitoring involves the following:
A. Clinical signs: PU/PD, polyphagia, body weight
B. Monitoring for glucosuria or ketonuria
C. Glucose curves
1. Measure glucose every 2 hours for at least 12 hours in animals receiving BID insulin, and for 24 hours in animals receiving SID insulin.
2. Insulin duration is defined as the number of hours after insulin administration that blood glucose remains below 200 to 250 mg/dL.
   a. If insulin duration is approximately 12 hours, give insulin BID.
   b. If insulin duration is approximately 24 hours, give insulin SID.
3. Adequate glycemic control is achieved when glucose concentrations over 12 to 24 hours are 100 to 250 mg/dL in dogs and 100 to 300 mg/dL in cats.
   a. If the animal is persistently hyperglycemic, increase the insulin dosage.
   b. If the animal is persistently hypoglycemic, decrease the insulin dosage.
4. Initially, perform glucose curves every 1 to 2 weeks until adequate glycemic control is achieved.
5. Perform follow-up glucose curves every 1 to 6 months, depending upon clinical signs and trends in monitoring at home.
6. Measurement of a single blood glucose concentration is not a useful monitoring tool owing to the Somogyi effect.
   a. The Somogyi effect is characterized by increased secretion of glucagon, catecholamines, glucocorticoids, and growth hormone in response to severe insulin-induced hypoglycemia.
   b. Pronounced compensatory hyperglycemia can occur as a result of an insulin overdose.

D. Glycosylated hemoglobin

1. Formed from an irreversible bond of glucose to hemoglobin
2. Reflects serum glucose concentrations during the prior 3 to 4 months

E. Fructosamine
1. Formed from an irreversible bond of glucose to various serum proteins
2. Reflects serum glucose concentrations during the preceding 1 to 3 weeks

F. Possible long-term complications: cataracts, uveitis, retinopathy, neuropathy, nephropathy

DIABETIC KETOACIDOSIS

Definition

I. Diabetic ketoacidosis (DKA) is a severe form of complicated DM that is a medical emergency.
II. DKA is characterized by acidosis and ketosis in animals with DM.

Causes and Pathophysiology

I. Ketones are synthesized from fatty acids as a substitute form of energy, because inadequate amounts of glucose enter into cells.
II. Concurrent diseases may contribute to development of DKA.
III. Excess ketoacids results in potentially life-threatening acidosis and electrolyte abnormalities.
A. Hypokalemia is common.
1. Acidosis results in a potassium shift out of the cell to electrically compensate for hydrogen movement into the cell.
2. Hypokalemia is further aggravated by diuresis, vomiting, potassium binding of ketoacids, and diffusion of potassium into the cells after insulin therapy.
3. Hypokalemia can lead to profound muscle weakness that may cause respiratory paralysis in extreme cases.

B. Hypophosphatemia is also common.
1. Hypophosphatemia develops when phosphate shifts from the intracellular space to the extracellular space as a result of hyperglycemia, acidosis, and hypoinsulinemia.
2. Osmotic diuresis or fluid therapy, along with insulin administration, causes extracellular phosphate depletion, leading to whole-body phosphate depletion.
3. Hypophosphatemia is associated with hemolysis and seizures.

C. Hyponatremia can occur from diuresis, vomiting, and sodium binding to ketoacids.
D. Hypomagnesemia occurs in cats, but is uncommon in dogs.

Clinical Signs

I. History and clinical signs
A. Similar to an uncomplicated diabetic
B. Anorexia and vomiting also possible
II. Physical examination findings
A. Similar to those of an uncomplicated diabetic
B. Dehydration
C. Depression and weakness
D. Acetone breath
E. Tachypnea

Diagnosis

I. Diagnostic findings are similar to DM, but ketonuria (or ketosis) and acidosis are also present.
II. Additional diagnostics are mandatory in DKA.
A. CBC, serum biochemistry profile
B. UA, urine C & S
C. Canine or feline pancreatic lipase immunoreactivity
D. Amylase, lipase (dogs)
E. Serum thyroxine concentration (cats and dogs) and serum thyroid hormone-stimulating concentration (dogs)

Differential Diagnosis

I. Ketosis
A. Starvation
B. Low-carbohydrate diet
C. Persistent hypoglycemia
D. Persistent fever
E. Pregnancy
II. Acidosis
A. Renal failure
B. Lactic acidosis
C. Toxin exposure
D. Severe tissue destruction
E. Severe diarrhea
F. Chronic vomiting

Treatment

I. Intravenous fluid therapy is the most important component of DKA treatment.
II. Correction of electrolyte abnormalities is imperative.
A. Add potassium to IV fluids and administer at a rate not to exceed 0.5 mEq/kg/hr (Box 44-1).
B. Correct hypophosphatemia with potassium phosphate (potassium 4.4 mEq/mL, phosphate 3 mM/mL) at 0.03 mM phosphate/kg/hr with IV fluids, calculating for concurrent administration of potassium.

Box 44-1

Potassium Supplementation in Hypokalemic Animals*

Serum potassium concentration (mmol/L)	Potassium (mEq) added to 250-mL fluid bag
6-2	20
1-2.5	15
6-3.0	10
1-3.5	7

*Not to exceed 0.5 mEq/kg/hr IV.

TABLE 44-2

Administration of Intravenous Insulin in Animals with Diabetic Ketoacidosis*

BLOOD GLUCOSE CONCENTRATION (mg/dL)	FLUID COMPOSITION	RATE OF ADMINISTRATION (mL/hr)
>250	0.9% NaCl	10
200-250	0.45% NaCl + 2.5% dextrose	7
150-200	0.45% NaCl + 2.5% dextrose	5
100-150	0.45% NaCl + 5% dextrose	5
<100	0.45% NaCl + 5% dextrose	Stop fluid administration

*Give 2.2 U/kg of regular crystalline insulin added to 250 mL of NaCl solution.

C. Correct hyponatremia with IV saline diuresis (0.9% saline).
D. Correct hypomagnesemia with magnesium sulfate (4 mEq/mL) at 1 mEq/kg/24 hr IV.

III. Correction of hyperglycemia is undertaken with insulin therapy.
A. Insulin is only administered IV (Table 44-2) or IM in animals with DKA.
B. IM insulin administration is as follows:
1. Give regular crystalline insulin IM every hour.
2. Begin with 0.2 U/kg insulin.
3. Then give 0.1 U/kg IM 1 hour later.
4. Treatment with IM regular insulin is continued based on blood glucose concentration
a. Give 0.05 U/kg/hr if blood glucose drops >75 mg/dL/hr.
b. Give 0.1 U/kg/hr if blood glucose drops 50 to 75 mg/dL/hr.
c. Give 0.2 U/kg/hr if blood glucose drops <50 mg/dL/hr.

IV. Acidosis is usually corrected with IV fluid administration and insulin therapy alone.
A. Bicarbonate is not needed for treatment of acidosis in most dogs and cats with DKA.
B. The use of bicarbonate for correction of acidosis is controversial and may be harmful.
C. If venous pH remains <7.1 after 1 hour of fluid therapy, consider administering sodium bicarbonate at one third to half the calculated bicarbonate need (0.3 × body weight × negative base excess) over 20 minutes and monitor venous pH every 1 hour until venous pH is ≥7.1.

V. Treat concurrent diseases to help decrease secretion of diabetogenic hormones and lessen insulin resistance.

Monitoring of Animal

I. Monitor hydration status continuously.
II. Monitor blood glucose every 2 hours.
III. Monitor electrolytes and venous pH every 4 hours.
IV. Monitor ketonuria once daily.
V. Continue monitoring as for DM once the ketoacidotic crisis resolves.

HYPEROSMOLAR NONKETOTIC DIABETES MELLITUS

Definition

I. A severe nonketotic form of complicated DM
II. Characterized by hyperosmolarity (>350 mOsm/kg)
III. A medical emergency

Cause and Pathophysiology

I. Severe hyperglycemia contributes to hyperosmolarity.
II. Ketosis may be prevented by residual insulin activity.
III. Increased plasma osmolarity results in movement of fluid from within the cells to the extracellular fluid space.

Clinical Signs

I. Similar to DKA without acetone breath or tachypnea
II. Possible mental obtundation, coma, and death

Diagnosis

I. Diagnostic findings are the same as for DKA except that animals are severely hyperglycemic and hyperosmolar (>350 mOsm/kg).
II. The animal may not be ketoacidotic.

Treatment

I. Similar to DKA, but use 0.45% NaCl to decrease serum sodium concentration; use 0.9% saline if the animal is in shock.
II. Rapid correction of hyperosmolarity is potentially fatal.

Monitoring of Animal

I. Monitoring is similar to DKA, with additional monitoring of osmolarity every 4 hours.
II. Mental status is monitored continuously.

NEOPLASIA

Insulinoma

See Chapters 45 and 73.

Glucagonoma

See Table 44-3 and Chapter 73.

Gastrinoma

See Table 44-3.

TABLE 44-3

Uncommon Tumors of the Pancreas

TUMOR TYPE	CELL ORIGIN	CLINICAL SIGNS	DIAGNOSIS	TREATMENT/PROGNOSIS
Glucagonoma	Pancreatic alpha cells	Middle-aged to older dogs	Presence of a pancreatic tumor containing glucagon and hyperglucagonemia	Surgical excision of pancreatic tumor Somatostatin (octreotide): 10-40 μg SC BID-TID
		Necrolytic migratory erythema	Painful crusting and erosions of foot pads Erythema and ulceration of muzzle, mucocutaneous junctions	Treatment of skin disease (Byrne, 1999)
		Diabetes mellitus or small amount of intestinal diarrhea possible	See text	Treatment of small-bowel diarrhea: see Chapter 33 Poor prognosis
Gastrinoma	Residual fetal delta cells or delta cells that revert back to their fetal function of gastrin secretion	Vomiting/hematemesis, diarrhea/hematochezia, melena, weight loss, anorexia, abdominal pain, polydipsia, lethargy, depression, regurgitation, steatorrhea, dehydration, tachycardia, fever, palpable pancreatic mass	Documentation of hypergastrinemia is necessary, but not solely sufficient for a diagnosis of gastrinoma Secretin stimulation test Calcium stimulation test A gastrin-containing pancreatic mass aids the diagnosis	Surgical excision of pancreatic tumor Somatostatin (octreotide): 10-40 μg SC BID-TID H_2-histaminergic blockers: cimetidine, ranitidine H^+ pump inhibitor: omeprazole Sucralfate, misoprostol

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CHAPTER 45

Diseases of the Adrenal Gland

Deborah S. Greco

HYPOADRENOCORTICISM

Definition

Hypoadrenocorticism (Addison's disease) arises from deficient secretion of mineralocorticoids (aldosterone) and glucocorticoids by the adrenal gland.

Causes and Pathophysiology

I. Naturally occurring, primary hypoadrenocorticism is usually caused by immune-mediated destruction of the adrenal cortex in cats and dogs.
II. Lymphoma of the adrenal glands is a cause of Addison's disease in cats.
III. Secondary hypoadrenocorticism results when the pituitary gland produces inadequate amounts of adrenocorticotropic hormone (ACTH).
  A. Secondary to chronic steroid therapy
  B. Associated with tumors, trauma, or congenital defects of the pituitary gland
IV. Hypoadrenocorticism associated with glucocorticoid deficiency only is termed *atypical Addison's disease.*
  A. Secondary hypoadrenocorticism is always atypical.
  B. Primary hypoadrenocorticism is atypical in the early stages of the disease, before destruction of the zona glomerulosa.

Clinical Signs

I. Signalment (Kintzer and Peterson, 1997)
  A. Young female dogs (70%) of any breed
  B. Reported in families of Leonbergers and standard poodles (Smallwood and Barsanti, 1995)
  C. Young cats of any breed or sex
II. Historical findings (Table 45-1)
  A. Gastrointestinal (GI) signs: intermittent vomiting, anorexia, diarrhea, melena, weight loss
  B. General signs: lethargy, depression, weakness
  C. Miscellaneous signs: hair loss, polyuria/polydipsia (PU/PD), waxing and waning course
  D. Hypoadrenal crisis: any of the GI, general, and miscellaneous signs plus collapse, hypothermia, shaking
III. Physical examination findings (Box 45-1)
  A. Acute addisonian crisis
    1. Weak pulses
    2. Bradycardia
    3. Prolonged capillary refill time
    4. Severe mental depression
    5. Profound muscle weakness
  B. Features increasing the index of suspicion of hypoadrenocorticism
    1. Normal or slow heart rate in the presence of circulatory shock
    2. Previous response to corticosteroid or fluid therapy
    3. Waxing and waning course of disease before collapse

Diagnosis

I. Serum biochemical abnormalities
  A. Classic electrolyte abnormalities: hyponatremia, hyperkalemia, hypochloremia
  B. Sodium: potassium ratios <27:1 suggestive
  C. Prerenal azotemia and hyperphosphatemia
  D. Hypercalcemia in 30% of cases (Peterson and Feinman, 1982)
  E. Metabolic acidosis
  F. Animals with glucocorticoid deficiency only
    1. No classic electrolyte imbalances
    2. Possible hypoglycemia
II. Complete blood count (CBC)
  A. Mild normocytic normochromic (nonregenerative) anemia (masked by dehydration)
  B. The absence of a stress leukogram
    1. Important feature of atypical hypoadrenocorticism
    2. Atypical hypoadrenocorticism likely with increased eosinophil or lymphocyte count
III. Urinalysis
  A. Urine specific gravity is frequently low owing to medullary washout and decreased medullary blood flow.
  B. Hormonal assays are required to differentiate between hypoadrenocorticism and renal failure.
IV. Electrocardiography (ECG) and radiography
  A. ECG findings: prolonged QRS complex, decreased R wave amplitude, increased T wave amplitude ("spiked" T waves), prolonged or absent P waves, heart block, and sinoatrial standstill
  B. Thoracic radiography: microcardia, narrowed vena cava, hypoperfused lungs, rarely megaesophagus
V. Dynamic adrenal testing (Table 45-2)

TABLE 45-1

Clinical Signs and Abnormal Laboratory Findings in Dogs and Cats with Primary Hypoadrenocorticism (Addison's Disease)

	CATS (%) (*n* = 10)	DOGS (%) (*n* = 225)
Clinical Signs		
Lethargy	100	95
Anorexia	100	90
Weight loss	100	50
Dehydration	88	45
Weakness	75	75
Slow capillary refill time	63	30
Weak pulses	50	20
Vomiting	25	75
Polyuria/polydipsia	25	25
Bradycardia	13	18
Diarrhea	—	40
Waxing/waning course	—	40
Previous response to therapy	—	35
Hypothermia	—	35
Shaking	—	27
Melena	—	15
Painful abdomen	—	8
Hair loss	—	5
Laboratory Findings		
Hyperkalemia	100	95
Hyponatremia	100	80
Hypochloremia	100	40
Azotemia	100	85
Hyperphosphatemia	88	85
Metabolic acidosis	—	40
Increased ALT/AST	—	30
Hyperbilirubinemia	—	20
Hypercalcemia	13	30
Hypoglycemia	—	17
Anemia	25	25
Eosinophilia	20	13
Lymphocytosis	38	10
Urine specific gravity < 1.030	—	75

Data from Kintzer PP, Peterson ME: Treatment and long-term follow-up of 205 dogs with hypoadrenocorticism. J Vet Intern Med 11:43, 1997; Peterson ME, Greco DS, Orth DR: Hypoadrenocorticism in ten cats. J Vet Intern Med 3:55, 1989.

ALT, Alanine transaminase; *AST,* aspartate transaminase.

Box 45-1

Comparison of the Clinical Features of Typical and Atypical Hypoadrenocorticism

Typical Hypoadrenocorticism	Atypical Hypoadrenocorticism
Pathogenesis	
Late primary adrenal insufficiency	Early primary adrenal insufficiency
Secondary adrenal insufficiency (ACTH deficiency)	
Signalment	
Young (<5 years)	Young (<5 years)
Dogs: female; cats: either sex	Dogs: female
Standard poodles, Leonbergers	Any breed
Clinical Signs	
Weakness	Anorexia
Lethargy	Lethargy
Depression	Depression
Vomiting	Vomiting
Diarrhea	Chronic diarrhea
Anorexia	Waxing and waning course
Previous response to therapy	Previous response to therapy
Collapse	Hair loss
Shock	
Hypothermia	
Shaking	
Polydipsia/polyuria	
Painful abdomen	
Melena	
Hair loss	
Laboratory Findings	
Lack of stress leukogram	Lack of stress leukogram
Eosinophilia	Eosinophilia
Hyponatrema	Lymphocytosis
Hyperkalemia	Hypoglycemia
Hypochloremia	
Na^+:K^+ ratio < 27	
Azotemia	
Hypercalcemia	
Metabolic acidosis	
Hypoglycemia	
Endocrine Testing	
Decreased cortisol before and after ACTH	Decreased cortisol before and after ACTH
High endogenous ACTH	Secondary: low endogenous ACTH

ACTH, Adrenocorticotropin hormone.

A. With ACTH response test serum samples are obtained before and at 30 minutes (cats) and 1 hour (cats and dogs) after IV administration of synthetic ACTH (cosyntropin 0.5 mg/kg IV, IM).
B. Baseline and post-ACTH cortisol concentrations are usually low or undetectable.

VI. Endogenous plasma ACTH

A. Collect blood in an ethylenediamine tetraacetic acid (EDTA) tube, separate, and store in plastic before the administration of any corticosteroids.
B. Primary hypoadrenocorticism has endogenous ACTH concentrations usually >100 pg/mL as a result of loss of negative feedback to the pituitary gland.

TABLE 45-2

Protocols for Dynamic Adrenal Function Testing in Dogs and Cats

SCREENING TEST	PROTOCOL	NORMAL VALUES
Corticotropin (ACTH) stimulation test		
Cosyntropin	Dog: 0.5 U/kg aqueous corticotropin IV, IM Serum samples at 0 and 1 hr Cat: 1/2 vial aqueous corticotropin IV, IM Serum samples at 0, 30, 60 min	Pre: 1-4 µg/dL (28-110 nmol/L) Post-ACTH: <20 µg/dL (550 nmol/L)
ACTH gel*	2.2 U/kg corticotropin gel IM (max 20 U in dog) Serum samples at 0 and 2 hr in dog Serum samples at 0, 1, 2 hr in cat	Same as for Cosyntropin
Endogenous ACTH	Single plasma sample (may be collected before screening test and frozen for later analysis) Collect in EDTA Vacutainer (with aprotinin) Centrifuge and store in plastic Ship at 4° C (or frozen if not collected in aprotinin)	20-80 pg/mL (4.4-17.6 pmol/L)

ACTH, Adrenocorticotropic hormone; *max,* maximum; *EDTA,* ethylenediamine tetraacetic acid.

*Efficacy of compounded gels vary (Kemppainen RJ, Behrend EN, Busch KA: Use of compounded adrenocorticotropin hormone (ACTH) for adrenal function testing in dogs. J Am Anim Hosp Assoc 41:368, 2005).

C. Secondary hypoadrenocorticism demonstrates the following:
   1. Decreased endogenous ACTH concentrations (<20 pg/mL)
   2. Diminished exogenous ACTH response
   3. Possibly normal baseline cortisol and post-ACTH cortisol concentrations

Differential Diagnosis

I. Inflammatory bowel disease
II. Intestinal parasitism: *Trichuris vulpis*
III. Bilious vomiting syndrome
IV. Acute renal failure
V. Other causes of hypercalcemia
VI. Postrenal azotemia

Treatment

I. Therapy of acute adrenal crisis
   A. Fluid therapy and stabilization of electrolytes with 0.9% NaCl at shock doses (see Chapter 132)
   B. Glucocorticoid replacement
      1. Dexamethasone sodium phosphate 2 to 4 mg/kg IV (no interference with the cortisol assay)
      2. Prednisolone sodium succinate 15 to 20 mg/kg IV
   C. Correction of life-threatening hyperkalemia
      1. Regular insulin (0.06 to 0.12 U/kg IV) and glucose (4 mL of 50% dextrose/unit insulin IV)
      2. 10% calcium gluconate 0.4 to 1.0 mL/kg IV over 10 to 20 minutes; maximum 10 mL
   D. Prevention and treatment of GI hemorrhage
      1. Treat shock aggressively, because GI hemorrhage occurs after poor intestinal perfusion.
      2. Treatment includes blood transfusion and GI protectants, such as sucralfate 0.5 to 1 g/25 kg PO TID to QID (dogs).
   E. Correction of metabolic acidosis
      1. Metabolic acidosis often resolves after fluid therapy.
      2. Severe acidosis (pH <7.1) is treated with sodium bicarbonate 0.5 mEq/kg IV for 1 to 2 doses.
   F. Treatment of any hypoglycemia: slow IV bolus of 50% dextrose (0.5 to 1.0 mL/kg)
II. Maintenance therapy
   A. Mineralocorticoid supplementation
      1. Oral fludrocortisone acetate 0.02 mg/kg PO SID
      2. Desoxycorticosterone pivalate (DOCP) 1.5 to 2.2 mg/kg IM, SC every 25 days
   B. Prednisone supplementation (0.22 mg/kg) with DOCP
      1. Administer 0.2 to 0.4 mg/kg PO SID to QOD to dogs on fludrocortisone.
      2. When DOCP is used, give 50% of prednisone dose required by fludrocortisone-treated dogs.
      3. Provide additional prednisone (double dose) during periods of stress.
   C. Injectable medication for affected cats
      1. Methylprednisolone acetate (Depo-Medrol) 10 mg IM every 3 to 4 weeks
      2. DOCP 12.5 mg IM every 3 to 4 weeks

Monitoring of Animal

I. Measure serum electrolytes every 3 weeks until optimum dosage and interval of administration are determined.
II. DOCP injections are usually required every 25 to 40 days in dogs, and every 30 days in cats.
III. Serum potassium often remains slightly elevated (4.5 to 5.2 mEq/L) in clinically controlled animals.

HYPERADRENOCORTICISM

Definition

The clinical syndrome of hyperadrenocorticism, or Cushing's syndrome, arises with chronic and/or excessive exposure to glucocorticoids.

Causes and Pathophysiology

I. Pituitary-dependent hyperadrenocorticism (PDH) (Feldman and Nelson, 1996)
   A. Approximately 85% of affected dogs and 90% of affected cats have PDH.
   B. Pituitary microadenomas (70%) and macroadenomas (30%) cause excessive endogenous ACTH secretion, with secondary adrenal hyperplasia.
II. Adrenal tumors (Feldman and Nelson, 1996)
   A. Approximately 15% of animals with hyperadrenocorticism have adrenal tumors.
   B. Of those tumors, 50% are malignant.
III. Iatrogenic hyperadrenocorticism
   A. Prolonged or excessive glucocorticoid administration
   B. Results in chronic negative feedback to the pituitary, decreased endogenous ACTH, and secondary adrenal atrophy

Clinical Signs

I. Signalment
   A. Middle-aged to older dogs or cats (7 to 12 years)
   B. PDH: miniature poodle, dachshund, boxer, Boston terrier, beagle
   C. Adrenal tumors: large-breed dogs, female (3:1) predilection
II. Common historical and clinical signs
   A. PU/PD
   B. Polyphagia, pica
   C. Heat intolerance, panting
   D. Lethargy, muscle weakness
   E. Obesity, abdominal enlargement or "pot belly" appearance
   F. Recurrent urinary tract infections
   G. Cutaneous manifestations (see Chapter 87)
III. Uncommon clinical manifestations of hyperadrenocorticism
   A. Hypertension
   B. Pulmonary thromboembolism
   C. Testicular atrophy in males, clitoral hypertrophy in females
   D. Congestive heart failure
   E. Prostatomegaly in castrated male dogs
   F. Perianal adenoma in a female or castrated male dog
   G. Bronchial calcification
   H. Corneal ulceration (nonhealing)
   I. Cranial cruciate rupture (small dog)
   J. Blindness
   K. Behavior changes: "steroid rage" in cats
   L. Pseudomyotonia
   M. Polyneuropathy and myopathy

Diagnosis

I. Minimum database
   A. Serum biochemistry profile
      1. Increased serum alkaline phosphatase (SAP), usually >1000 IU/L (except in cats)
      2. Increased alanine transaminase
      3. Hypercholesterolemia
      4. Hyperglycemia
      5. Decreased blood urea nitrogen
   B. CBC changes
      1. Nucleated red blood cells
      2. Erythrocytosis
      3. Stress leukogram
      4. Basophilia
   C. Urinalysis findings
      1. Bacteriuria without pyuria
      2. ± Glycosuria
      3. Hyposthenuria or minimally concentrated urine
      4. ± Proteinuria
II. Screening tests (Table 45-3)
   A. Low-dose dexamethasone suppression (LDDS) test
      1. The LDDS is an extremely sensitive test (92% to 95%) (Feldman, 1983a).
      2. Only 5% to 8% of dogs with PDH exhibit suppressed cortisol concentrations at 8 hours (i.e., 5% to 10% false negatives).
      3. Some (30%) dogs with PDH exhibit suppression at 3 to 4 hours, followed by "escape" of suppression at 8 hours; this pattern is diagnostic for PDH, and makes further testing unnecessary.
      4. The major disadvantage of the LDDS test is the lack of specificity in dogs with nonadrenal illness; over 50% of dogs with nonadrenal illness have a positive LDDS test (Box 45-2) (Kaplan and Peterson, 1995).
   B. Modified high-dose dexamethasone suppression (HDDS) test
      1. Dexamethasone 0.1 mg/kg IV
      2. Used to screen cats for hyperadrenocorticism
   C. ACTH (corticotropin) stimulation test
      1. ACTH stimulation test has a sensitivity of approximately 80% to 85% for the diagnosis of naturally occurring hyperadrenocorticism (Peterson et al., 1982).
      2. Specificity is higher than the LDDS test, and only 15% of dogs with nonadrenal disease showed an exaggerated response to ACTH stimulation.
      3. Adrenal tumors are difficult to diagnose using the ACTH stimulation test.
      4. Cortisol samples are collected at 30 and 60 minutes post-ACTH injection in cats.
   D. Urine cortisol: creatinine ratio (UCCR)
      1. The UCCR is a highly sensitive (99%) screening test with few false-negative results (Feldman and Mack, 1992; Mack et al., 1994).
      2. The test is not specific for hyperadrenocorticism, because dogs with moderate to severe nonadrenal illness may also have elevated ratios.

TABLE 45-3

Protocols for Screening and Differentiation Tests for Hyperadrenocorticism

	PROTOCOL	NORMAL VALUES
Screening Tests		
Low-dose dexamethasone suppression test	1. 0.015 mg/kg dexamethasone solution *(Azium)* IV, IM 2. 0.01 mg/kg dexamethasone sodium phosphate IV Samples at 0, 3-4 and 8 hr	Pre: 1-4 µg/dL (28-110 nmol/L) 3 hr: < 1.5 µg/dL (40 nmol/L) 8 hr: < 1.5 µg/dL (40 nmol/L)
Corticotropin (ACTH) stimulation test	1. 0.5 U/kg aqueous corticotropin IV Samples at 0 and 1 hr 2. 2.2 U/kg corticotropin gel IM (max 20 U in dogs) Samples at 0 and 2 hr	Pre: 1-4 µg/dL (28-110 nmol/L) Post-ACTH: <20 µg/dL (550 nmol/L)
Urine cortisol: creatinine ratio	Single urine sample, voided or collected by cystocentesis	Dependent on laboratory
Alkaline phosphatase isoenzyme	Single serum sample SAP should be at least 2-3 times greater than normal	< 150 U/L
Differentiation Tests		
High-dose dexamethasone suppression test	1. 1 mg/kg dexamethasone sodium IV 2. 0.1 mg/kg dexamethasone sodium phosphate IV Samples at 0 and 8 hr	Suppression to < 1.5 µg/dL (40 nmol/L) at 8 hr
Endogenous ACTH	Single plasma sample (may be collected before screening test and frozen for later analysis) Collect in EDTA Vacutainer (with aprotinin) Centrifuge and store in plastic Ship at 4° C (or frozen if not collected in aprotinin)	20-80 pg/mL (4.4-17.6 pmol/L)

ACTH, Adrenocorticotropin; *max,* maximum; *SAP,* serum alkaline phosphatase; *EDTA,* ethylenediamine tetraacetic acid.

3. Collect three samples at home to decrease the probability of stress-associated false-positive results.
4. An increased UCCR is followed by an ACTH stimulation test or an LDDS test.

E. SAP isoenzyme
1. Advantages of SAP isoenzyme determination: wide availability, low cost
2. Disadvantages
   a. Elevations possibly induced by small amounts of exogenous steroids (e.g., ocular preparations)
   b. Low specificity (<44%)
   c. Affected by stress and nonadrenal diseases
   d. Questionable quality of some assays
   e. No differentiation between endogenous and iatrogenic hyperadrenocorticism

F. Dogs suffering from adrenal sex steroid excess may have negative ACTH stimulation and LDDS tests because serum cortisol concentrations are normal.
1. Excessive cortisol precursors may be present.
2. Increases in progesterone, 17-OH-progesterone, androstenedione, testosterone, and estrogens may require dynamic adrenal testing using the ACTH stimulation test and measurement of sex steroids (in addition to cortisol).

III. Differentiation tests (see Table 45-3)

A. HDDS
1. ACTH secretion is suppressed maximally in dogs with functioning adrenal tumors; therefore, serum cortisol concentrations remain elevated.
2. In dogs with PDH, high doses of dexamethasone suppress ACTH and cortisol secretion.
3. Some animals with pituitary macroadenomas (15% to 50% of dogs with PDH) do not suppress on the HDDS test (Mack and Feldman, 1990).

B. Endogenous plasma ACTH concentrations
1. Reliable method of discriminating between PDH and adrenal tumors
2. Tumors: low to undetectable ACTH concentrations
3. PDH: normal to elevated ACTH concentrations

C. Diagnostic imaging of the pituitary and/or the adrenal glands
1. Survey radiographs of 30% to 50% of dogs with adrenal tumors show a mineralized adrenal mass (Pennick et al., 1988).
2. Abdominal ultrasonography is a more sensitive method of identifying tumors, liver metastasis, or vena caval invasion.
3. Abdominal ultrasonography helps to identify adrenomegaly in dogs with PDH.
4. Computed tomography and/or magnetic resonance imaging of the brain and/or abdominal cavity may demonstrate unilateral or bilateral adrenal enlargement and pituitary adenomas (Box 45-3).

Differential Diagnosis

I. Cutaneous lesions (see Chapter 87)
A. Hypothyroidism
B. Adrenal sex steroid excess

Box 45-2

Comparison of Screening Tests for Hyperadrenocorticism

Advantages	Disadvantages
Low-Dose Dexamethasone Suppression Test	
Easy to perform	Lower specificity than ACTH stimulation, especially in stressed dogs (56% false positives)
Reliable	Requires 8 hours of testing
High sensitivity (92% to 95%)	Three samples required
May be diagnostic for PDH if suppression and escape are noted	
Corticotropin Stimulation Test	
Easy to perform, reliable	Lower sensitivity overall than LDDS (85%), especially for AT (50% to 60%)
Higher specificity that LDDS (85%)	Laboratory variation in normal range
Fewer serum samples required	Does not differentiate PDH from AT
Hospitalization not required	
1- or 2-hour test	
Differentiates iatrogenic versus endogenous hyperadrenocorticism	
Provides baseline for therapy	
Urine Cortisol:Creatine Ratio	
Highly sensitive	Low specificity (24%)
Single voided urine sample	Must confirm positive result with an LDDS or ACTH stimulation test
Increased convenience to owner	
Decreased cost: single sample	
Alkaline Phosphate Isoenzyme	
Widely available	Not diagnostic for iatrogenic hyperadrenocorticism
Inexpensive	Affected by stress
Single serum sample	Confirm with LDDS or ACTH stimulation
	Questionable results on some assays

PDH, Pituitary-dependent hyperadrenocorticism; *ACTH*, adrenocorticotropic hormone; *LDDS*, low-dose dexamethasone suppression test; *AT*, adrenal tumor.

Box 45-3

Comparison of Tests and Techniques for Differentiation of Pituitary versus Adrenal Hyperadrenocorticism

Advantages	Disadvantages
High-dose Dexamethasone Suppression Test	
Does not require special facilities	Inconvenient
Inexpensive	8-hour sampling period
	Pituitary macroadenomas may not suppress
Endogenous Adrenocorticotropin Measurement	
Single plasma sample	Expensive
May be collected before screening tests and frozen for later analysis	Analysis restricted to certain laboratories
More reliable than HDDS	Special handling required
Ultrasonography of Adrenals	
Differentiates tumors from PDH	Requires adequate equipment
Noninvasive	Requires skilled ultrasonographer
Relatively inexpensive and widely available	
Computed Tomography/Magnetic Resonance Imaging	
Noninvasive	Expensive
Identifies pituitary tumor	Requires sophisticated equipment
Estimates size of tumor	Not universally available

HDDS, High-dose dexamethasone suppression test; *PDH*, pituitary-dependent hyperadrenocorticism.

C. Growth hormone deficiency

II. PU/PD
- A. Renal disease
- B. Liver disease
- C. Pyometra
- D. Hypoadrenocorticism
- E. Hypercalcemia
- F. Diabetes mellitus
- G. Diabetes insipidus: central, nephrogenic

Treatment and Monitoring

I. Mitotane *(Lysodren)* for PDH
- A. Normal induction protocol
  1. Dosage is 25 to 50 mg/kg/day PO for 5 to 10 days.
  2. Monitor appetite and water consumption.
  3. Discontinue if adverse effects occur (e.g., vomiting, anorexia, weakness).
  4. Assess effectiveness using ACTH stimulation tests (Figure 45-1).
- B. Production of hypoadrenocorticism
  1. Mitotane 50 mg/kg/day PO for 30 days causes complete destruction of the adrenal cortex; then the animal is managed as an Addisonian case.
  2. Physiological doses of prednisolone at 0.2 mg/kg day PO SID are subsequently given.
- C. Slow induction protocol
  1. For cases with dermatological conditions only
  2. Low dose of mitotane 25 mg/kg PO weekly for 1 month
- D. Monitor mitotane therapy with ACTH response tests
  1. Goal is for post-ACTH cortisol concentrations to be in the normal range (1 to 5 μg/dL, or 25 to 150 nmol/L)
  2. Measure at termination of the induction period (7 to 10 days).
  3. Monitor electrolytes weekly for evidence of mineralocorticoid deficiency (hypoadrenocorticism).
  4. Measure at the end of 1 month if the reduced dosage protocol is used.
- E. Maintenance therapy

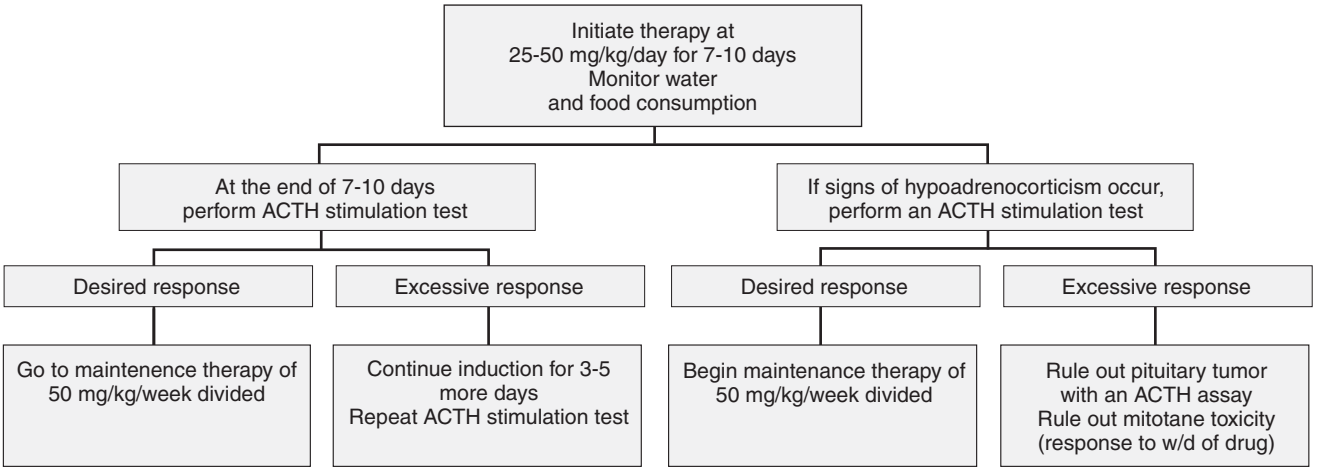

FIGURE 45-1 Outline for the treatment of hyperadrenocorticism with oral mitotane. *ACTH,* Adrenocorticotropic hormone; *w/d,* withdrawal.

1. Mitotane 50 mg/kg/wk PO is divided into two doses, 3 to 4 days apart.
2. ACTH stimulation tests are performed every 4 months.
3. Relapses are common within 12 months of initiating maintenance therapy.

F. Prolonged effects
1. Mitotane causes adrenal necrosis and effects persist for several days.
2. Withdrawal does not result in immediate improvement of side effects.

II. Trilostane

A. It is a competitive 3β-hydroxysteroid dehydrogenase inhibitor that affects both the production of glucocorticoids and aldosterone.
B. Duration of effect is approximately 20 hours in the dog, which is a major advantage in comparison to mitotane.
C. It has been used primarily for PDH, but it has also been used in a few dogs with functional adrenal tumors (Eastwood et al., 2001, 2003).
D. Some dogs respond to once daily administration.
1. Starting dose is 6 mg/kg PO SID.
2. ACTH response tests are performed 4 to 6 hours after administration, which is thought to be the time of peak activity.
3. Goal for post-ACTH cortisol concentrations is 1 to 5 μg/dL (Alenza et al., 2006).

E. Some dogs do better on twice-daily administration.
1. Clinical signs persist in some dogs on SID therapy, probably because cortisol values rise toward the end of the day.
2. Starting dose is 3 mg/kg PO BID.
3. ACTH response tests are performed 8 to 12 hours post-pill to evaluate the drug's duration and effects on cortisol reserves (Alenza et al., 2006).
4. Goal for post-ACTH cortisol concentrations is 2 to 10 μg/dL (Alenza et al., 2006).
5. Yorkshire terriers may require higher doses (Alenza et al., 2006).
6. Although BID administration is more expensive, side effects may be fewer.

F. ACTH response tests are performed 7 days, and 1, 3, and 6 months (or as needed) after starting therapy and dosage adjustments (Alenza et al., 2006).
G. Because of its inhibition of aldosterone synthesis, hyperkalemia is a common side effect, and electrolytes must be monitored in addition to ACTH response tests.
H. Other adverse effects include rare cases of acute death and prolonged hypoadrenocorticism (Eastwood and Elwood, 2003).

III. Ketoconazole

A. Ketoconazole is a steroid inhibitor with a transient effect in dogs.
B. Initial dosage is 7.5 mg/kg PO BID.
C. Increase dose slowly (over 3 weeks) to 15 mg/kg PO BID.
D. Ketoconazole is not often used, owing to its expense and possible severe anorexia.
E. Use is primarily before surgical adrenalectomy or radiation therapy.
F. Goal is for post-ACTH cortisol concentrations of 1 to 5 μg/dL (25 to 150 nmol/L).

IV. L-Deprenyl *(Anipryl)*

A. Monoamine oxidase B inhibitor that increases hypothalamic dopamine concentrations
B. Initial dosage: 1 mg/kg/day PO
C. Used for PDH only; questionable effectiveness
D. Indications
1. Mild hyperadrenocorticism: skin disease only
2. Intolerance to other therapies

E. Laboratory monitoring unnecessary
1. ACTH response tests do not return to normal.
2. Use clinical response as a guide to therapy.

V. Surgical therapy

A. Surgical treatment consists of unilateral (dogs with unilateral tumors) or bilateral (cats with PDH) adrenalectomy (Anderson et al., 2001).

B. Medical management during the intra- and postoperative periods is critical.
C. Mineralocorticoid (DOCP 2.2 mg/kg IM, SC every 25 days) and glucocorticoid (prednisone 0.2 mg/kg/day PO) supplementation are initiated immediately after adrenalectomy.
D. Complications following adrenalectomy are as follows:
1. Dehiscence, poor wound healing
2. Addisonian crisis
3. Pituitary tumor enlargement with subsequent blindness or seizures (Nelson's syndrome)

VI. Radiation therapy of pituitary tumors
A. Effective method of treatment with low morbidity
B. Requires several months for PDH to subside
C. Expensive and time consuming (3 weeks)
D. Good long-term results

PHEOCHROMOCYTOMA

Definition and Cause

I. Pheochromocytoma is a tumor arising from chromaffin cells of the adrenal medulla that hypersecretes catecholamines.
II. Actual cause of the tumor is unknown.

Pathophysiology

I. Cats secrete predominantly norepinephrine; dogs secrete primarily epinephrine from the adrenal medulla.
II. Clinical signs result from overproduction of catecholamines and from direct invasion of adjacent organs and structures.
III. This tumor is uncommon in dogs and extremely rare in cats.

Clinical Signs and Diagnosis

I. Signalment (Feldman and Nelson, 1996)
A. Older dogs (mean age = 11 years)
B. No sex predilection
C. Boxers, miniature poodles, and German shepherd dogs predisposed

II. Historical findings
A. Signs may be chronic (present for >1 year) or acute (often fatal).
B. Thirty percent are identified at necropsy (Feldman and Nelson, 1996).
C. Signs include dyspnea, whining, shaking, shivering, and pacing.
D. Signs may be constant or paroxysmal.

III. Physical examination findings
A. Tachyarrhythmias, weakness, systolic murmur
B. ± Rales from pulmonary edema
C. Possible weight loss secondary to hypermetabolism
D. Ascites, edema, abdominal mass and pain from the tumor, local metastases, or both
E. Anorexia, vomiting, weight loss, diarrhea
F. Hypertension from α_1-mediated increased peripheral vascular resistance
G. Epistaxis, pale mucous membranes, blindness, and hyperemic mucous membranes from hypertension

IV. Clinical pathology
A. CBC: nonregenerative anemia, hemoconcentration, leukocytosis
B. Serum biochemistries
1. Mild hyperglycemia, carbohydrate intolerance, and occasionally overt diabetes mellitus may occur from stimulation of hepatic glycogenolysis and gluconeogenesis, inhibition of insulin secretion, and peripheral insulin resistance.
2. Other possible laboratory abnormalities include mild uremia, increased liver enzyme activity, hypoalbuminemia, and hypocalcemia.
C. Proteinuria: variable

V. Radiographic and ultrasonographic findings
A. Presence of abdominal mass on plain radiography: 30% of cases (Feldman and Nelson, 1996)
B. Ultrasonography superior to radiography for identification of adrenal glands
C. Calcification of adrenal mass
D. Abnormal renal contour, displacement
E. Generalized cardiomegaly
F. Possibly pulmonary edema

VI. Arterial blood pressures
A. Normal canine values
1. Systolic: 148 ± 16 mm Hg (unstressed)
2. Diastolic: 87 ± 8 mm Hg
3. Mean: 102 ± 9 mm Hg
B. Hypertension: systolic >180 or diastolic >95 mm Hg in a nonazotemic, relaxed dog
C. Detectable hypertension in only 50%, owing to the episodic secretion of some tumors (Feldman and Nelson, 1996)

VII. Other diagnostic testing
A. Plasma catecholamines levels >2000 pg/mL are diagnostic.
B. On a clonidine suppression test, clonidine suppresses catecholamine levels in normal animals, but not in those with pheochromocytomas (see Chapter 2).
C. Total excretion of urinary catecholamine and catecholamine metabolites for 24 hours may be determined.
1. Normal vanillylmandelic acid: <7.0 mg/day
2. Normal metanephrine/normetanephrine: <1.3 mg/day
3. Normal total urinary catecholamines: <250 mg/day

Treatment

I. Surgical removal of tumor
A. It is the treatment of choice but is technically demanding.
B. Metastasis is present in 33% of cases at the time of surgery (Feldman and Nelson, 1996).

II. Anesthetic management
A. Phenoxybenzamine 0.2 to 1.5 mg/kg PO BID for 1 to 2 weeks before surgery
B. Propranolol 0.15 mg/kg PO TID, for tachycardia and severe hypertension, with phenoxybenzamine

C. Drugs to avoid: phenothiazines (hypotension), atropine (tachycardia), barbiturates for induction (arrhythmias), halothane (arrhythmias)

III. Medical, palliative therapy
   A. Phenoxybenzamine 0.2 to 1.5 mg/kg PO BID
   B. Addition of propranolol for tachyarrhythmias

Monitoring of Animal

I. If hypertension does not resolve with excision of the mass, suspect an additional tumor.
II. In general, prognosis is fair to poor owing to difficulties commonly associated with surgery and the likelihood of metastases.

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CHAPTER 46

Miscellaneous Endocrine Disorders

Stephanie A. Smith

HYPERLIPIDEMIA

Definition

I. Hyperlipidemia is an increased level of lipid in the blood and is only physiologically relevant when it occurs in the fasted state.
   A. *Hypertriglyceridemia* is defined as a triglyceride concentration >150 mg/dL in dogs and >100 mg/dL in cats.
   B. *Hypercholesterolemia* is defined as a cholesterol concentration >300 mg/dL in dogs and >200 mg/dL in cats.
   C. *Hyperchylomicronemia* is defined as an excessive concentration of chylomicrons (see later).

II. Visible lipemia is apparent when triglycerides are >400 mg/dL and the resulting opacity interferes with various laboratory evaluations, depending on the method used.
   A. Total solids via refractometer: falsely increased
   B. Albumin and bilirubin: falsely increased
   C. Bile acids, alkaline phosphatase, alanine transaminase, and aspartate transaminase: ± erroneously increased
   D. Sodium: falsely decreased
   E. Amylase: falsely decreased
   F. Mean corpuscular hemoglobin (MCH) concentration: falsely increased (possibly marked)
   G. Also causes in vitro hemolysis

Causes and Pathophysiology

I. Normal lipid metabolism
   A. Lipids are water insoluble and are transported in the blood by lipid-protein complexes.
   B. Types of lipoproteins include the following:
      1. Chylomicrons, which are formed in intestines and hydrolyzed in the circulation to triglyceride (available for tissue use and storage) and cholesteryl-ester remnants (taken up by the liver)
      2. Very-low-density lipoproteins, which are synthesized in the liver and transport endogenous triglyceride to muscles or fat
      3. Low-density lipoproteins, which are formed in the circulation and transport cholesterol to tissues
      4. High-density lipoproteins, which are the major cholesterol carrier in dogs and cats
         a. Synthesized in the intestine and liver
         b. Transport excess cholesterol to the liver for biliary excretion

II. Relationship of hyperlipidemia to diet
   A. Postprandial
      1. Persistent hyperchylomicronemia up to 12 hours after a meal
      2. Most common cause of lipemia
   B. Diet type
      1. In normal animals: fasting hyperlipidemia possible with extremely high dietary fat content (>55%)
      2. Hypertriglyceridemia or hypercholesterolemia also possible

III. Secondary hyperlipidemia: see Table 46-1

IV. Primary hyperlipidemia associated with inherited metabolic abnormalities: see Table 46-2

Clinical Signs

I. Clinical signs with secondary hyperlipidemia
   A. Signs associated with hypertriglyceridemia
      1. Abdominal pain or discomfort: chronic, acute, or episodic
      2. Possible seizures with marked hypertriglyceridemia
      3. Nonspecific gastrointestinal (GI) signs: vomiting, diarrhea, lethargy, anorexia
      4. Visible lipemia of the vessels of the bulbar conjunctiva, episclera, and retina (lipemia retinalis)
      5. Lipid deposition in abnormal locations
         a. Cutaneous xanthomas: deposits in macrophages forming granulomas
         b. Arcus lipoides: corneal lipid deposits
         c. Lipemic aqueous: lipid in the aqueous humor
   B. Signs from hypercholesterolemia
      1. Atherosclerosis with accompanying thrombosis and/or loss of vascular supply, seen particularly with hypothyroidism and diabetes mellitus
      2. Arcus lipoides

II. Signs possible with primary hyperlipidemia
   A. Idiopathic schnauzer hyperlipidemia
      1. May be clinically asymptomatic
      2. Nonspecific signs of discomfort or GI disturbances, similar to secondary hypertriglyceridemia
      3. Possible polydipsia
      4. Acute pancreatitis as a secondary complication (not well documented but suspected)
   B. Briard hypercholesterolemia: usually no clinical signs

TABLE 46-1

Causes of Secondary Hyperlipidemia

DISORDER	HYPERCHOLESTEROLEMIA	HYPERTRIGLYCERIDEMIA	PATHOGENESIS	NOTES	SEE CHAPTER
Hypothyroidism	Occurs in 2/3 canine cases Degree: mild to marked	Possible Degree: mild	Not clearly defined	Possible atherosclerosis if cholesterol > 750 mg/dL	42
Diabetes mellitus	Possible Degree: mild to moderate	Common Degree: may be marked	Increase fatty acid mobilization from peripheral fat stores causing increased hepatic VLDL synthesis Decreased production of lipoprotein lipase as a result of hypoinsulinemia	Possible atherosclerosis	44
Pancreatitis	Possible Degree: mild	Common Degree: mild to marked	Likely caused by decreased lipoprotein lipase excretion from the pancreas, or inhibition of lipoprotein lipase by inflammatory mediators	Hyperlipidemia or impaired lipid metabolism may be the cause of pancreatitis in some animals, rather than an effect of pancreatitis (speculative)	36
Hyperadrenocorticism	Common Degree: mild to marked	Possible Degree: mild	Peripheral insulin resistance induced by hypercortisolemia Peripheral lipolysis stimulated by glucocorticoids	Not generally associated with atherosclerosis	45
Cholestatic hepatic disease	In some cases	Not present	Decreased cholesterol excretion through the biliary tract Increased cholesterol synthesis possible in some biliary diseases		37
Nephrotic syndrome	Common	Not present	Likely associated with decreased lipoprotein lipase activity resulting from any of the following: • Production of an inhibitor substance • Renal secondary hyperparathyroidism suppressing insulin release • Changes in apolipoprotein synthesis and release		48
Drugs: Glucocorticoids Progestogens			Decreased lipoprotein lipase activity through insulin antagonism Iatrogenic or associated with diestrus in the bitch Progesterones also increase growth hormone secretion, which has an antiinsulin effect	Megestrol acetate, particularly in cats	

VLDL, Very low density lipoproteins.

TABLE 46-2

Primary Hyperlipidemia Associated with Inherited Metabolic Abnormalities

DISORDER	REPORTED BREEDS	TYPE OF HYPERLIPIDEMIA	ADVERSE EFFECTS	NOTES
Idiopathic hyperlipidemia	Frequent in miniature schnauzers Occasionally in beagles and Shetland sheepdogs	Marked hypertriglyceridemia Cholesterol usually normal or mildly elevated, rarely markedly elevated	May be associated with increased risk for pancreatitis	
Hypercholesterolemia	Briards Rough collie (one family)	Triglycerides normal Cholesterol elevated	Not associated with any pathologic accumulation of cholesterol May be linked to development of retinal pigment epithelial dystrophy in the briard Corneal lipidosis in the collie	Likely caused by increased apoprotein E containing high-density lipoprotein
Hyperchylomicronemia	Domestic cats (20 related cats in New Zealand) Sporadic in some breeds and domestic cats Single 4-week-old mixed-breed puppy Two related Brittany spaniels	Fasting lipemia, hypertriglyceridemia, and hypercholesterolemia	Lipid deposition in eye Lipid granulomas in abdomen and skin Peripheral neuropathies	Suspected autosomal recessive inheritance causing deficient lipoprotein lipase activity Affected cats may not show signs until maturity

C. Rough collie hypercholesterolemia: may be associated with corneal lipidosis
D. Inherited hyperchylomicronemia
   1. Inappropriate lipid deposition in skin, eye, and other soft tissues
   2. Peripheral neuropathies (Horner's syndrome, radial or tibial palsy) owing to nearby compression from xanthomas

Diagnosis and Differential Diagnosis

I. Postprandial hyperlipidemia
   A. Confirmed by evaluating triglyceride and cholesterol levels following a ≥12-hour fast
   B. Duration of fast important
II. Secondary hyperlipidemia
   A. History of signs suggestive of underlying disease process
   B. Minimum database
      1. Complete blood count (CBC)
      2. Serum biochemistry panel with pancreatic enzymes
      3. Urinalysis (UA)
   C. Additional tests to consider
      1. Total thyroxine (thyroid concentration) ± other thyroid testing (see Chapter 42)
      2. Adrenocorticotropin (ACTH) stimulation or dexamethasone suppression test (see Chapter 45)
      3. Urine protein: creatinine ratio if proteinuric (see Chapter 48)
      4. For suspected pancreatic disease: abdominal ultrasonography, possibly pancreatic lipase immunoreactivity (cPLI)
      5. For suspected cholestatic liver disease and/or bile duct obstruction (icteric animal): abdominal ultrasonography
III. Primary hyperlipidemia
   A. Exclude all causes of secondary hyperlipidemia.
   B. Measure fasting serum triglycerides and cholesterol.
   C. Consider lipoprotein electrophoresis for further characterization of idiopathic schnauzer hyperlipidemia and inherited chylomicronemia.
   D. No further testing needed for hypercholesterolemia of briard or rough collies.

Treatment

I. Secondary hyperlipidemia
   A. Manage any diagnosed underlying disorder.
   B. Provide nutritional support by selecting a fat-restricted enteral or parenteral diet.
II. Primary hyperlipidemia
   A. Intervention is indicated when hyperlipidemia is associated with clinical signs.

TABLE 46-3

Fat-Restricted Commercial Pet Foods

	% kcal FROM FAT
Canine Diets	
Canned Hill's Prescription Diet w/d	31.0
Canned Purina CNM-OM	28.1
Dry Iams Less Active	28.0
Dry Purina ProPlan Reduced Calorie	24.1
Dry Hill's Prescription Diet r/d	24.0
Canned Hill's Prescription Diet r/d	24.0
Canned Iams Less Active	23.1
Dry Hill's Prescription Diet w/d	23.0
Dry Eukanuba Reduced Fat Formula	23.0
Dry Waltham/Pedigree Calorie Control	22.7
Canned Hill's Science Diet Maintenance Light	22.0
Dry Purina One Reduced Calorie	20.4
Dry Purina CNM-OM	17.7
Dry Purina Fit and Trim	17.4
Dry Eukanuba Restricted Calorie	15.0
Feline Diets	
Canned Hill's Prescription Diet w/d	38.0
Dry Iams Less Active	29.0
Canned Hill's Prescription Diet r/d	24.0
Dry Hill's Prescription Diet r/d	24.0
Dry Purina ProPlan Reduced Calorie	23.4
Dry Hill's Prescription Diet w/d	23.0
Dry Eukanuba Restricted Calorie	23.0
Dry Hill's Science Diet Maintenance Light	22.0

B. Dietary management with fat restriction is the mainstay of treatment.
   1. Keep fasting triglyceride <500 mg/dL and cholesterol <400 mg/dL.
   2. See Table 46-3 for fat-restricted diet information.
C. Lipid-lowering drugs have not been well evaluated in the dog and cat, and are used with caution.
   1. Dogs: gemfibrozil 200 mg/day PO
   2. Dogs: niacin 100 mg/day PO
   3. Dogs: fish oil (eicosapentaenoic, docosahexaenoic acid) 200 mg/kg/day PO

Monitoring of Animal

I. Secondary hyperlipidemia
   A. Most secondary hyperlipidemias resolve with proper management of the primary disorder.
   B. Reevaluate for lipemia once the underlying disease is well controlled, and consider instituting dietary fat restriction if needed.
II. Primary hyperlipidemia
   A. Evaluate fasting serum triglycerides and cholesterol 4 to 6 weeks after dietary change and every 3 to 4 months thereafter.
   B. Primary disorders are much more difficult to treat.

ERYTHROPOIETIN ABNORMALITIES

Definition

I. Erythropoietin (EPO) is a glycoprotein produced by renal interstitial cells that stimulates red blood cell (RBC) production in the bone marrow.
II. Abnormal EPO concentrations cause abnormal circulating RBC mass.

Causes and Pathophysiology

I. Decreased EPO production
   A. Chronic renal failure
      1. As senescent RBCs are removed from the circulation, renal hypoxia triggers EPO production.
      2. Nephron loss prevents adequate response to decreasing RBC mass, resulting in gradual development of anemia.
   B. Polycythemia vera (primary polycythemia)
      1. Myeloproliferative disease with clonal proliferation of erythroid progenitors leads to increased peripheral RBC mass.
      2. Marrow production of RBCs is autonomous and not subject to EPO-negative feedback.
      3. EPO production is appropriately decreased.
II. Appropriately increased EPO production from renal stimulus
   A. Decreased renal perfusion associated with aberrant renal blood vasculature or compression of blood flow
      1. Renal neoplasia
      2. Parenchymal disease
         a. Cystic kidneys: polycystic or single renal cysts
         b. Hydronephrosis
      3. Congenital abnormality of renal vasculature
      4. Compressive neoplasm
      5. Thrombus obstructing renal arterial flow
   B. Decreased renal oxygen delivery
      1. Anemia
      2. Hemoglobinopathy
   C. Hypoxemia (decreased blood oxygen)
      1. Right-to-left cardiovascular shunting, particularly reversed patent ductus arteriosus
      2. Chronic pulmonary disease
      3. High altitudes: decreased inspired oxygen content
      4. Hypothalamic disease: depressed respiration
III. Autonomous secretion of EPO or EPO-like substances by tumors
   A. Renal neoplasia
      1. Lymphosarcoma
      2. Renal carcinoma
   B. Extrarenal neoplasia (paraneoplastic effect)
      1. Hepatoma
      2. Uterine or cecal leiomyosarcoma
      3. Ovarian carcinoma
      4. Nasal fibrosarcoma
      5. Pheochromocytoma and other adrenal tumors
      6. Granular cell tumor
      7. Schwannoma

Clinical Signs

I. Anemia and decreased tissue oxygen delivery: weakness, collapse, exercise intolerance, pallor, ± soft heart murmur (see Chapter 64)
II. Polycythemia (primary or secondary): hyperemia of mucous membranes, skin, sclera, signs of hyperviscosity (see Chapter 64)

Diagnosis and Differential Diagnosis

I. Anemia of EPO deficiency
  A. Evaluate for chronic renal failure.
  B. See Chapter 48 for discussion of appropriate laboratory tests.
II. Polycythemia
  A. Confirm increased RBC mass to rule out relative polycythemia from dehydration.
  B. Investigate causes of hypoxemia causing excessive EPO secretion.
    1. Confirm hypoxemia.
      a. Pulse oximetry: arterial oxygen saturation <90% on room air
      b. Arterial blood gas: Pao_2 <80 mm Hg on room air
    2. Evaluate cardiopulmonary status.
      a. Thoracic radiography
      b. Echocardiography
      c. Electrocardiography
    3. Measure serum EPO concentration (should be normal to increased).
  C. Normal oxygenation with excessive EPO secretion warrants investigation for renal disease or masses.
    1. CBC, serum biochemistry profile, UA, radiographs, abdominal ultrasonography
    2. Serum EPO concentration: normal or high despite polycythemia
  D. Polycythemia vera is a diagnosis of exclusion.
    1. Dyserythropoiesis on bone marrow evaluation
    2. Low serum EPO concentration

Treatment

I. Anemia of EPO deficiency: see Chapter 48
II. Polycythemia from excessive EPO secretion
  A. Therapeutic phlebotomy is indicated for polycythemic animals experiencing clinical signs associated with hyperviscosity.
    1. Place a peripheral and jugular IV catheter or large-bore butterfly catheter.
    2. Slowly withdraw 10% to 25% blood volume from the jugular catheter, with a goal of reducing packed cell volume (PCV) to 55% to 60%.
    3. Replace removed blood volume with a similar volume of IV crystalloid fluids via the peripheral catheter.
    4. Possible complications include catheter clotting, acute hypotension, and volume overload.
  B. Treatment of EPO secretion associated with hypoxemia requires management of the underlying cardiopulmonary disease.
  C. Elevated EPO secretion from renal disease may require the following:
    1. If only one kidney is abnormal (cysts, neoplasia, vascular disorder), surgical removal of the affected kidney is indicated.
    2. Chemotherapy may be tried for bilateral renal lymphosarcoma.
  D. EPO secretion caused by extrarenal neoplasia may improve with surgical removal of the neoplasm.

Monitoring of Animal

I. Anemia of EPO deficiency with chronic renal failure (see Chapter 48)
  A. Deficiency is life-long, so continued EPO administration is required.
  B. Prognosis is guarded but depends on the rate of advancement of renal failure.
II. Polycythemia from excessive EPO secretion
  A. Complications from recurring hyperviscosity include neurological signs, hemorrhage, and stroke.
  B. PCV is monitored weekly to biweekly initially, but long-term observation is based on rapidity of recurrence of polycythemia.
  C. Hypoxemia-induced secondary polycythemia is highly manageable with use of intermittent phlebotomy, with prognosis and monitoring dependent on the underlying cardiopulmonary disorder.
  D. When renal disease is present, monitoring is dependent on the underlying cause.
    1. Prognosis is good for resolution of polycythemia if a cyst or tumor is completely resected or remission is induced with chemotherapy.
    2. Prognosis is guarded with nonresectable disease.
  E. With extrarenal neoplasia, monitoring and prognosis vary with the etiology.
    1. Monitoring depends on tumor type, with a good prognosis if the tumor is completely resectable and guarded prognosis if it is nonresectable.
    2. If polycythemia recurs postoperatively (suggesting recurrence and/or metastasis), the prognosis is worse.

HYPOGLYCEMIA

Definition

I. In the normal dog and cat, blood glucose (BG) is maintained within a fairly small normal range.
II. Unlike people, normal dogs and cats do not become hypoglycemic even in the face of fasting or starvation.
III. Hypoglycemia is defined as resting serum glucose <60 mg/dL, but varies slightly depending on the laboratory methodology.
IV. Hypoglycemia is defined as low serum BG on repeated assays, rather than a single assay.

Causes

I. Spurious hypoglycemia
  A. Serum not promptly separated from cells
  B. Poor technique or poor quality control of in-house analyzers

C. Underestimation of BG by cage-side glucometers measuring whole BG instead of serum glucose

II. Neonatal and toy-breed juvenile hypoglycemia
  A. Insufficient muscle mass glycogen reserves and body fat stores to provide substrate for glycogenolysis and gluconeogenesis
  B. Difficulty maintaining euglycemia
    1. Nutritional stressors, such as inadequate nursing, fasting, and poor diet
    2. Physiological stressors, such as parasitism, diarrhea, and hypothermia

III. Ingestion of oral hypoglycemic agents
  A. Ingestion may be accidental or intentional.
  B. Sulfonylureas (glipizide, glyburide) cause hypoglycemia by stimulating increased release of insulin from β cells.
  C. Xylitol sweetened products (sugar-free gum and foods) promote insulin release in dogs.

IV. Hypoadrenocorticism (cortisol deficiency) (see Chapter 45)
  A. Cortisol is the main hormonal antagonist to insulin.
  B. Cortisol deficiency (with or without aldosterone deficiency) may lead to hypoglycemia.

V. Iatrogenic insulin administration (see Chapter 44)
  A. Otherwise well-regulated diabetics may become hypoglycemic from the following:
    1. Accidental insulin overdose
    2. Excessive exercise
    3. Lack of food ingestion
    4. Effects of a concurrent illness
  B. Insulin needs may vary considerably in some poorly regulated diabetics, with hypoglycemia being a frequent complication.
  C. Diabetic cats occasionally revert from insulin-dependent to non–insulin-dependent, so insulin administration results in hypoglycemia.

VI. Insulinoma (see Chapter 73)
  A. This is a functional β cell tumor of the pancreas that secretes insulin.
  B. Increased BG may provoke insulin release.
  C. Hypoglycemia does *not* suppress insulin release from neoplastic β cells.
  D. Clinical signs of hypoglycemia are often precipitated by fasting, eating, excitement, or exercise.

VII. Paraneoplastic hypoglycemia (see Chapter 73)
  A. Nonpancreatic neoplasms may cause hypoglycemia as a paraneoplastic effect through secretion of polypeptides that behave like insulin.
  B. Possible tumor types include hepatocellular carcinoma, renal adenocarcinoma, hepatoma, leiomyoma, and leiomyosarcoma, although any tumor has the potential to cause hypoglycemia.

VIII. Glycogen storage diseases
  A. Inherited errors in the glycogenolytic pathway inhibit normal glucose homeostasis secondary to a lack of production of glucose from glycogen.
  B. Deficiencies of glucose-6-phosphatase or α-1,4-glucosidase lead to hypoglycemia and abnormal deposition of glycogen in soft tissues.

IX. Sepsis
  A. Gluconeogenesis may become impaired with overwhelming sepsis through poorly understood mechanisms.
  B. Sepsis is also associated with increased peripheral glucose utilization associated with a hypermetabolic state.

X. Hepatic failure (see Chapter 37)
  A. Markedly decreased hepatic function (>70% lost) can lead to hypoglycemia from impaired gluconeogenesis.
  B. When hypoglycemia is present, other substances synthesized in the liver (albumin, cholesterol, and blood urea nitrogen [BUN]) are also decreased.

XI. Hunting dog (exertional) hypoglycemia
  A. Active, lean-bodied hunting dogs may become hypoglycemic after extreme exercise.
  B. Exertional hypoglycemia occurs from depletion of stored glycogen or increased glucose utilization.

Pathophysiology

I. Maintenance of normal BG is a balance between absorption, production, and utilization of glucose.
  A. Glucose from dietary intake is absorbed from the intestine.
  B. Glucose can be synthesized or released from degradation of stored carbohydrate.
    1. Substrates for gluconeogenesis: amino acids (especially alanine), fatty acids, and lactate
    2. Conversion of stored hepatic and muscular glycogen to glucose via glycogenolysis
  C. Glucose uptake and utilization by most peripheral tissues is dependent on insulin.

II. Insulin is a hypoglycemic hormone.
  A. Secreted by pancreatic islet β cells in response to hyperglycemia
  B. Impairs glycogenolysis
  C. Impairs gluconeogenesis directly by inhibition of enzymes necessary for amino acid mobilization
  D. Suppresses glucagon secretion
  E. Suppression of adipocyte lipolysis and increased fatty acid esterification via lipoprotein lipase
  F. Stimulates uptake and utilization of glucose
  G. Tissues dependent on insulin for glucose uptake: brain, RBCs, leukocytes, hepatocytes, renal tubular cells, and pancreatic β cells

III. Other hyperglycemic hormones include the following:
  A. Glucagon
    1. Actions directly opposed to those of insulin
    2. Secreted by pancreatic islet β cells in response to hypoglycemia
    3. Increases hepatic glycogenolysis
    4. Dramatically increases hepatic gluconeogenesis
  B. Cortisol
    1. Secreted by zona fasciculata of the adrenal cortex in response to stimulation by ACTH from the pituitary gland
    2. Stimulates hepatic gluconeogenesis
    3. Decreases the uptake and utilization of glucose by peripheral tissues

C. Epinephrine
   1. Increases hepatic and muscle glycogenolysis
   2. Promotes lipolysis
D. Growth hormone
   1. Promotes lipolysis
   2. Decreases peripheral tissue uptake and utilization of glucose

Clinical Signs

I. The severity of clinical signs is dependent on the degree of hypoglycemia, duration of hypoglycemia, and rapidity of the decline in BG.
   A. Episodic signs of neuroglycopenia (inadequate central nervous system glucose) occur.
   B. Apparent lack of clinical signs occurs from neural adaptation to chronic hypoglycemia.
   C. Lack of mental abnormalities in a profoundly hypoglycemic animal suggests previous episodes or chronic occurrence of low BG.
II. Neuroglycopenia occurs because brain cells are profoundly affected by hypoglycemia, owing to their inability to store glycogen and requirement for glucose as an energy source.
   A. Signs include tremors, seizures, depression or mental dullness, weakness, collapse, increased appetite, and bizarre behavior.
   B. Severe or prolonged neuroglycopenia causes brain injury and alterations in nervous system function that persist beyond the correction of the hypoglycemia.
      1. Temporary or permanent cortical blindness
      2. Chronic seizures following neural hypoxic injury
      3. Peripheral nerve demyelination

Diagnosis and Differential Diagnosis

I. Suggestive clinical signs and history
II. Laboratory confirmation
   A. Evaluate BG immediately with rapid whole-blood glucometer assessment.
   B. Confirm hypoglycemia on serum biochemical analyzer.
III. Definitive diagnosis of hypoglycemia via Whipple's triad
   A. Clinical signs of hypoglycemia
   B. Laboratory confirmation of hypoglycemia
   C. Resolution of signs with dextrose administration
IV. Further assessment of underlying cause
   A. History: known administration or accidental exposure to insulin or oral hypoglycemic agents
   B. CBC
      1. Sepsis: marked inflammatory leukogram
      2. Cortisol deficiency: eosinophilia, lymphocytosis, or lack of stress leukogram
   C. Serum biochemistry profile
      1. Hepatic failure: decreased albumin, BUN, or cholesterol; or increased hepatic enzyme activity
      2. Hypoadrenocorticism: hyponatremia with hyperkalemia
   D. Serum insulin concentration
      1. A sample for insulin evaluation is collected during confirmed hypoglycemia.
      2. If hypoglycemia is present, normal or increased insulin concentration confirms hyperinsulinism.
         a. Iatrogenic administration must be ruled out.
         b. Hyperinsulinism may develop with insulin secretion by either pancreatic or extrapancreatic neoplasms.
   E. Miscellaneous secondary testing
      1. Urinalysis
      2. ACTH stimulation test to rule out cortisol deficiency
      3. Bile acids to assess hepatobiliary function
      4. Thoracic or abdominal radiography, or both, to search for neoplasia or metastatic disease
      5. Abdominal ultrasonography to identify a pancreatic mass, although β cell neoplasms often small and not identifiable
      6. Abdominal computed tomography for detection and localization of pancreatic or metastatic masses
      7. Exploratory laparotomy for positive identification of a cause in hyperinsulinism where other tests are inconclusive

Treatment

I. Neuroglycopenic crisis
   A. Feed animal.
   B. Give enteral glucose.
      1. Apply a monosaccharide (50% dextrose, corn syrup, fruit juice, or honey) to the oral cavity.
      2. Perform orogastric intubation and give 10 to 20 mL/kg of 20% dextrose to the neonate or tractable animal when IV access is limited.
   C. Give dextrose IV.
      1. Dextrose 50% via central IV line
      2. Dextrose ≤20% for peripheral vein administration
      3. Initial dose: 0.5 g/kg dextrose or 1 mL/kg of a 50% solution
      4. Administration of a constant-rate infusion (CRI) of 2.5% to 10% dextrose until resolution of signs or cause
   D. Consider glucagon CRI.
      1. Indicated for iatrogenic insulin shock unresponsive to dextrose infusion, or prevention of rebound hypoglycemia with hyperinsulinism and paraneoplastic hypoglycemia.
      2. Add contents of a 1-mg reconstituted vial of glucagon to 1 L of 0.9% NaCl to make a 1000 ng/mL solution.
      3. Administer glucagon as an initial bolus of 50 ng/kg IV, then a CRI of 10 to 15 ng/kg/min IV to maintain euglycemia.
   E. Monitor BG frequently.
II. Treatment of specific underlying causes
   A. Juvenile hypoglycemia and hunting dog (exertional) hypoglycemia: frequent feeding
   B. Accidental or intentional ingestion of oral hypoglycemic agents: maintenance of glucose support as needed until drug has been completely metabolized
   C. Hypoadrenocorticism (see Chapter 45)

D. Iatrogenic insulin administration
   1. Maintain glucose support as needed until drug has been completely metabolized.
   2. Adjust insulin protocol (see Chapter 44).
E. Insulinoma
   1. Surgical resection
   2. Frequent feeding of small meals
   3. Prednisone
      a. A dosage of 0.5 to 1.0 mg/kg/day PO temporarily counteracts the insulin effects.
      b. The dose may be gradually increased to 4 mg/kg/day PO, but expect adverse effects.
   4. Diazoxide
      a. Inhibits secretion of insulin from pancreatic β cells
      b. Inhibits peripheral uptake of glucose
      c. Dose: 5 to 10 mg/kg PO BID initially, then increased to 20 mg/kg PO BID
      d. Limited availability, expensive
      e. Possible adverse effects: anorexia, vomiting, diarrhea, tachycardia, hematological changes
   5. Streptozocin
      a. Cytotoxic to pancreatic β cells
      b. Indication: known metastatic disease or nonresectable tumors
      c. Seven-hour administration protocol
         (1) Pretreatment fluid diuresis for 3 hours with NaCl 18.3 mL/kg/hr 0.9% IV
         (2) Streptozocin at 500 mg/m^2 mixed into NaCl 36.6 mL/kg 0.9% and administered at 18.3 mL/kg/hr over 2 hours IV
         (3) Posttreatment fluid diuresis for 2 hours with NaCl 18.3 mL/kg/hr 0.9% IV
         (4) Posttreatment butorphanol 0.4 mg/kg IM as needed for emesis
      d. Adverse effects
         (1) Transient anorexia and/or vomiting for 24 hours after dose: common
         (2) Mild neutropenia: rare
         (3) Nephrotoxicity: extremely rare with diuresis protocol
         (4) Secondary diabetes mellitus: transient or permanent, in up to 33% of treated dogs
   6. Octreotide: use and efficacy not well documented
F. Paraneoplastic hypoglycemia
   1. Surgical resection of tumor whenever possible
   2. Prednisone and frequent feeding, as noted previously
G. Glycogen storage diseases: no specific therapy
H. Sepsis
   1. Nutritional support: enteral or total parenteral
   2. CRI of dextrose
   3. Elimination of underlying cause of sepsis with surgery and/or antibiotics
I. Hepatic failure
   1. Nutritional support: enteral or total parenteral
   2. CRI of dextrose
   3. Treatment of specific underlying hepatic disease

Monitoring of Animal

I. Neuroglycopenic crisis
   A. Monitor vital signs every 1 to 2 hours until clinically alert and stable.
   B. Monitor BG every 1 to 2 hours until euglycemia is established and maintained for >4 hours.
   C. Monitor neurological status hourly.
   D. If seizure activity recurs once euglycemic, diazepam or phenobarbital is indicated (see Chapter 22).
II. Specific monitoring for postoperative insulinoma cases
   A. Measure BG intraoperatively, immediately postoperatively, and every 2 to 4 hours thereafter until stable euglycemia is maintained for >12 hours.
   B. If animal is persistently hypoglycemic postoperatively, tumor was incompletely resected and other therapy (described earlier) is warranted.
   C. If animal becomes hyperglycemic postoperatively, transient regular insulin therapy 0.5 U/kg SC, IM is indicated, and continue to monitor BG every 2 to 4 hours.
   D. Discharge animal when clinically stable, euglycemic, and eating.
   E. Recheck for metastatic disease with fasting BG evaluated monthly.

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CHAPTER 47

Introduction

Cathy E. Langston

ASSESSMENT OF RENAL FUNCTION

Azotemia

Definition

I. Azotemia is elevation of blood urea nitrogen (BUN) or creatinine.
II. Uremia is the constellation of clinical signs associated with renal failure.

Creatinine

I. Creatinine concentration is a more reliable measure of renal function than BUN.
II. Extensive variation between laboratories makes comparisons difficult (Boozer et al., 2002).
III. Creatinine concentration correlates poorly with glomerular filtration rate (GFR) at low levels of dysfunction.
   A. Major changes in GFR may cause very minor changes in creatinine.
   B. When GFR is markedly reduced, small changes in GFR cause large changes in creatinine (DiBartola, 2005).

Blood Urea Nitrogen

I. Increased by ingestion of high-protein diet, gastrointestinal hemorrhage, and prerenal factors (e.g., dehydration, hypotension, decreased cardiac output)
II. Decreased by low-protein diet, hepatic dysfunction

Glomerular Filtration Rate

I. GFR provides a more accurate assessment of renal function than creatinine or BUN, but measurement is more involved.
II. Multiple methods are available (Kerl and Cook, 2005).
III. Urinary clearance methods involve collecting urine over a specified time, as well as a blood sample at the midpoint of the collection period.
   A. Endogenous or exogenous creatinine or inulin is measured.
   B. The substance must be at steady state during the collection period.
IV. Plasma clearance methods involve collecting multiple blood samples after injection of a test substance.
   A. Exogenous creatinine, iohexol, inulin, Tc99m-diethylenetriamine pentaacetic acid (Tc-99m-DTPA) are measured.
   B. Iohexol is readily available and can be assayed (by Michigan State University Toxicology Section, www.animalhealth.msu.edu).
V. Renal scintigraphy involves measuring clearance of radiolabeled Tc-99m-DTPA.
   A. Requires special equipment (gamma camera)
   B. Only method that can determine left or right kidney function separately

Tubular Function

I. Hypersthenuria: urine specific gravity (USG) ≥1.030 in dogs or ≥1.035 in cats
II. Minimally concentrated urine: USG of 1.013 to 1.029 in dogs or 1.013 to 1.034 in cats
III. Isosthenuria: USG of 1.008 to 1.012 (or urine osmolality of 250 to 350 mOsm/kg) in dogs and cats
IV. Hyposthenuria: USG ≤1.007 in dogs and cats

Proteinuria

Definition

I. Prerenal proteinuria: induced by exposure to extreme heat or cold, seizures, fever, pathologic protein disorders (e.g., Bence Jones proteins, hemoglobinuria, myoglobinuria)
II. Renal proteinuria: glomerular, tubular, renal parenchymal inflammation (e.g., pyelonephritis, renal tumor)
III. Postrenal proteinuria: induced by lower urinary tract inflammation (e.g., bacterial cystitis, cystic calculi, neoplasia)

Measurement

I. Urine dipstick: semiquantitative assessment
  A. Dipsticks primarily measure albumin present in concentrations >30 mg/dL.
  B. Trace to 1+ with USG <1.020 or ≥2+ at any USG is likely significant.
  C. Consider postrenal sources if urine sediment is consistent with inflammation (pyuria, hematuria, bacteriuria).
II. Sulfosalicylic acid (SSA) protein precipitation test
  A. Recommended to confirm any positive dipstick tests
  B. No false-positive results with alkaline or highly concentrated urine (as occurs with dipstick assay)
III. Urine protein:creatinine ratio (UPC)
  A. It standardizes protein measurement despite differences in urine concentration.
  B. It is a reliable substitute for 24-hour urine collection.
  C. Results of serial samples must differ by ≥40% to conclude magnitude of proteinuria has changed.
IV. Microalbuminuria
  A. Defined as albumin concentration in urine between 1 to 30 mg/dL
  B. Commercially available test for dogs and cats (ERD HealthScreen; Heska Co., Fort Collins, Colo.)

Evaluation for Proteinuria

I. Any animal with illness serious enough to prompt complete blood count (CBC) and serum biochemical profile (Lees et al., 2005)
II. Any healthy animal undergoing a routine evaluation that includes a CBC and serum biochemical profile
III. Animals with chronic illness that may be associated with proteinuria (monitor at ≥6-month intervals)
IV. Azotemic animals

Evaluation for Microalbuminuria

I. Animals with serious illness (especially those associated with proteinuria) when standard proteinuria testing is negative (Lees et al., 2005)
II. Apparently healthy dogs >6 years old and cats >8 years old when standard proteinuria testing is negative and sensitive testing desired
III. Dogs or cats at risk for developing glomerular disease (predisposed breeds) when early detection is desired

Response to Proteinuria

I. Monitoring is recommended in the following instances:
  A. Nonazotemic dogs and cats with UPC ≥0.5
  B. Nonazotemic dogs and cats with persistent microalbuminuria
II. Diagnostic evaluation to find an underlying disease is combined with continued monitoring in the following cases:
  A. Nonazotemic dogs and cats with rising proteinuria
  B. Nonazotemic dogs and cats with UPC ≥1.0
  C. Azotemic dogs with UPC <0.5
  D. Azotemic cats with UCP <0.4
III. Therapeutic intervention (diet and/or drugs) is recommended after investigation and treatment of underlying disease in the following:
  A. Nonazotemic dogs and cats with UPC ≥2.0
  B. Azotemic dogs with UPC ≥0.5
  C. Azotemic cats with UPC ≥0.4

STAGING OF CHRONIC RENAL FAILURE

Definition

I. International Renal Interest Society (IRIS) has proposed a staging system for chronic renal failure.
II. System was developed to help design and apply clinical practice guidelines for therapy and prognosis (Polzin et al., 2005).

Criteria

I. They are intended to be used after diagnosis of chronic renal failure.
II. Renal function should be stable for 2 weeks for accurate categorization.
III. Four stages of disease are recognized.
  A. Stage I
    1. Kidney disease present but no azotemia
    2. Markers of kidney disease present: proteinuria, renal cysts
  B. Stage II
    1. Mild azotemia
    2. Clinical signs (except polyuria/polydipsia) absent or minimal
  C. Stage III
    1. Moderate azotemia
    2. Clinical signs generally present
  D. Stage IV
    1. Severe azotemia: chronic kidney failure
    2. Uremic syndrome present
IV. Three categories may be considered.
  A. Level of azotemia (Table 47-1)
  B. Presence of proteinuria: proteinuric (p), nonproteinuric (np), borderline proteinuria (bp)
  C. Presence of hypertension (see Chapter 48)
    1. Hypertensive with complications (hc)
    2. Hypertensive with no complications (hnc)

TABLE 47-1

Staging Scheme for Chronic Renal Failure

STAGE OF DISEASE	SERUM CREATININE (mg/dL)	
	Cats	Dogs
I	<1.6	<1.4
II	1.6-2.8	1.4-2.0
III	2.8-5.0	2.1-5.0
IV	>5.0	>5.0

3. Not hypertensive (nh)
4. Borderline hypertensive (bh)
5. Hypertension not determined (hnd)

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CHAPTER 48

Diseases of the Kidney

Cathy E. Langston | Lauren Boyd

CONGENITAL/DEVELOPMENTAL DISORDERS

See Tables 48-1 and 48-2.

DEGENERATIVE DISORDERS

Feline Perinephric Pseudocysts

Definition and Cause

I. Perinephric pseudocysts (perirenal cysts) are accumulations of fluid in fibrous sacs around the kidney.
II. These are not true cysts, because they are not lined by epithelium and the cyst wall is thought to be the renal capsule.
III. Affected cats have the following characteristics:
  A. Generally older (>11 years), but may occur in younger cats (Ochoa et al., 1999)
  B. No gender or breed predisposition
IV. The cause is unknown.

Clinical Signs

I. Abdominal enlargement or detection of an abdominal mass
II. Signs of uremia
  A. The majority of affected cats have chronic renal failure (CRF).
  B. Pseudocysts may be unilateral or bilateral.

Diagnosis

I. On abdominal ultrasonography, anechoic fluid accumulation is seen between the renal capsule and parenchyma.
II. The kidney is often smaller than normal with changes consistent with CRF.
III. Fluid analysis is not necessary for diagnosis but generally reveals a transudate or modified transudate.
  A. Cell count and protein content are low.
  B. Fluid urea nitrogen or creatinine concentrations are lower than serum concentrations.
  C. Occasionally blood contamination is present.
  D. Fluid is generally sterile.
IV. Affected cats have a higher incidence of urinary tract infection (UTI).

Differential Diagnosis

I. Hydronephrosis
II. Renal lymphosarcoma, other renal neoplasia
III. Polycystic kidney disease (PKD)

TABLE 48-1

Congenital Renal Diseases

DISORDER	DEFECT	CLINICAL SIGNS	DIAGNOSIS	TREATMENT
Renal dysplasia	Disorganized development of renal parenchyma	Polyuria, polydipsia, azotemia Age of onset usually <5 years	Considered a possibility from early age of onset of CRF, ± small kidneys Diagnosed by renal biopsy	See Treatment of CRF
X-linked nephropathy	Complete absence of type IV collagen in the basement membrane	Male dogs: severe, rapidly progressive nephropathy with proteinuria Carrier (heterozygous) female dogs: slower progression to CRF at >5 years	Considered a possibility with proteinuria before 6 months of age Definitive diagnosis: immunofluorescent staining of the epidermal basement membranes for type IV collagen	Therapy as for other types of glomerulonephritis: ACE inhibitors, dietary restriction of protein, lipid, calcium, and phosphorus Treatment does not prevent progression of disease but delays onset

CRF, Chronic renal failure; *ACE,* angiotensin converting enzyme.

Treatment

I. Small fluid accumulations may need no specific therapy.
II. Treatment is recommended if abdominal distention is severe enough to cause abdominal pain or other clinical signs.
   A. Laparoscopic or surgical excision of the capsule without nephrectomy
   B. Concurrent nephrectomy (associated with shorter survival times)
   C. Ultrasound-guided drainage
III. Most pseudocysts recur over time.
IV. Drainage does not appear to improve renal function.

Monitoring of Animal

I. Serial abdominal ultrasounds are used to monitor changes in pseudocyst size over time and after drainage procedures.
II. Monitoring appropriate for the stage of CRF present (see Chronic Renal Failure) is also done.

Polycystic Kidney Disease

Definition

I. PKD is an inherited degeneration of the renal parenchyma, with development of multiple cysts throughout the kidney.
   A. Affected cats may also have hepatic and pancreatic cysts.
   B. About 40% of Persian cats genetically carry the PKD trait (DiBartola, 2000).
II. Persian-related cats, other longhaired breeds, and shorthaired cats may also be affected, although incidence in non-Persian cats is 14% (DiBartola, 2000).

TABLE 48-2

Familial Renal Diseases in Dogs and Cats

BREED	DISEASE	AGE OF ONSET (yr)	CLINICAL FINDINGS
Basenji	Fanconi's syndrome: proximal tubular defect	1-5	Glucosuria, metabolic acidosis, aminoaciduria
Beagle	Amyloidosis	5-11	Azotemia, proteinuria
Beagle	Membranoproliferative glomerulonephritis (GN)	2-8	Azotemia, proteinuria
Bernese mountain dog	Membranoproliferative GN	2-5	Azotemia, proteinuria
Brittany spaniel	Membranoproliferative GN: complement 3 deficiency	4-9	Recurrent bacterial infections, ± azotemia, proteinuria
Bullmastiff	GN	1-11	Azotemia, proteinuria
Bull terrier	Polycystic kidneys	0-2	Azotemia, ± cardiac disease
Bull terrier	Basement membrane disorder	0-10	Azotemia, proteinuria, ± hematuria
Cairn terrier	Polycystic kidneys	6 wk	Abdominal distention, hepatic cysts
Doberman pinscher	Basement membrane disorder	0-6	Azotemia, proteinuria
English cocker spaniel	Basement membrane disorder	0-2	Azotemia, proteinuria
English foxhound	Amyloidosis	5-8	Azotemia, proteinuria, renomegaly
Norwegian elkhound	Periglomerular fibrosis	0-5	Azotemia
Norwegian elkhound	Tubular dysfunction	Not reported	Glucosuria, ± azotemia
Rottweiler	Glomerular disease	0-1	Azotemia, proteinuria
Samoyed	Basement membrane disorder	0-1	Azotemia, proteinuria
Shar-pei	Amyloidosis	1-6	Azotemia, proteinuria, ± hepatic involvement, ± fever, joint swelling
Soft-coated Wheaten terrier	Membranoproliferative GN	2-11	Azotemia, proteinuria
Welsh corgi, Pembroke	Telangiectasia	≥5	Hematuria, anemia
West Highland white terrier	Polycystic kidneys	5 wk	Hepatic failure
Abyssinian cat	Amyloidosis	1-5	Azotemia, ± proteinuria
Oriental shorthair cat	Amyloidosis	0-5	Azotemia, ± hepatic involvement
Persian cat	Polycystic kidney disease	3-10	Azotemia, renomegaly, ± hepatic cysts
Siamese cat	Amyloidosis	0-5	Azotemia, ± hepatic involvement

Modified from Abraham LA, Beck C, Slocombe RF: Renal dysplasia and urinary tract infection in a bull mastiff puppy. Aust Vet J 81:336, 2003; Casal ML, Dambach DM, Meister T et al: Familial glomerulonephropathy in the bullmastiff. Vet Pathol 41:319, 2004; DiBartola SP: Familial renal disease in dogs and cats. p. 1819. In Ettinger SJ, Feldman EC (eds): Textbook of Veterinary Internal Medicine. 6th Ed. Elsevier Saunders, St. Louis, 2005.

III. An inherited form has also been described in bull terriers in Australia.

Causes and Pathophysiology

I. A mutation of the PKD1 gene causes autosomal dominant PKD (Lyons et al., 2004).
II. Excessive apoptosis (programmed cell death) destroys the renal parenchyma, allowing cystic epithelial cells to proliferate, which creates multiple and often large cysts.
III. In addition to the inherited genetic defect, an acquired somatic mutation may also be necessary for cyst development.

Clinical Signs

I. Clinical signs may not be present until late in the course when uremia occurs.
II. Palpation or radiographic imaging may detect abnormal renal size and shape.
III. Clinical signs of uremia may prompt investigation of affected cats.
IV. Age at onset of renal failure ranges from 3 to 10 years, with an average of 7 years (DiBartola, 2000).

Diagnosis

I. Screening tests
  A. Abdominal ultrasonography is 75% sensitive and 100% specific in cats <16 weeks of age, and sensitivity increases to 91% at 36 weeks (Biller et al., 1996).
  B. Genetic testing of cats >8 weeks of age is available using cheek swabs (www.vgl.ucdavis.edu).
II. Symptomatic cats with renal failure
  A. Perform diagnostic testing recommended for CRF.
  B. Abdominal ultrasonography reveals multiple, variably sized cysts in the renal parenchyma.

Treatment

I. Cats with PKD are removed from the breeding population.
II. Cats with CRF from PKD are treated as appropriate for the stage (see Chronic Renal Failure).

Monitoring of Animal

I. Onset of renal failure is variable.
II. Routine annual monitoring of adult cats known to have PKD for renal failure is prudent.
III. Once renal failure is apparent, monitor as appropriate for stage present.

INFECTIOUS AND INFLAMMATORY DISEASES

Leptospirosis

Definition and Causes

I. Leptospirosis is a bacterial zoonotic disease of particular importance in dogs that can cause acute or subacute hepatic and/or renal failure.
II. More than 200 serovars have been identified.
  A. The most common serovars causing clinical disease in dogs include *Leptospira kirschneri* serovar *grippotyphosa* and *Leptospira interrogans* serovars *bratislava*, *icterohaemorrhagiae, canicola, pomona,* and *autumnalis* (Birnbaum et al., 1998; Goldstein et al., 2006).
  B. The individual pathogenic significance of other serovars is unknown.
III. Cats are less susceptible than dogs.

Pathophysiology

I. Shedding by infected animals occurs primarily through the urine.
  A. The most common mode of transmission is via stagnant or slow-moving water contaminated with leptospires.
  B. The spirochete may live for several months in optimal environmental conditions.
II. Once the organism enters the host, it replicates in the kidney, liver, spleen, central nervous system (CNS), eyes, and genital tract.
III. The incubation period is usually 5 to 7 days but may vary.
IV. Antibody production appears around day 7 or 8, and the organism is cleared from most organs except the kidneys.
V. The organism replicates and persists in renal tubular epithelial cells, causing shedding for weeks to months after infection.

Clinical Signs

I. Severity of clinical signs varies based on the age and immunity of the host, environmental factors affecting the organism, and virulence of the infecting serovar (Greene et al., 2006).
II. Acute and subacute infections may affect many organs (see Chapter 113).
III. Acute urogenital signs include renal pain, renomegaly, oliguria; anuria with renal failure; and polyuria/polydipsia, with or without renal failure.
IV. Chronic infections may result in CRF, chronic active hepatitis, or hepatic fibrosis.
V. Dogs may be subclinically infected and have prolonged shedding of the organism but exhibit no clinical signs.

Diagnosis

I. Suggestive history and clinical signs
  A. Potential exposure to stagnant water, host animals (e.g., rats, raccoons, deer, cattle), wooded areas, lack of prior vaccination, fever, and renal and/or hepatic dysfunction are suggestive.
  B. Increased risk factors have been identified for leptospirosis.
    1. Middle-aged dogs
    2. Large breed, mixed breed, and hound dogs (Adin and Cowgill, 2000; Ward et al., 2002)
    3. Male dogs
    4. Dogs living in recently urbanized areas
II. Laboratory findings
  A. Hematology
    1. Leukopenia during leptospiremia: subsequent development of leukocytosis, with or without a left shift

2. Thrombocytopenia: may progress to disseminated intravascular coagulation (DIC)
3. Normocytic normochromic anemia

B. Serum biochemistry profile
1. Azotemia, hyperphosphatemia, hypercalcemia
2. Severe vomiting: hyponatremia, hypochloremia, hypokalemia
3. Hyperkalemia with oliguria or anuria
4. Hypoalbuminemia with hypocalcemia
5. Evidence of hepatic involvement
a. Elevated alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and total bilirubin concentrations, with hypoglycemia
b. May lag behind azotemia by 6 to 8 days

C. Urinalysis
1. Tubular or glomerular proteinuria with an elevated urine protein:creatinine ratio (UPC)
2. Bilirubinuria
3. Hematuria with pyuria
4. Granular casts

III. Specific testing
A. Microscopic agglutination test (MAT): most common method
1. A fourfold increase in titers over a 2- to 4-week period, or a single test result of 1:800 or higher, is diagnostic.
2. It may take 10 days or more for antibody titers to develop (Brown et al., 1996).
3. It has a poor predictive value for shedding leptospires in the urine (Harkin et al., 2003).
4. It cannot distinguish between vaccinal and natural antibodies.

B. Polymerase chain reaction (PCR) assay
1. It becomes positive before seroconversion, so earlier diagnosis is possible.
2. Sensitivity (100%) and specificity (83%) are high (Harkin et al., 2003).
3. Sensitivity may result in false-positive results.

C. Enzyme-linked immunosorbent assay (ELISA)
1. Distinguishes between immunoglobulin (Ig) M (acute) and IgG (chronic) antibody titers
2. May be more sensitive than MAT in subacute infections
3. Paired IgM and IgG titers best to distinguish infection from vaccinal titers
4. Not widely available for clinical use

D. Other test options (see Chapters 2 and 113)

Differential Diagnosis

I. Other causes of acute renal failure (ARF)
A. Ethylene glycol, other renal toxins
B. Acute pyelonephritis
C. Borreliosis, other tick borne diseases

II. Other causes of acute hepatitis
A. Infectious canine hepatitis
B. Other bacterial infections
C. Hepatic toxins

Treatment

I. Supportive care and fluid therapy (see Acute Renal Failure)

II. Elimination of leptospiremia
A. Initially give parenteral penicillins, then switch to oral forms once the animal stops vomiting.
B. IV route has the most consistent absorption and is preferred.
C. Appropriate antibiotics include the following:
1. Ampicillin 22 mg/kg IV, SC QID for 2 weeks
2. Amoxicillin 22 mg/kg PO TID to BID for 2 weeks
3. Penicillin G 25,000 to 40,000 U/kg IM, SC BID for 2 weeks

III. Elimination of the carrier state
A. Treatment is started when animal is discharged from hospital.
B. Appropriate antibiotics include the following:
1. Doxycycline 5 mg/kg PO, IV BID for 2 weeks
2. Tetracycline 22 mg/kg PO TID for 2 weeks (infrequently used)
3. Azithromycin 20 mg/kg PO SID for 1 week

Monitoring of Animal

I. Renal function is monitored as described later for ARF.

II. Serum MAT titers are measured initially and repeated in 2 to 4 weeks.

III. To determine elimination of the carrier state, perform PCR assay 2 to 4 weeks after treatment with doxycycline or azithromycin.

IV. Dogs are immunized after recovery to prevent infection by a different serovar.

Borreliosis

See Chapter 113.

Pyelonephritis

Definition and Causes

I. Pyelonephritis is inflammation of the renal pelvis and parenchyma.
A. Usually associated with bacterial infections
B. Renal medulla more susceptible to infection than renal cortex

II. Common bacterial pathogens include (in descending order of incidence) *Escherichia coli*, *Staphylococcus aureus*, *Proteus mirabilis*, and *Streptococcus* spp. (Barsanti et al., 1994; Barsanti, 2006).
A. Less common are *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Enterobacter* spp. (Barsanti et al., 1994)
B. Occasionally caused by fungal agents, usually *Candida* spp.

Pathophysiology

I. Route of infection may be ascending or hematogenous.
A. Ascending infection is believed to be the most common route.
B. Hematogenous infection is uncommon, owing to the resistance of the renal cortex to infection (Greene et al., 2006).

II. Abnormalities of the urinary tract may enhance renal susceptibility to infection.
  A. Congenital anomalies: ectopic ureters, vaginal strictures, recessed vulva, bladder diverticuli
  B. Acquired abnormalities: urolithiasis, neoplasia, granulomatous disease, fibrous scar tissue of renal parenchyma
  C. Functional and metabolic abnormalities
    1. Vesicoureteral reflux
    2. Disorders of micturition: decreased detrusor contractility, increased outflow resistance, decreased sphincter competence
    3. Diabetes mellitus
    4. Hyperadrenocorticism
    5. Systemic immunosuppression
  D. Urinary catheterization
    1. Associated with both temporary and indwelling catheters
    2. Risk of infection increases with duration of catheterization
III. Pyelonephritis occurs when lower UTI exists along with factors that predispose the kidney to colonization.
IV. Pyelonephritis may be a progressive disease.
  A. Chronic pyelonephritis may exist without progression to renal failure, especially in the absence of underlying renal disease (e.g., nephroliths).
  B. In acute infections, renal tubular cells produce inflammatory mediators (e.g., cytokines, nitrous oxide) that induce renal injury by recruiting neutrophils and macrophages.
  C. Renal scarring and atrophy may lead to end-stage kidney disease.

Clinical Signs

I. Acute pyelonephritis
  A. Fever, depression, anorexia, vomiting
  B. Renal pain
  C. Polyuria, polydipsia
II. Chronic pyelonephritis
  A. Polyuria, polydipsia
  B. Nonspecific signs of anorexia, lethargy, weight loss
  C. May be asymptomatic

Diagnosis

I. Suspicious history and physical examination findings
II. Complete blood count (CBC)
  A. May have a neutrophilic leukocytosis, with or without a left shift (especially in acute or complicated chronic pyelonephritis)
  B. May be normal
III. Serum biochemistry profile
  A. ± Azotemia, hyperphosphatemia with bilateral pyelonephritis
  B. Hyperglobulinemia possible with chronic infections
  C. May be normal
IV. Urinalysis
  A. Bacteriuria, pyuria, hematuria
  B. Possibly cellular or granular casts
  C. Isosthenuria
  D. Glucosuria with normoglycemia
V. Urine culture
  A. Pyelocentesis is definitive for pyelonephritis but is technically difficult if dilation is minimal.
  B. Ultrasound-guided percutaneous nephropyelocentesis may be done to retrieve urine for culture.
  C. Urine culture is best obtained by cystocentesis.
  D. Positive culture on cystocentesis does not localize infection to a site in the urinary tract.
VI. Radiographic imaging
  A. Excretory urography findings that are compatible with pyelonephritis include the following:
    1. Renal pelvic and/or proximal ureteral dilation
    2. Decreased opacity of the vascular nephrogram
    3. Blunting or distortion of renal pelvic diverticula
    4. Prolonged retention of contrast media in the renal pelvis
    5. May be normal
  B. Ultrasound findings that are compatible with pyelonephritis are as follows:
    1. Dilatation of the renal pelvis and proximal ureter
    2. Generalized hyperechoic renal cortex
    3. Increased prominence of the pelvic and ureteral mucosa
    4. Poor corticomedullary distinction
    5. Renal asymmetry

Differential Diagnosis

I. Other causes of fever, leukocytosis, and painful abdomen: peritonitis, pancreatitis, early gastrointestinal (GI) distention or torsion
II. Nephrolithiasis, ureterolithiasis, stricture
III. Lower UTI
IV. Bacterial prostatitis

Treatment and Monitoring

I. Correct any underlying predisposing factors.
II. Antibiotic therapy is selected based on bacterial culture and sensitivity.
  A. Antibiotics that penetrate renal tissue (specifically medulla) are preferred.
    1. Fluoroquinolones: enrofloxacin, marbofloxacin, orbifloxacin, difloxacin
    2. Ampicillin, amoxicillin, amoxicillin-clavulanic acid
    3. Cephalosporins
    4. Trimethoprim-sulfa drugs
      a. Sulfonamides do not reach effective intrarenal concentrations.
      b. Only the trimethoprim component is effective (Bergeron, 1995).
    5. Aminoglycosides as a last resort because of their potential nephrotoxicity
  B. Antibiotic therapy is continued for a total of 6 weeks.
  C. Repeat culture 1 week after completion of antibiotics.
  D. Fluconazole is the antifungal agent of choice, because it is excreted in urine in the active form (Pressler et al., 2003).
  E. Avoid indwelling urinary catheters.

III. Increase water intake to prevent urine stasis and encourage diuresis.
IV. Treat ARF or CRF, if present.

RENAL PARASITES

See Table 48-3.

NEPHROTOXICOSIS

Definition and Causes

I. Nephrotoxins are chemicals or drugs that produce acute tubular injury ranging from sublethal cell injury to cellular necrosis and apoptosis.
II. Toxins can also decrease renal blood flow and induce hypoxia that results in cell injury or death.
III. Nephrotoxins are a major cause of ARF in animals.
IV. For a list of causes, see Table 48-4.

Pathophysiology

I. Acute tubular injury is the most common sequela of a toxic insult to the kidney.
   A. Acute tubular injury can result in either sublethal cell damage or cell death.
   B. In nephrotoxic ARF, tubular injury is characterized by patchy distribution of degenerative or necrotic foci of tubular epithelium, with little or no evidence of interstitial inflammation (Cowgill and Francey, 2005).
II. Nephrotoxic injury to the glomerulus can be caused by loss of capillary surface area (aminoglycosides), disruption of endothelial cell integrity (doxorubicin), and mesangial cell proliferation and hypertrophy (azathioprine) (Brown and Grauer, 2002).
III. Duration of exposure, quantity and type of nephrotoxicant, and predisposing factors determine the severity and reversibility of renal damage.
IV. Predisposing factors can potentiate the damage caused by nephrotoxicosis.
   A. Hypotension
   B. Preexisting renal insufficiency
   C. Fever, sepsis
   D. Dehydration
   E. Hypokalemia (Brinker et al., 1981)
   F. Liver disease and dysfunction
   G. Decreased protein intake (Grauer et al., 1994)
   H. Concurrent use of two or more substances with nephrotoxic potential

Clinical Signs

I. Clinical signs are consistent with ARF.
   A. Polyuria, oliguria, or anuria
   B. Depression, lethargy, anorexia
   C. Vomiting and diarrhea, with or without melena
   D. Uremic breath
   E. Evidence of platelet dysfunction: petechiae, excessive bleeding
II. Laboratory findings may include the following:
   A. Metabolic acidosis
   B. Hyperkalemia or hypokalemia
   C. Azotemia
   D. Hyperphosphatemia
   E. Normoglycemic glucosuria
   F. Proteinuria

TABLE 48-3

Renal Parasites

PARASITE	INTERMEDIATE HOSTS	CLINICAL SIGNS	DIAGNOSIS	TREATMENT
Capillaria plica (cats and dogs)	Earthworm	Ova in urine often incidental finding Possible dysuria, pollakiuria, hematuria	Double operculated ova in urine False-positive results from *Trichuris* spp. with fecal contamination	Spontaneous resolution within 3-4 months in some animals Fenbendazole 50 mg/kg/day PO for 5-10 days Ivermectin 200 µg/kg PO once (not safe in collie-type dogs)
Capillaria feliscati (cats)	Earthworm	Same as for previous parasite	Same as for previous parasite	Fenbendazole 22 mg/kg PO BID for 3-10 days
Dioctophyma renale	Worms ingested by fish or frogs Raw fish or frogs then ingested by dogs or cats	May be asymptomatic Uremia if bilateral Hematuria or signs of ureteral obstruction	Ova in urine or abdominal fluid Adult nematodes seen on ultrasonography or at surgery	Surgical removal of adult worm or nephrectomy Possible aberrant migration in peritoneal cavity

Data from Associate: Texas Medical Informatics, Inc. Fact sheet: Capillariasis. http://www.vin.com/Members/Associate/Associate.plx?DiseaseId=263, 2006a; Associate: Texas Medical Informatics, Inc. Fact sheet: Dioctophymosis. http://www.vin.com/Members/Associate/Associate.plx?DiseaseId=1452, 2006b; Bowman DD: Georgis' Parasitology for Veterinarians. 7th Ed. WB Saunders, Philadelphia, 1999; Brown SA, Prestwood AK: Parasites of the urinary tract. In Kirk RW (ed): Current Veterinary Therapy IX: Small Animal Practice. WB Saunders, Philadelphia, 1986; Brown CA, Roberts AW, Miller MA et al: *Leptospira interrogans* serovar *grippotyphosa* infection in dogs. J Am Vet Med Assoc 209:1265, 1996; Kirkpatrick CE, Nelson GR: Ivermectin treatment of urinary capillariasis in a dog. J Am Vet Med Assoc 191:701, 1987; Senior DF, Solomon GB, Goldschmidt MH: *Capillaria plica* infection in dogs. J Am Vet Med Assoc: 176:901, 1980.

TABLE 48-4

Potential Nephrotoxins in Dogs and Cats

CLASS OF AGENT	EXAMPLES
Antimicrobials	Aminoglycosides, cephalosporins, penicillins, sulfonamides, quinolones, tetracyclines, vancomycin, carbapenems, aztreonam, rifampin, nafcillin
Antiprotozoals	Trimethoprim-sulfamethoxazole, sulfadiazine, thiacetarsamide, pentamidine, dapsone
Antifungals	Amphotericin B
Antivirals	Acyclovir, foscarnet
Chemotherapeutics	Cisplatin, carboplatin, doxorubicin, methotrexate
Immunosuppressives	Cyclosporine, azathioprine, interleukin 2
Nonsteroidal anti-inflammatory drugs	All
Angiotensin-converting enzyme inhibitors	All
Diuretics	All
Radiocontrast agents	Hyperosmolar ionic water-soluble contrast media
Miscellaneous therapeutics	Allopurinol, cimetidine, apomorphine, dextran 40, penicillamine, streptokinase, methoxyflurane, tricyclic antidepressants, lipid-lowering agents, calcium antagonists
Heavy metals	Mercury, uranium, lead, bismuth salts, chromium, arsenic, gold, cadmium, thallium, copper, silver, nickel, antimony
Organic compounds	Ethylene glycol, chloroform, pesticides, herbicides, solvents, carbon tetrachloride
Other exogenous toxins	Gallium nitrate, disphosphonates, mushrooms, grapes, raisins, snake venom, bee venom, lilies, vitamin D_3-containing rodenticides
Endogenous toxins	Hemoglobin, myoglobin, hypercalcemia

G. Urine sediment: renal epithelial cells, granular casts, red blood cells (RBCs) or white blood cells (WBCs) secondary to tubular cell necrosis

Diagnosis and Differential Diagnosis

I. Known potential exposure to nephrotoxin increases suspicion.
II. Clinical signs and laboratory findings are consistent with ARF.
III. Presence of granular casts in the urine or urine enzyme: creatinine excretion ratios may be early markers of gentamicin-induced nephrotoxicity (Grauer et al., 1995).
IV. Severe hypercalcemia may lead to increased suspicion of vitamin D_3 intoxication.
V. Confirmation of ethylene glycol toxicosis involves the following:
   A. High anion gap, metabolic acidosis
   B. Ethylene glycol test kit to confirm exposure
      1. It can detect levels as early as 30 minutes and for up to 12 hours after exposure.
      2. Negative test after 12 hours does not rule out exposure.
      3. It tests for the parent compound, not toxic metabolites.
      4. Most widely used test kit (PRN Pharmacal, Pensacola, FL) may not be sensitive enough to detect levels that are lethal to cats.
      5. Newer test has lower (20 parts per million [ppm] vs 50 ppm) detection limits (Kacey, Asheville, NC).
      6. Toxicology laboratories can quantify concentrations (vs qualitative results with test kits).
   C. Evidence of CNS abnormalities (e.g., seizures, ataxia, disorientation), polyuria, polydipsia
   D. Monohydrate calcium oxalate crystalluria
   E. Supportive ultrasonographic findings
      1. ± Normal kidneys
      2. Increased corticomedullary echogenicity consistent with renal mineralization or deposition of calcium oxalate crystals
   F. Renal biopsy
      1. Confirms acute tubular injury and presence of calcium oxalate crystals
      2. Helps determine prognosis

Treatment and Monitoring

I. Therapy includes measures to resolve ARF and supportive care (see Acute Renal Failure).
II. Resolution of electrolyte abnormalities is important.
III. Therapy for ethylene glycol ingestion includes hemodialysis or administering specific antidotes.
   A. Hemodialysis is the therapy of choice, because it can completely remove ethylene glycol and its metabolites and may prevent renal damage if performed within 5 to 6 hours of ingestion.
   B. If the animal arrives at the clinic within 2 hours of ingestion, then treatment with an emetic followed by activated charcoal and a cathartic is indicated (see Chapter 128).
   C. If the animal arrives at the clinic more than 2 hours after ingestion, then treatment with ethanol or 4-methyl-pyrazole (4-MP) is indicated to inhibit further ethylene glycol metabolism (Dorman and Dye, 2005).
      1. 4-MP is the preferred treatment in dogs (not effective in cats).
      2. The initial dose of 4-MP is 20 mg/kg IV, followed by 15 mg/kg IV at 12 hours, again at 24 hours, and then 5 mg/kg IV at 36 hours.

3. Additional doses of 3 mg/kg IV BID may be necessary if the dog is not fully recovered or if ethylene glycol levels are still detectable in the blood.

D. If 4-MP is not available, then ethanol is administered IV to produce CNS depression but not a comatose state.
   1. In dogs, administer a 20% solution in 0.9% saline at a dose of 5.5 mL/kg IV every 4 hours for five treatments and then QID for four treatments.
   2. In cats, 20% ethanol is given at 5 mL/kg IV QID for five treatments, then TID for four treatments (Langston, 2005).

IV. Dialyzable toxins include ethylene glycol, methanol, salicylate, lithium, ethanol, phenobarbital, acetaminophen, aminoglycosides, and tricyclic antidepressants.

V. Prognosis for most nephrotoxicants is guarded, and removal of the toxin may or may not result in restoration of renal function.

IMMUNE-MEDIATED DISEASES

Glomerular Diseases

Definition

I. Glomerulonephritis (GN) is inflammation of the glomerulus.
   A. More common in middle-aged to older dogs
   B. Uncommon in cats

II. Glomerulopathies do not have an inflammatory component and include hereditary nephritis and some renal diseases classically considered to be forms of GN (membranous nephropathy).

III. Amyloidosis is deposition of fibrils of protein in the glomerulus (most common), medulla, or possibly other organs.
   A. The Chinese shar-pei is predisposed to medullary amyloidosis, and affected dogs may have a history of tibiotarsal swelling and fever (shar-pei fever).
   B. Abyssinian and Siamese cats are predisposed to medullary amyloidosis.

IV. Protein-losing nephropathy includes GN, glomerulopathy, and amyloidosis.

Causes and Pathophysiology

I. GN is caused by immune complex deposition in the glomerulus.
   A. Antigen excess or large numbers of circulating antigen-antibody complexes lodge in the glomerular membrane, eliciting an immune response characterized by inflammatory cell influx, complement activation, and cellular damage.
   B. The renal response is cellular and mesangial matrix proliferation, as well as thickening of the glomerular basement membrane.
   C. Approximately 50% of GN in dogs is primary or idiopathic.
   D. Multiple secondary causes of GN have been identified (Table 48-5).

TABLE 48-5

Diseases Associated with Glomerulonephritis in Dogs

CAUSES	EXAMPLES
Infectious diseases	Canine adenovirus type 1, babesiosis, bacterial endocarditis, bartonellosis, blastomycosis, borreliosis, brucellosis, coccidioidomycosis, dirofilariasis, ehrlichiosis, hepatozoonosis, leishmaniasis, pyelonephritis, pyometra, trypanosomiasis, chronic bacterial infections
Neoplasia	Hemangiosarcoma, hepatocellular carcinoma, lymphocytic leukemia, transitional cell carcinoma, lymphoma, bronchogenic adenocarcinoma, mastocytoma
Inflammatory, noninfectious disorders	Systemic lupus erythematosus, polyarthritis, other immune-mediated diseases, pancreatitis, periodontal disease, inflammatory bowel disease
Miscellaneous factors	Excessive corticosteroids, familial disorders, diabetes mellitus

II. Reactive amyloidosis may occur when serum amyloid A, an acute-phase reactant protein, is present in large quantities over prolonged periods of time.
   A. Chronic inflammation is a predisposing cause.
   B. The shar-pei disease resembles human familial Mediterranean fever, in which defective down-regulation of mediators of inflammation exist.

Clinical Signs

I. Clinical signs may not be apparent if proteinuria is diagnosed on routine urine screening.

II. Signs are usually vague and include weight loss, anorexia, poor hair coat, or body condition.
   A. Clinical signs of uremia may be present (vomiting, anorexia, uremic halitosis).
   B. Peripheral edema or evidence of thromboembolism may occur in advanced cases.

III. Clinical signs of underlying causes may be detected (e.g., coughing with heartworm disease).

Diagnosis

I. Urinalysis
   A. An elevated UPC >0.5 in the absence of inflammation (pyuria, hematuria, bacteriuria) is suggestive of glomerular disease.
   B. Dogs with amyloidosis or membranous nephropathy tend to have the highest UPC values.

C. Isosthenuria may or may not be present.
D. Dogs with protein-losing nephropathy may have urine specific gravity >1.035, with azotemia.
E. Urine sediment examination may reveal the following abnormalities:
1. Casts are generally hyaline, but any type is possible.
2. Microscopic hematuria with dysmorphic RBCs is uncommon in dogs.

II. Serum biochemical profile and hematology
A. Azotemia is present in late stages.
B. Other findings associated with CRF may be present in late stages.
C. Hypoalbuminemia occurs in 61% of dogs with GN (Grant and Forrester, 2001).
D. Hypercholesterolemia is common (50%) (Grant and Forrester, 2001).

III. Infectious disease screening for underlying causes of GN

IV. Radiographic imaging
A. Abdominal imaging may show normal, small, or enlarged kidneys.
B. Thoracic radiographs are recommended in middle-aged to older animals.

V. Renal biopsy
A. For definitive diagnosis, unless proteinuria resolves after treatment of underlying condition
B. Biopsy method
1. Ultrasound-guided needle biopsy: provides small sample of tissue
2. Laparoscopic biopsy: larger tissue sample
3. Keyhole wedge biopsy: small incision over flank
4. Open laparotomy: most invasive
C. Biopsy handling
1. Presence of several glomeruli (preferably >5) is ascertained at the time of biopsy using a dissecting microscope.
2. Needle biopsy specimen (or portion of wedge biopsy) is fixed in formalin.
3. Second needle biopsy (or portion of wedge) is split and fixed for immunofluorescence (freezing, Michel's solution) and for electron microscopy (4% formalin plus 1% glutaraldehyde).
D. Biopsy processing
1. Multiple stains are used on thin sections of tissue.
2. Immunofluorescence or immunohistochemical staining for IgA, IgG, IgM, and complement are recommended on all biopsies.
3. Electron microscopy is reserved for difficult cases.
E. Biopsy results
1. Membranoproliferative GN is probably the most common type in the dog and is characterized by thickened capillary loops and mesangial hypercellularity (Vaden, 2005).
a. Type I (mesangiocapillary GN): infectious diseases possible cause
b. Type II: uncommon in dogs
c. Rapidly progressive form with tubular necrosis and interstitial inflammation: associated with *Borrelia burgdorferi* infection in dogs
2. Membranous nephropathy is the second most common GN in dogs, the most common type in cats, and affects male cats more than females.
a. Generally it is an idiopathic disease.
b. The basement membrane becomes thickened with immune complex deposits.
3. Proliferative GN is poorly defined in dogs.
a. Histologically, mesangial cell proliferation occurs.
b. Antibodies directed against the glomerular basement membrane have not been described in dogs or cats.
4. Many dogs are positive for IgA on immunofluorescence, but this may reflect the polymeric nature of IgA and nonspecific binding.
5. Hereditary nephritis includes a variety of inherited glomerular defects of basement membrane collagen type IV.
a. Light microscopic changes include membranoproliferative or sclerosing GN.
b. Electron microscopy is necessary for a definitive diagnosis.
6. Glomerulosclerosis is a possible end-stage lesion of any glomerular injury.
7. Amyloidosis is characterized by acellular material in the glomerulus.

Differential Diagnosis

I. Lower urinary tract disease: UTI, neoplasia, sterile cystitis
II. Tubular disease: pyelonephritis
III. Transient glomerular insult: fever, seizures, extremes of temperature
IV. Hemoglobinuria, myoglobinuria, Bence Jones proteinuria

Treatment

I. Start specific therapy for any underlying disease.
II. Decrease proteinuria.
A. Give enalapril or benazepril 0.25 to 1.0 mg/kg PO SID to BID unless creatinine >5 mg/dL.
B. Start a protein-restricted diet and avoid supplemental protein (e.g., egg whites).

III. Inhibit platelets.
A. Aspirin (0.5 to 2.0 mg/kg PO SID in dogs and QOD in cats) inhibits platelet aggregation.
B. Coumadin is difficult to titrate, requires careful monitoring, and is rarely used.

IV. Control hypertension.
A. Hypertension is more common and more difficult to control compared with hypertension associated with other types of renal disease.
B. See later discussion of hypertension treatment.

V. Consider immunosuppressive drugs.
A. No evidence of efficacy exists in dogs or cats; they should be used with caution and based on renal biopsy results.
B. Immunosuppressive therapy may be warranted with membranous GN.
C. Corticosteroids can cause proteinuria and are not recommended in dogs unless the underlying disease is steroid responsive (e.g., systemic lupus erythematosus).

D. Corticosteroids may be helpful in cats.
E. Drugs with no proven benefit include the following:
1. Dogs: azathioprine 2 mg/kg PO SID to QOD
2. Cyclophosphamide 50 mg/m^2 PO SID for 3 to 4 days, then off for 3 to 4 days
3. Cyclosporine, may worsen prognosis (Vaden et al., 1995)

VI. Treat amyloidosis.
A. Colchicine (0.01 to 0.03 mg/kg PO SID) is given during febrile episodes in affected shar-peis.
1. It may decrease amyloid deposition.
2. No evidence of effectiveness is seen once renal failure has occurred.
3. The primary side effect is GI upset.
B. Dimethyl sulfoxide (DMSO) 90 mg/kg PO, SC three times weekly has questionable benefit; anorexia, nausea, and an unpleasant odor are possible side effects.

Monitoring of Animal

I. Proteinuria is monitored monthly when starting or adjusting therapy, then every 3 months if the animal is stable.
II. Serum biochemical profiles are monitored every 3 to 6 months and more frequently if azotemia is present.
III. Systemic blood pressure is evaluated every 3 to 6 months in normotensive or controlled hypertensive animals (and more frequently during dose changes).

NEPHROLITHIASIS

Definition

I. Nephroliths are calculi that form in the kidneys.
II. These calculi are usually located in the renal pelvis or diverticula.

Causes

I. Calcium oxalate or mixed-oxalate calculi
A. Comprise 40% of canine nephroliths (Ross et al., 1999)
B. Comprise 75% to 98% of feline nephroliths (Ling et al., 1998; Kyles et al., 2005)
II. Struvite calculi
A. Comprise 33% of canine nephroliths
B. More common in female dogs (75% of nephroliths) than male dogs (20%) (Ross et al., 1999)
III. Urate calculi: 12% of canine nephroliths (Ross et al., 1999)
IV. Other mineral types: xanthene, silica, cystine, compound, or mixed calculi

Pathophysiology

I. Breed predispositions and concurrent diseases increase the risk of urolith formation (see Chapter 50).
II. Incidence of ureteroliths and (presumptively) nephroliths is increasing in cats, although the cause for this change is unknown (see Chapter 49).

Clinical Signs

I. None: nephroliths detected serendipitously during abdominal radiography or ultrasonography
II. Hematuria, unassociated with dysuria
III. Signs of lower UTI: pollakiuria, stranguria
IV. Abdominal or flank pain: infrequent
V. Signs associated with uremia

Diagnosis

I. Abdominal imaging
A. Radiography: majority of calculi are radiopaque; small calculi often missed
B. Ultrasonography: occasionally difficult to differentiate calculi from renal mineralization
C. Excretory urography (IV pyelography): sensitive method of detection
D. Computed tomography (CT): sensitive method of detection
II. Additional recommended diagnostic tests
A. Serum biochemical profile
B. Urine culture
C. Renal scintigraphy to evaluate function of individual kidneys if nephrectomy considered

Differential Diagnosis

I. Renal mineralization
II. Traumatic renal injury
III. Renal neoplasia
IV. Pyelonephritis

Treatment

I. Asymptomatic calculi, no renal dysfunction
A. Treatment is aimed at slowing progression or dissolving the calculi.
1. If struvite is considered a possibility (female dog with concurrent UTI), then stone dissolution diets (Hill's s/d diet, Royal Canin SO Diet) and concurrent antibiotics are started.
2. If calcium oxalate is considered a possibility (cats), then avoidance of acidifying diets, addition of potassium citrate, and feeding a canned diet are begun because medical dissolution is not possible.
3. If urate is considered a possibility (dalmatians), then dietary therapy with restricted protein, restricted purine, alkalinizing properties (Hill's u/d), and allopurinol 10 mg/kg/day PO may cause stone dissolution.
B. Monitor progression of calculi and renal function.
1. If condition is worsening, then consider more active management (lithotripsy, surgery).
2. Surgical intervention decreases renal function by 20% (Bollinger et al., 2005).
II. Calculi and significant associated renal impairment
A. Medical management may be a better alternative than surgery.
B. Decision on type of therapy depends on extent of disease, involvement of contralateral kidney, and stone type.
III. Calculi causing obstruction or recurrent UTI
A. Surgical removal of calculus via pyelotomy or nephrotomy

1. Staged surgery (2 to 4 weeks apart) preferable for bilateral disease
2. Nephrectomy for irreversible renal damage and minimal function

B. Extracorporeal shockwave lithotripsy
1. Less invasive than surgery
2. Faster results than medical dissolution
3. Limited availability

C. Percutaneous lithotripsy
1. Small incision over kidney provides access by ultrasound or laser lithotripter
2. Causes less renal functional impairment than surgery
3. Procedure has limited availability

Monitoring of Animal

I. Abdominal radiographs every 2 to 6 months to assess size and recurrence of calculi
II. Serum biochemical profile at least every 3 to 6 months
III. Urinalysis and urine culture every 3 months

CHRONIC RENAL FAILURE

Definition

I. CRF is defined as azotemia in the presence of inadequately concentrated urine (urine specific gravity <1.035 in cats, <1.030 in dogs).
II. Disease must be present for >3 months.
III. A staging system for chronic kidney disease is presented in Chapter 47.

Causes

I. Tubulointerstitial nephritis is the most common histopathologic lesion, but it may be the end result of a variety of insults.
II. Other causes include GN, hereditary nephritis, amyloidosis, renal dysplasia, PKD, tubulonephrosis, lymphoma, chronic pyelonephritis, nephroliths or ureteroliths (causing partial obstruction), vasculitis, infarction, and incomplete resolution of ARF.

Pathophysiology

I. Irreparable damage to the glomerulus, tubule, or interstitium leads to loss of the entire nephron (because each nephron acts as a unit).
II. Remaining nephrons become hypertrophic.
III. Although initially an adaptive response, glomerular hypertension damages the nephron, leading to further nephron loss.
IV. After a certain level of damage has been sustained (generally when creatinine >3.5 mg/dL), renal failure becomes progressive despite resolution of the initiating cause.

Clinical Signs

I. Historical signs
A. Polyuria, polydipsia
B. Anorexia, weight loss, lethargy
C. Vomiting
D. Halitosis
E. Altered consciousness, seizures
F. Bleeding problems

II. Physical examination findings
A. Dehydration
B. Frequently small, irregular, or asymmetrical kidneys
C. Rarely, large kidneys
D. Renal pain uncommon
E. Uremic halitosis, oral ulceration
F. Poor hair coat, poor body condition
G. Mild pallor

Diagnosis

I. Serum biochemistry panel
A. Magnitude of abnormalities greater as severity progresses
B. Elevated blood urea nitrogen (BUN), creatinine
C. Hyperphosphatemia
D. Hypokalemia: more common in cats
E. Metabolic acidosis: more common in cats
F. Mild hypercalcemia or hypocalcemia

II. CBC
A. Nonregenerative anemia in some animals from decreased erythropoietin
B. Normal platelet count, decreased platelet function

III. Urinalysis
A. Isosthenuria or inadequately concentrated urine in addition to dehydration or azotemia (urine specific gravity <1.035 in cats, 1.030 in dogs) is expected, but urine concentrating ability may rarely be retained.
B. Casts indicate ongoing renal damage.
C. WBCs or bacteria may be detected (if active pyelonephritis or secondary bladder infection present).

IV. Radiographic imaging
A. Radiography may show small and irregular kidneys, kidneys of normal size and shape, enlarged kidneys, nephroliths, or ureteroliths.
B. Abdominal ultrasonography frequently shows increased echogenicity from fibrosis and deranged architecture, as well as renal pelvic dilation from infection, obstruction, or aggressive diuresis.
C. Excretory urography may show poor contrast uptake or structural abnormalities (see Chapter 4).

V. Other diagnostic tests
A. Blood pressure measurement
1. Hypertension occurs in about 20% to 90% of cases (Cook and Cowgill, 1996; Syme et al., 2002).
2. Risk of complications of hypertension increases with higher blood pressure (Table 48-6).

B. Measurement of glomerular filtration rate (GFR)
1. Not necessary if azotemia present
2. Useful in detecting early kidney disease

C. Parathyroid hormone measurement: renal secondary hyperparathyroidism

Differential Diagnosis

I. Prerenal azotemia from dehydration, high-protein diet, or GI bleeding is characterized by high urine specific gravity.

TABLE 48-6

Risk of Adverse Effects of Hypertension Based on Peripheral Indirect Arterial Blood Pressure

SYSTOLIC (mm Hg)	DIASTOLIC (mm Hg)	RISK CATEGORY
>180	>120	High
160	100	Moderate
150	95	Low
<150	<95	Minimal

II. Azotemia with inadequately concentrated urine may arise from the following:
  A. Renal failure: ARF, CRF
  B. Dehydration combined with extrarenal impairment of urine concentration
    1. Drug therapy: diuretics, glucocorticoids
    2. Osmotic diuresis: diabetes mellitus
    3. Impaired medullary concentration gradient: hypoadrenocorticism, portosystemic shunting
    4. Central diabetes insipidus
    5. Nephrogenic diabetes insipidus: hypercalcemia, pyometra, pyelonephritis
III. Postrenal azotemia (urinary obstruction, rupture) is differentiated from intrinsic renal failure by history, physical examination, and imaging studies.

Treatment

I. Prevention of progression
  A. Dietary therapy
    1. Renal diets contain restricted quantities of protein with high biological value, restricted phosphorus, and supplemental omega-3 polyunsaturated fatty acids.
    2. Dietary therapy prolongs survival in dogs and cats and diminishes the number of uremic crises requiring hospitalization in dogs (Jacob et al., 2005; Ross et al., 2005).
    3. Renal diets are instituted at the time of diagnosis, even if no clinical signs are apparent.
  B. Control of proteinuria
    1. Angiotensin converting enzyme (ACE) inhibitors (enalapril or benazepril 0.25 to 0.5 mg/kg PO SID to BID) slow progression of renal failure in dogs with GN.
    2. ACE inhibitors do not prolong survival in most cats with CRF.
      a. Some benefit in cats with UPC >1 (Gunn-Moore, 2003)
      b. Considered in cats with UPC >0.4 (Syme et al., 2006)
  C. Control of secondary hyperparathyroidism
    1. Calcitriol (2.5 ng/kg PO SID) prolongs survival in dogs (Polzin et al., 2005).
      a. Contraindicated: uncontrolled hyperphosphatemia, hypercalcemia
      b. Adverse effects: hypercalcemia, soft-tissue mineralization
      c. Careful monitoring: calcium, phosphorus, parathormone levels
    2. Beneficial in dogs (may not benefit cats)
  D. Control of conditions associated with renal damage
    1. Hypertension (Jacob et al., 2003)
    2. Infections
    3. Dehydration, hypoperfusion
    4. Avoidance of nephrotoxic drugs or substances
II. Treatment of uremic signs
  A. Dehydrated animals that are unwilling or unable to tolerate oral fluids or those with hypotension are admitted to the hospital for IV fluid therapy.
    1. Balanced polyionic fluids are used for initial therapy (lactated Ringer's, 0.9% saline, Plasmalyte).
    2. Fluids with lower sodium content (0.45% saline + 2.5% dextrose) are appropriate after initial rehydration period.
    3. Maintenance fluid needs (66 mL/kg/day) plus dehydration deficit (body weight (kg) × % dehydration = deficit in L) are replaced over 4 to 48 hours.
      a. Longer replacement time of large deficits in animals with cardiovascular compromise
      b. More rapid replacement in hypotensive or oliguric animals
    4. After rehydration, maintenance fluid need plus 2.5% to 6% of body weight is given every 24 hours to promote diuresis.
    5. When the lowest creatinine level is reached, fluid dose is tapered gradually.
  B. Chronically dehydrated animals being maintained at home may benefit from regular SC fluid therapy.
    1. Dosing is empirical and adjusted based on hydration status and sense of well-being.
    2. Consider 100 to 150 mL SC SID two to three times weekly for cats.
    3. Cats tend to respond better than dogs.
  C. Appetite stimulants may be needed for anorexia.
    1. Cat: cyproheptadine 1 to 2 mg PO SID to BID
    2. Cat: oxazepam 2 mg PO BID
  D. Feeding tube placement allows administration of an appropriate quantity of the desired diet, easy administration of oral medications, and is strongly recommended in animals not voluntarily consuming adequate calories.
  E. One or more of the following may be given for nausea or vomiting:
    1. Inhibitors of gastric acid secretion
      a. Famotidine 0.5 mg/kg IV, SC, PO SID (not given IV in cats)
      b. Ranitidine 0.5 to 2.5 mg/kg SC, PO SID
      c. Cimetidine 5 to 10 mg/kg PO BID
      d. Omeprazole 0.7 mg/kg PO SID
    2. Antiemetics
      a. Metoclopramide 0.2 to 0.4 mg/kg SC QID or 0.01 to 0.02 mg/kg/hr IV as constant rate infusion (CRI)

b. Chlorpromazine 0.2 to 0.5 mg/kg IM, SC TID to QID
c. Ondansetron 0.1 mg/kg PO BID to TID, 0.1 to 0.3 mg/kg IV BID to TID
d. Dolasetron 0.5 mg/kg PO, SC, IV SID
3. Motility modifiers: cisapride 0.1 to 0.5 mg/kg PO BID to TID
4. Dogs: sucralfate 0.25 to 1 g PO TID if GI ulceration known or considered a possibility (hematemesis, melena, anemia)

F. Hyperphosphatemia requires treatment.
1. Phosphate-restricted diet
2. Phosphate binders to prevent absorption of phosphorus from ingested food
a. Aluminum hydroxide or aluminum carbonate 30 to 90 mg/kg/day PO divided BID to QID and administered with meals
b. Calcium acetate 60 to 90 mg/kg/day PO; hypercalcemia a possible side effect

G. Hypokalemia is more likely in cats than dogs.
1. Potassium gluconate 0.45 mEq/kg/day PO
2. Potassium citrate 40 to 75 mg/kg PO BID

H. Metabolic acidosis is more likely in cats than dogs.
1. Consider treatment if total CO_2 <16 mEq/L or blood pH <7.2.
2. Give potassium citrate 40 to 75 mg/kg PO BID (also addresses hypokalemia).
3. Give sodium bicarbonate 10 mg/kg PO BID.

I. Several therapies are available for anemia.
1. Transfusion: based on clinical need
2. Human recombinant erythropoietin (EPO)
a. Starting dose is 100 U/kg SC three times a week until packed cell volume (PCV) nears the target value, then gradually decrease to 50 to 100 U/kg SC every 4 to 7 days.
b. Target PCV is 25% to 30% in cats and 30% to 35% in dogs.
c. Monitor PCV weekly during the initial period.
d. Administer iron during initial therapy to ensure adequate response.
e. Antibody formation occurs in 25% of animals, necessitating discontinuation of therapy (Cowgill, 2003).
3. Darbepoetin: a newer erythropoiesis-stimulating protein
a. Starting dose of 0.45 μg/kg SC once weekly, tapered to every 2 to 3 weeks
b. Unknown risk of antibody formation in dogs and cats

J. Treatment of hypertension helps prevent end-organ damage.
1. Goal is to decrease systolic pressure to <160 mm Hg.
2. Medications may be combined to achieve the desired blood pressure.
3. Amlodipine 0.625 mg PO SID is a good first drug in cats.
a. Dose for dogs is 0.5 to 1.0 mg/kg PO SID or 0.2 to 0.4 mg/kg PO BID
b. If it does not control hypertension, then add an ACE inhibitor.
4. ACE inhibitors are good first choices if proteinuria is present.
a. Enalapril 0.25 to 0.5 mg/kg PO SID to BID
b. Benazepril 0.25 to 1.0 mg/kg PO SID to BID
c. BUN, creatinine, and potassium (checked 1 week after dose adjustments)
5. Beta-antagonists are helpful if tachycardia is present.
a. Atenolol 2 mg/kg PO SID to BID
b. Propranolol 5 to 80 mg PO BID to TID in dogs and 2.5 to 10 mg PO BID to TID in cats
6. Hydralazine 0.25 to 2.0 mg/kg PO BID is reserved for unmanageable hypertension.

Monitoring of Animal

I. Recheck examinations include physical examination, body weight, biochemistry panel, and CBC or PCV, and the frequency depends on severity of the disease.
A. Stage 2 (creatinine <2.1 mg/dL in dogs, <2.8 mg/dL in cats), relatively asymptomatic: recheck every 6 months
B. Stage 3 (creatinine 2.8 to 5.0 mg/dL), stable on therapy: recheck every 2 months
C. Stage 4 (creatinine >5 mg/dL): recheck monthly

II. Urinalysis and urine culture are performed at least twice a year.

III. Blood pressure measurement is performed at least every 6 months or 1 week after adjusting antihypertensive drugs.

IV. Changes in clinical signs warrant recheck examination.

V. Longevity is difficult to predict and can range from days to years.

VI. Cats tend to live longer than dogs.
A. Cats: survival of >3 years possible (in asymptomatic cats)
B. Dogs: survival of >2 years possible

ACUTE RENAL FAILURE

Definition

I. ARF is an abrupt decrease in renal function.

II. Acute kidney injury is generally not recognized until late in the course of disease when clinical signs are present.

Causes

I. Prerenal azotemia occurs when renal blood flow decreases, such as with dehydration or hypotension.

II. Ischemic damage can occur from progression of prerenal azotemia, hypotension, hypovolemia, circulatory collapse, excessive renal vasoconstriction, or renal vascular disease (e.g., thrombosis, DIC, stenosis).

III. Nephrotoxins may be endogenous (hemoglobin, myoglobin, calcium) or exogenous (see Nephrotoxicosis).

IV. Primary renal diseases include infectious, immune, neoplastic, or degenerative conditions that primarily affect the kidneys.

V. Systemic diseases that may cause ARF include pancreatitis, sepsis, hemolytic anemia, and heat prostration.

VI. Postrenal azotemia arises when obstruction or diversion of urine occurs, such as with urethral obstruction; ureteral obstruction; or uroabdomen from rupture of the ureter, bladder, or urethra.

Pathophysiology

I. Ischemic and toxic insults to the kidney lead to acute tubular injury, which varies in severity from sublethal cell damage to cellular necrosis.
II. Four phases of acute kidney injury exist.
  A. Initiation: when damage occurs; early intervention may prevent progression
  B. Extension: renal hemodynamic alterations, sublethal injury to eventual cell death; intervention possibly unsuccessful
  C. Maintenance phase: critical amount of irreversible damage
  D. Recovery: regeneration and repair of renal tissue, lasts weeks to months

Clinical Signs

I. Polyuria, polydipsia
II. Anorexia, nausea, vomiting, diarrhea
III. Listlessness or depression
IV. Possible dehydration, depression, hypothermia
V. Oral ulceration, uremic halitosis, tongue necrosis
VI. Tachypnea, tachycardia or bradycardia
VII. Enlarged, painful kidneys: suggestive of ARF
VIII. Uncommon: dyspnea, seizures, syncope, ataxia, muscle fasciculations, oliguria, anuria

Diagnosis

I. Serum biochemistry panel
  A. Azotemia, hyperphosphatemia, metabolic acidosis, elevated anion gap
  B. Variable electrolyte disorders: hyperkalemia, hypokalemia
  C. ± Hypoproteinemia, especially hypoalbuminemia
II. CBC: normal, hemoconcentration, blood loss anemia (GI ulceration)
III. Urinalysis
  A. Isosthenuria is expected.
  B. Glucosuria without hyperglycemia indicates proximal tubular damage.
  C. Proteinuria may occur from tubular or glomerular damage.
  D. Urine sediment examination may reveal casts, WBCs, RBCs, or possible crystalluria (ethylene glycol toxicosis).
  E. Urine culture is performed.
IV. Abdominal imaging
  A. Radiography typically shows normal or enlarged kidneys with normal contours.
    1. Renal asymmetry may be detected if unilateral obstructive ureterolithiasis is present.
    2. Check for mineral density; however, in 20% to 30% of cats with ureteral obstruction, no calcification is seen (Kyles et al., 2005).
  B. Ultrasonography evaluates renal size, shape, and architecture, and is invaluable in differentiating acute from chronic disease.
  C. IV or antegrade pyelography may be helpful in cases of hydronephrosis or possible ureteral obstruction.
V. Renal histopathology
  A. Histopathology provides more information about the cause if less invasive testing does not confirm a diagnosis.
  B. Because uremia induces a platelet function defect, assessment of a buccal mucosal bleeding time is recommended before biopsy.
VI. Specific tests for certain causes
  A. Serological testing for leptospirosis is performed in all dogs in endemic areas with ARF.
  B. Test for ethylene glycol is indicated (see Nephrotoxicosis).
  C. Other tests to consider include serological assays for infectious diseases (e.g., borreliosis, leishmaniasis) or evaluations for systemic diseases (e.g., pancreatitis, DIC).

Differential Diagnosis

I. ARF must be differentiated from CRF to provide an accurate prognosis.
  A. Long-standing polyuria and polydipsia, as well as poor body condition suggest chronicity.
  B. Ultrasonographic evidence of altered renal architecture may suggest chronicity.
  C. Enlargement of parathyroid glands (detected by ultrasonography) also indicates chronicity.
II. Prerenal or postrenal azotemia generally resolves rapidly with therapy.

Treatment

I. Fluid therapy is the mainstay of treatment.
  A. The calculated fluid deficit (body weight [kg] × % dehydration = fluid deficit in L) is administered IV over 4 to 6 hours.
  B. If cardiovascular compromise is present, then rehydration may be done over a longer period.
  C. Maintenance fluid rate is 66 mL/kg/day based on average urine production.
  D. Additional fluids (2.5% to 5% of body weight per day) may be administered to induce diuresis.
    1. If the kidneys cannot excrete the additional fluid load, then overhydration occurs.
    2. Oliguric or anuric animals are given 20 mL/kg/day for insensible needs (fluid lost via respiration and normal bowel movements), plus replacement of measured urine output, plus replacement of any other losses (e.g., vomiting, diarrhea).
II. Urine output is ideally monitored via a urinary catheter and closed collection system.
  A. Collecting naturally voided urine or estimating volume is less precise.
  B. If urine output is low (<0.5 mL/kg/hr), and the animal is hydrated with a systolic blood pressure >80 mm Hg, consider diuretics.

1. Mannitol 0.5 g/kg IV over 20 minutes (avoided if animal overhydrated)
2. Furosemide 1 to 2 mg/kg IV
   a. If no response occurs in 20 to 30 minutes, then double the dose.
   b. Follow with CRI of 0.25 to 1.0 mg/kg/hr IV or 1 to 2 mg/kg IV QID.
   c. Although furosemide increases urine volume, it does not improve renal function.

III. Uremic manifestations require specific or supportive treatment.
   A. Hyperkalemia is treated via translocation of potassium until urine flow can be reestablished or dialysis instituted.
      1. Regular insulin (0.25 U/kg IV) and dextrose (1 to 2 g/U insulin IV, then 1 to 2 g/U IV over next 4 to 6 hours) requires 30 minutes for onset of action.
      2. Sodium bicarbonate (1 to 2 mEq/kg IV over 10 to 20 minutes) is contraindicated if partial pressure of carbon dioxide (PCO_2) is elevated, and it may cause hypernatremia or paradoxical CNS acidosis.
      3. Calcium gluconate 10% (0.5 to 1.0 mL/kg IV over 10 minutes) is cardioprotective, but it does not decrease potassium concentrations and requires concurrent electrocardiographic monitoring.
   B. Acidosis is treated if blood pH is <7.1.
      1. One half of the calculated sodium bicarbonate dose (body weight [kg] × 0.3 × [desired bicarbonate – measured bicarbonate]) is administered over 20 to 30 minutes, and the rest is given over the next 2 to 4 hours.
      2. Hypernatremia is a possible complication, and bicarbonate is contraindicated if PCO_2 is elevated.
   C. For treatment of GI disorders, see CRF section.
   D. Hypocalcemia is treated cautiously and only if the animal is symptomatic.

IV. Early nutritional support may improve outcome.
   A. If vomiting prohibits enteral feeding, then total or partial parenteral nutrition may be used.
   B. Once vomiting is controlled, a feeding tube is placed if the animal remains inappetent.
   C. A protein-restricted diet (such as used for CRF) is appropriate in most situations.
   D. Oral phosphate binders can be added when enteral feeding is started.

V. Specific treatments exist for certain causes of ARF, including antibiotics for pyelonephritis or leptospirosis, or 4-MP for ethylene glycol toxicosis.

Monitoring of Animal

I. Frequency of monitoring depends on the severity of disease.

II. Check hydration status at least BID, namely skin turgor, mucus membrane tackiness, body weight, urine output, blood pressure, PCV, total solids, and central venous pressure.

III. Acid-base and electrolyte determinations are done multiple times daily if severe abnormalities exist.

IV. BUN and creatinine are measured SID to QOD.

V. Mortality is about 60%, and 60% of survivors have subsequent CRF (Vaden et al., 1997; Worwag and Langston, 2004; Cowgill and Francey, 2005).

DIALYSIS

Definition

I. Hemodialysis removes uremic toxins and other solutes from the blood by diffusion from the blood into dialysate, with treatments varying in length (generally several hours).

II. Continuous renal replacement therapy (CRRT) removes uremic toxins and other solutes from the blood by diffusion (hemodialysis), by convection (hemofiltration via ultrafiltration), or by both.

III. Peritoneal dialysis (PD) removes uremic toxins by diffusion across a semipermeable peritoneal membrane into dialysate that is instilled into the abdominal cavity and drained after variable dwell times.

Principles

I. Molecules in solution diffuse from an area of high concentration to an area of low concentration.
   A. Blood, with high concentrations of uremic solutes, is placed in apposition to dialysate, a solution similar to plasma without the proteins.
   B. A semipermeable membrane separates the blood and dialysate.
   C. In hemodialysis and CRRT, the semipermeable membrane is housed in the dialyzer, or artificial kidney.
      1. The dialyzer membrane has pores that allow small molecules to diffuse freely but restricts movement of proteins and cells.
      2. Some membranes allow diffusion of middle molecules (e.g., parathyroid hormone, vitamin B_{12}).
   D. In PD, the semipermeable membrane is the animal's own peritoneum.

II. Solute removal kinetics vary with the type of treatment.
   A. In hemodialysis and CRRT, continual flow of fresh dialysate maximizes the concentration gradient difference, thereby increasing efficiency of treatment.
   B. In PD, uremic solute diffusion is most rapid when dialysate is first infused, when the gradient between blood and dialysate is highest, and with frequent exchanges and short dwell times (45 to 60 minutes).

III. Excess fluid can be removed from the animal by applying hydrostatic or osmotic pressure to the system to cause water to move from the blood compartment to the dialysate compartment.
   A. The solutes dissolved in the water are also removed in a process called *convective clearance*.
   B. With hemodialysis and CRRT, the pressure is hydrostatic and created by the machine.
   C. With PD, adding dextrose to the dialysate creates an osmotic gradient.

Indications

I. ARF unresponsive to traditional medical management
   A. Oliguria, anuria
   B. Life-threatening volume overload (pulmonary edema)
   C. Hyperkalemia
   D. Lack of improvement of azotemia after 24 hours of diuresis
   E. Severe azotemia (BUN >100 mg/dL, creatinine >10 mg/dL)
II. Intoxications with substances that can be removed by dialysis
   A. In general, hemodialysis is the most efficient and rapid method to remove toxins, compared with CRRT or PD.
   B. Ethylene glycol is the most common indication.
   C. Other toxic drugs include methanol, salicylate, lithium, ethanol, phenobarbital, acetaminophen, theophylline, aminoglycosides, and tricyclic antidepressants.
III. CRF, as long as the client is fully committed to therapy
   A. Geographic availability of hemodialysis unit is necessary.
      1. Transport to and from unit is necessary three times a week.
      2. Expense is high.
      3. Before renal transplantation, two to four treatments are used to improve stability.
   B. Complications associated with PD have limited its application in CRF.
   C. CRRT is not appropriate for CRF.
IV. Choice of modality (hemodialysis, CRRT, or PD) frequently based on availability

Technique

I. Hemodialysis and CRRT
   A. Access to the bloodstream is via a double-lumen catheter in most cases.
      1. Blood is circulated from the animal through the dialyzer and returned in a continuous loop.
      2. Volume of blood removed varies with dialyzer size and tubing set (60 to 150 mL) and limits patient size to >2.5 kg.
   B. Dialysate is either produced by the dialysis machine (hemodialysis) or supplied in sterile bags (CRRT).
      1. Dialysate flow rate is much higher in hemodialysis than CRRT, allowing greater diffusive clearance.
      2. Dialysate composition (e.g., sodium, potassium, calcium, magnesium concentrations) is selected to fit individual needs.
   C. Schedule for dialysis varies based on patient factors and modality used.
      1. Hemodialysis for ARF is generally 3 to 5 hours per day for 4 to 7 days, then three times weekly.
      2. Hemodialysis for CRF is generally 4 to 5 hours, three times weekly.
      3. CRRT is 24 hours per day until renal function returns or the animal is hemodynamically stable; then intermittent hemodialysis is started, if available.
   D. Anticoagulation of blood is required, with heparin infusion used most frequently.
II. Peritoneal dialysis
   A. The PD catheter is sterilely placed in the abdominal cavity percutaneously or surgically.
      1. PD catheters have multiple fenestrations to avoid occlusion by omentum.
      2. Acute PD catheters can be placed with a trocar, with the tip directed caudally toward the bladder.
      3. Chronic PD catheters are placed surgically and frequently have one to two Dacron cuffs that are imbedded in the rectus muscle and subcutis to anchor the catheters and limit infection from the skin.
   B. Warm dialysate is infused into the abdomen.
      1. Commercially produced dialysate is available.
      2. Sterile 0.9% saline or lactated Ringer's solution can be adapted for use.
      3. Additional potassium is added as needed.
      4. Dextrose is added based on the animal's volume status.
         a. If no fluid removal is desired, then add 1.5% dextrose.
         b. If moderate fluid removal is desired, then add 2.5% dextrose.
         c. If maximal fluid removal is desired, then add 4.5% dextrose.
      5. Dwell times vary.
         a. With acute, severe uremia, frequent exchanges (hourly) are needed the first day to decrease the degree of azotemia.
         b. Less frequent exchanges with longer dwell times are used as the animal improves.
      6. Dialysate solution is then drained from the abdomen and discarded, followed by infusion of fresh dialysate to start the cycle again.
   C. Strict attention to aseptic technique is necessary.
      1. Connections are scrubbed with antiseptic solution before connection and disconnection.
      2. Sterile gloves must be worn.

Complications

I. Hemodialysis and CRRT
   A. Hypotension associated with the volume of blood removed is most likely in smaller or hypotensive animals, so systolic blood pressure should be >80 mm Hg before instituting therapy.
   B. Hemorrhagic complications may be associated with excessive anticoagulation.
   C. Partial catheter tip thrombosis occurs within several weeks in many cases.
II. Peritoneal dialysis
   A. Catheter occlusion by the omentum is common.
      1. Acute PD catheters may function poorly within 24 hours of placement.
      2. A fluted T catheter (Ash Advantage) occludes less frequently and is considered if dialysis catheter placement is a scheduled event rather than emergency procedure.
   B. Peritonitis is common.

1. Cloudy dialysate or abdominal pain may be a sign of peritonitis.
2. Intraperitoneal antibiotics may be sufficient therapy.
3. If fever or signs of systemic infection occur, then systemic antibiotics are also used (Chew et al., 2000; Ross and Labato, 2006).

C. Hypoalbuminemia from loss into the dialysate can complicate case management.

Monitoring of Animal

I. Hydration, attitude, body weight, electrolytes, and blood pressure are assessed multiple times each day initially.
II. BUN, creatinine, and PCV are also assessed initially.

RENAL TRANSPLANTATION

Definition

I. A kidney from a healthy donor is placed in the recipient to provide adequate renal function.
II. Immunosuppressive therapy is necessary to prevent the host (recipient) immune system from rejecting the transplanted tissue.

Recipient Selection

I. Cause of renal failure is generally unresolved CRF or ARF.
   A. Infectious causes (pyelonephritis) are contraindications.
   B. Risk of recurrence is high if calcium oxalate nephrolithiasis or ureterolithiasis is the initial cause of renal failure.
II. Absence of concurrent conditions, including hyperthyroidism, diabetes mellitus, and inflammatory bowel disease is required.
III. Normal cardiac function is a prerequisite.
IV. Tractable animal that permits intensive handling and monitoring is also necessary.
V. Owners must be committed to patient care, associated costs, and willing to provide a home for the donor cat.

Timing of Transplantation

I. The appropriate stage of disease for transplantation is undetermined.
II. Transplantation is usually recommended at the first sign of decompensation, as determined clinically (i.e., inability to maintain condition despite medical therapy).
III. Some cats decompensate very rapidly and in an unpredictable fashion, so transplantation is sometimes based on clinicopathologic parameters (e.g., creatinine >4.0 mg/dL).

Technique

I. The renal artery and vein of the transplanted kidney are usually anastomosed to the aorta and caudal vena cava.
   A. The native kidneys are left in place, because they may provide some function if the transplanted kidney does not function immediately.
   B. Extremely large kidneys (PKD) may be removed to improve abdominal comfort.
II. The ureter is implanted into the bladder.
III. The transplanted kidney usually starts to function within 7 days.
IV. Immunosuppression is necessary to prevent rejection.
   A. Cyclosporine and prednisone are the standard drugs used in cats.
   B. A combination of cyclosporine, prednisone, and azathioprine; a combination of cyclosporine, prednisone, and leflunomide; or pretransplantation whole-body irradiation, followed by autologous bone marrow transplantation are used in dogs.
V. When renal function has stabilized and immunosuppressive drug levels are regulated, the animal is discharged from the hospital (usually 1 to 2 weeks after surgery).

Monitoring of Animal

I. Intensive postoperative monitoring (e.g., blood pressure, temperature, fluid status, mentation) is required for the first 24 to 48 hours.
II. During the first 2 weeks, serum creatinine, urine output, and urine specific gravity are monitored SID and cyclosporine blood levels are monitored every few days.
III. Weekly rechecks are done for the first month.
IV. Monthly rechecks are done for 3 months and are followed by quarterly rechecks.

NEOPLASIA

See Table 48-7.

TRAUMATIC DISORDERS

Definition

I. Renal contusion or bruising results from compression, with disruption of intraparenchymal blood vessels.
II. Laceration is tearing of the renal parenchyma.
III. Avulsion of the renal pedicle may sever the renal artery, vein, or ureter.

Causes

I. Blunt trauma: automobile accident
II. Sharp, penetrating wounds: gunshot, stab wounds

Pathophysiology

I. Substantial hemorrhage may lead to significant cardiovascular compromise.
II. Urine leakage may lead to uremia.

Clinical Signs

I. Hematuria
II. Hemorrhage, hypovolemia
III. Abdominal or flank pain from capsular swelling or local accumulation of blood or urine
IV. Uremia

Diagnosis

I. History or evidence of trauma
II. Physical examination findings of enlarging abdominal mass, pain, or fluid accumulation

TABLE 48-7

Renal Neoplasia

TUMOR TYPE	SPECIES/INCIDENCE	CLINICAL FEATURES	TREATMENT/PROGNOSIS
Lymphosarcoma	Dogs and cats	Most common renal tumor of cats: 50% of cats FeLV positive 40% have metastasis to CNS	Median survival time with chemotherapy: 3-6 months in cats
Renal cell carcinoma	Dogs: 70% Cats: 68%	Most common renal tumor of dogs: middle-aged to older dogs (7-9 years), more common in males Local invasion common 30% have metastasis at diagnosis	Median survival time with nephrectomy: 8 months
Transitional cell carcinoma	Dogs: 15% Cats: 16%	Arise from renal pelvis May cause obstruction	Nephrectomy, piroxicam Prognosis poor
Mesenchymal tumors: sarcoma, fibroma, hemangiosarcoma	Dogs and cats: 5%-10%	Nonspecific findings	Nephrectomy Prognosis poor
Renal adenoma	Dogs and cats: 2%-5%	Nonspecific findings	Long-term survival possible
Nephroblastoma	Dogs and cats: 4%-5%	Dogs <1 yr of age: 60% Metastasis at time of diagnosis: 65%	Nephrectomy Prognosis poor
Renal cystadenocarcinoma	German shepherd dogs	Inherited as autosomal-dominant trait Accompanied by nodular dermatofibrosis and uterine leiomyoma	Nephrectomy Prognosis poor

Data from Henry CJ, Turnquist SE, Smith A et al: Primary renal tumors in cats: 19 cases (1992-1998). J Feline Med Surg 1:165, 1999; Klein MK, Cockerell GL, Harris CK et al: Canine primary renal neoplasms: a retrospective review of 54 cases. J Am Anim Hosp Assoc 24:443, 1988; Moe L, Lium B: Hereditary multifocal renal cystadenocarcinomas and nodular dermatofibrosis in 51 German shepherd dogs. J Small Anim Pract 38:498, 1997; Mooney SC, Hayes AA, Matus RE et al: Renal lymphoma in cats: 28 cases (1977-1984). J Am Vet Med Assoc 191:1473, 1987; Morrison WB: Cancers of the urinary tract. p. 545. In Morrison WB (ed): Cancer in Dogs and Cats: Medical and Surgical Management. 2nd Ed. Teton NewMedia, Jackson, Wyo, 2002; Vonderhaar MA, Morrison WB: Lymphosarcoma. p. 641. In Morrison WB (ed): Cancer in Dogs and Cats: Medical and Surgical Management. 2nd Ed. Teton NewMedia, Jackson, Wyo, 2002.

FeLV, Feline leukemia virus; *CNS,* central nervous system.

III. Imaging procedures
   A. Plain abdominal radiography may show decreased serosal detail from fluid or expansion of retroperitoneal space.
   B. Excretory urography generally indicates the site of rupture (contrast extravasation).
IV. Abdominal paracentesis to distinguish hemorrhage from urine leakage

Differential Diagnosis

I. Renal neoplasia with disruption of tubular or vascular components
II. Traumatic injury to other abdominal organs

Treatment

I. Contusions may need no specific therapy.
II. Therapy depends on type and severity of lesion and may involve IV fluid administration, blood transfusion, or surgical exploration to repair defects.

Monitoring of Animal

I. Serial evaluation of PCV is used to detect ongoing hemorrhage.
II. Serial evaluations of creatinine and/or BUN are used to assess renal function and possible urine leakage.
III. Late complications (2 to 6 weeks) include abscess formation (penetrating wounds) or urinoma (blunt trauma causing retroperitoneal urine leakage with subsequent encapsulation by fibrous tissue).

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CHAPTER 49

Diseases of the Ureter

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CONGENITAL DISORDERS

Ectopic Ureter

Definition

I. It is an embryologic abnormality that results in one or both ureters terminating distal to the bladder trigone.
II. Ectopic ureters are either extramural or intramural.
  A. An extramural ectopic ureter bypasses the urinary bladder entirely and inserts in the bladder neck, urethra, vagina, or uterus.
  B. An intramural ectopic ureter enters the bladder externally at the normal location but does not terminate in the trigone.
    1. The ureter traverses beneath mucosa and opens in a distal location.
    2. The ureteral opening may appear as a trough or as multiple openings along the submucosal tunnel.
    3. Bilateral ectopic ureters may open in a single orifice.

Causes

I. Congenital condition (likely genetic in dogs)
II. Reported rarely in cats
III. Females affected more often than males

Pathophysiology

I. During embryologic development the metanephric duct, which becomes the ureter, originates at an abnormal location or migrates in an abnormal fashion and prevents the development of a normal ureteral opening in the bladder.
II. Urinary incontinence results from the distal position of the ureteral opening and possibly from the presence of the submucosal tunnel within the urethra.
III. Associated conditions include absent or abnormally shaped kidneys, hydronephrosis, hydroureter, urethral sphincter incompetence, ureterocele, bladder hypoplasia, urachal remnants, and infection.

Clinical Signs

I. Continuous or intermittent incontinence may be noted since birth or weaning.
II. Normal urine voiding may also be seen.
III. Less urine dribbling may occur in male dogs because of their longer urethra.
IV. Urine may soak or stain the perineum of females.

Diagnosis

I. Physical examination may be normal or may reveal perineal urine staining or perivulvar dermatitis.
II. Male cats may have a constricted preputial orifice and urine accumulation within the sheath.
III. Results of hematological tests and serum biochemistry profile are normal or reveal concurrent renal disease.
IV. Urinalysis commonly reveals evidence of bacterial urinary tract infection (UTI).
V. Contrast radiography may provide a definitive diagnosis.
  A. Excretory urography (see Chapter 4) allows identification of the distal ureteral opening and is most likely to provide a diagnosis when combined with pneumocystography and/or fluoroscopy.
    1. A dilated ureter is the most common finding.
    2. The diagnosis may be missed from lack of opacification of the distal ureter secondary to peristalsis, poor renal excretion, or superimposition of other structures.
  B. Retrograde urethrography or vaginourethrography may cause filling of the ectopic ureter with contrast medium, thereby allowing its identification.
VI. Ultrasonography may be as accurate as contrast radiography for making the diagnosis (Lamb, 1998).
VII. Helical computed tomography (CT) might be more useful than excretory urography or urethrography when combined with fluoroscopy (Samii et al., 2004).
VIII. Cystoscopy of the urinary tract allows direct visualization of the normal or ectopic ureteral orifice, and evaluation of concurrent abnormalities.
  A. Single or multiple ureteral openings are seen in the urethra or vagina.
  B. A submucosal tunnel may also be detected.
IX. Cystometrography and urethral pressure profiles help identify concurrent functional abnormalities and provide information on likely prognosis after surgical correction (Lane et al., 1995).

Differential Diagnosis

I. Congenital structural anomalies of the urinary tract: urethral hypoplasia, urethrovaginal fistula, ureterocele, patent urachus
II. UTI
III. Congenital urethral sphincter incompetence
IV. Neurogenic disorders of micturition (see Chapter 51)
V. Partial obstruction or overflow associated with calculi or neoplasia
VI. Disorders causing polyuria: endocrine, renal, hepatic

Treatment

I. Surgery is the treatment of choice, and the procedure performed depends on the type of ectopic ureter and function of the associated kidney.
   A. Extramural ectopic ureters are ligated where they attach to the urethra, vagina or uterus, and they are reimplanted into the bladder cranial to or within the trigone (neoureterocystostomy).
   B. Two techniques have been described for intramural ectopic ureters.
      1. A new ureteral opening (neoureterostomy) is created where the ureter traverses the trigone, and the distal submucosal ureteral segment is ligated to prevent urine flow distal to the new opening.
      2. The submucosal ureteral segment is completely resected from the urethra and bladder neck before creating a new ureterostomy cranial to the trigone.
         a. The defect that was created by resecting the submucosal tunnel from the bladder neck and urethra is sutured closed.
         b. This technique may result in less postoperative incontinence because the submucosal tunnel disrupts the internal urethral sphincter mechanism (McLoughlin and Chew, 2000).
   C. Nephroureterectomy is performed if the kidney of origin is nonfunctional or chronically infected, providing the other kidney is functioning normally.
II. Additional procedures may be performed during or after surgical correction to improve postoperative incontinence associated with sphincter incompetence.
   A. Colposuspension, which involves suturing the vaginal stump to the body wall, increases pressure on the urethra.
   B. Endoscopic submucosal urethral injections of collagen or other substances increase resistance to urine flow (Barth et al., 2005).
III. Medical management is used to control UTIs or incontinence associated with concurrent bladder and urethral sphincter incompetence.
   A. Antibiotics are used to control UTI before surgery and may also be needed postoperatively.
   B. Alpha-adrenergic agonists may be helpful for postoperative incontinence (dogs).
      1. Phenylpropanolamine 12.5 to 50 mg PO TID
      2. Ephedrine 2 to 4 mg/kg PO BID to TID

Monitoring of Animal

I. The most common complication after surgery is persistent urinary incontinence.
II. Urinalysis, urine culture, cystoscopy, IV pyelography, cystourethrography, abdominal ultrasonography, and/or CT are used to evaluate the animal for the following possible causes of postoperative incontinence:
   A. Presence of a submucosal ureteral remnant or recanalization of a ligated distal ureteral segment
   B. Primary sphincter incompetence
   C. UTI
   D. Other congenital abnormalities of the urogenital tract
III. Dysuria is commonly seen for a few days after surgery.
IV. Hydroureter and hydronephrosis may occur from temporary obstruction of the ureter by inflammation, edema, or blood clots; permanent obstruction may result from stricture.

Ureterocele

Definition and Cause

I. It is a cystic dilation of the submucosal segment of the ureter near the ureteral orifice.
II. Ureteroceles are classified by location of the cystic dilation.
   A. When the dilation occurs in the normal location in the bladder trigone, the ureterocele is classified as orthotopic.
   B. An ectopic ureterocele occurs in a location distal to the bladder trigone.
III. Grading system proposed to identify presence of concurrent renal or ureteral disease is as follows (Stiffler et al., 2002):
   A. Grade 1: no concurrent ureteral or renal disease
   B. Grade 2: ipsilateral ureteral or renal disease
   C. Grade 3: bilateral ureteral or renal disease
IV. The embryologic cause of ureteroceles is unknown.

Clinical Signs

I. Animals may be asymptomatic.
II. Animals usually develop signs at a young age.
   A. Hematuria and dysuria may be related to UTI.
   B. Signs may result from the ureterocele obstructing the urethra or ureter.
   C. Incontinence may be seen with ectopic ureteroceles.

Diagnosis

I. Contrast radiography and ultrasonography allow a definitive diagnosis.
   A. An IV pyelogram combined with pneumocystography shows a contrast-filled dilation of the ureter.
   B. Retrograde urethrocystography reveals a filling defect.
   C. Ultrasonography usually identifies the ureterocele as a round, fluid-filled cystic structure in the bladder or proximal urethra.
II. Hydroureter or hydronephrosis indicating obstruction or pyelonephritis may also be seen.
III. Cystoscopy allows direct visualization of the ureterocele.

Differential Diagnosis

I. Other causes of congenital or acquired urinary incontinence
II. Urinary obstruction caused by uroliths or a blood clot in the trigone

Treatment

I. Cystoscopic incision or cystotomy with open resection is used to treat orthotopic ureteroceles.
II. Ectopic ureteroceles are treated by resection of the ureterocele, neoureterocystostomy, and reconstruction of the bladder neck and urethra.
III. If severe hydronephrosis or chronic infection (abscessation) of the associated kidney is found, then ureteronephrectomy may be performed if the contralateral kidney is functioning normally.

Monitoring of Animal

I. UTI is treated with appropriate antimicrobials.
II. Incontinence may persist in animals with an ectopic ureterocele.
III. IV pyelography, ultrasonography, and/or cystoscopy are warranted if clinical signs persist after correction.
IV. Because this condition is rare, prognosis is undetermined.

VESICOURETERAL REFLUX

Definition

I. Vesicoureteral reflux is the retrograde flow of urine into the ureter and renal pelvis from the urinary bladder.
II. Retrograde flow is the result of incompetence of the vesicoureteral junction.

Causes and Pathophysiology

I. Primary vesicoureteral reflux arises from maldevelopment of the vesicoureteral junction.
   A. Reflux occurs in many normal immature dogs but usually resolves with maturity.
   B. Primary reflux is usually bilateral and more prevalent in females.
   C. Maldevelopment of the junction can be associated with ectopic ureters.
II. Secondary vesicoureteral reflux is an acquired disorder that may lead to compression or obstruction of the vesicoureteral junction.
III. Causes of secondary reflux include inflammation, obstruction distal to the trigone, iatrogenic damage to the trigone, neurogenic diseases of the urinary bladder, and manual compression of the urinary bladder.
IV. Vesicoureteral reflux may be associated with pyelonephritis.
   A. Reflux may cause postvoiding retention of urine in the ureters that predisposes to infection.
   B. Pyelonephritis can result if reflux occurs during a lower UTI, but renal damage and pyelonephritis do not seem to occur without UTI.

Clinical Signs

I. Signs related to pyelonephritis, renal insufficiency, or failure
II. Signs of persistent UTI

Diagnosis

I. Contrast radiography may identify the reflux.
   A. Compression cystourethrography and maximal distention retrograde cystourethrography may be helpful.
   B. Poor positioning, the degree of distention, depth of anesthesia, and maturity of the animal may produce inaccurate results.
II. Cystoscopy is helpful to assess presence of ureteral ectopia or structural abnormalities of the vesicoureteral junction and trigone.

Treatment

I. Vesicoureteral reflux usually resolves as the animal matures.
II. Control lower UTIs to prevent pyelonephritis.

Monitoring of Animal

I. Frequent urine cultures followed by appropriate antibiotics are used to control UTIs.
II. Periodic assessment of biochemistry profile and urine specific gravity are performed to monitor for onset of renal insufficiency.

URETERAL OBSTRUCTION

Definition and Causes

I. Intraluminal obstruction
   A. Ureteroliths originating from the kidney are most commonly composed of calcium oxalate in dogs and cats.
   B. Blood clots may develop that are associated with severe hematuria from serious trauma or renal biopsy.
II. Intramural obstruction
   A. Primary neoplasia: transitional cell carcinoma
   B. Metastatic neoplasia
III. Extramural
   A. Compression
      1. Neoplasia of surrounding structures: uterus, bladder, trigone, bony pelvis, lymph nodes, gastrointestinal tract
      2. Perineal hernia with bladder entrapment
      3. Prostatic enlargement from inflammation, infection, neoplasia, or hypertrophy
   B. Iatrogenic surgical ligation
      1. It occurs most often during ovariohysterectomy.
      2. Most common site of ligation is near the uterine body.

Pathophysiology

I. The effect on renal function or glomerular filtration rate (GFR) depends on the duration and severity of the obstruction.
   A. Significant loss of function occurs in 24 hours, but normal GFR can return if the duration is <7 days (Kerr, 1956; Vaughn and Gillenwater, 1971; Yarger and Griffith, 1974).
   B. Permanent loss of function results with obstructions of >4 weeks.
II. Postobstructive diuresis occurs from an inability of the kidney to concentrate urine (which results from increased

blood flow and medullary washout), loss of response to antidiuretic hormone, and attempts to remove nitrogenous waste and restore electrolyte concentrations.
III. Impaired hydrogen ion excretion and increased potassium excretion occurs despite systemic hypokalemia, which leads to acid-base and electrolyte derangements.
IV. Hydroureter and hydronephrosis often occur with chronic obstruction.
V. Although the incidence of ureteral calculi is increasing, the pathogenesis is poorly understood (see Chapters 48 and 50).

Clinical Signs

I. Clinical signs are nonspecific and may include inappetence, lethargy, vomiting, and weight loss.
II. Bilateral ureteral obstruction results in severe clinical signs from uremia and hyperkalemia.

Diagnosis and Differential Diagnosis

I. A rectal examination is performed to assess for masses, prostatic disease, or perineal hernia with bladder entrapment.
II. Abdominal radiography may show radiopaque stones in the ureter or kidney, abdominal masses, or bony abnormalities of the pelvis.
III. Abdominal ultrasonography may identify hydronephrosis and hydroureter proximal to the obstruction.
IV. A combination of survey radiography and abdominal ultrasonography is 90% diagnostic in cats with ureteroliths (Kyles et al., 2005a).
V. Additional imaging studies, such as excretory urography, antegrade pyelography, or CT may be necessary to definitively diagnose the obstruction (Adin et al., 2003).

Treatment

I. Treat dehydration, hyperkalemia, and acid-base abnormalities first.
II. IV fluid diuresis is started to improve renal function and promote movement of a calculus.
III. Dialysis helps stabilize cats with ureteral obstruction but may not improve survival (Kyles et al., 2005b).
IV. Surgical correction is warranted if the obstruction cannot be relieved with medical management.
   A. Remove the obstruction as soon as the animal is stable enough for general anesthesia, because preservation of kidney function is inversely related to the duration of obstruction.
   B. If the obstruction is secondary to iatrogenic ligation, then remove the suture and assess ureteral damage.
      1. Neoureterocystostomy may be performed if ligation occurred close to the bladder.
      2. Resection of the damaged area and ureteral anastomosis are performed if ligation occurred at the midddle to proximal ureter.
   C. Surgical treatment of ureteroliths involves the following:
      1. Calculi are located by careful palpation and visualization.
      2. The ureter is usually dilated proximal to the obstructing stone.
      3. Because the ureter is typically embedded in mucosa and does not tend to move easily with flushing, the ureter is incised over the calculus.
      4. Once the stone is removed, a cannula or catheter is placed into the ureterotomy site and flushed to ensure patency.
      5. Alternatively, a piece of suture can be passed normograde or retrograde through the ureter to ensure patency.
      6. Ureteral leakage and persistent ureteral obstruction are common postoperative complications.
   D. Shockwave lithotripsy has been described in dogs but is not tolerated in cats (Block et al., 1996).
   E. If renal damage is severe or if abscessation has occurred and contralateral kidney function is normal, then consider ureteronephrectomy.
   F. Nephroureterectomy is often the only treatment for ureteral neoplasia that results in complete obstruction.
   G. See treatment of Ureteral Trauma in the following section.

Monitoring of Animal

I. Serial abdominal radiographs and abdominal ultrasonography are performed to assess patency of the surgical repair and to monitor for recurrence of ureteroliths.
II. Consider changing the urine pH, depending on type of calculus (see Chapter 50).
III. Monitor urinalysis and urine culture for recurrent UTI, especially if uroliths are still present in the kidney.

NEOPLASIA

See Chapter 50.

TRAUMA

Definition and Causes

I. Iatrogenic injury may arise from any abdominal surgery, abdominocentesis, cystocentesis, or needle biopsy of abdominal organs.
II. Penetrating or blunt trauma can cause laceration or rupture of the ureter.

Clinical Signs

I. Clinical signs are often nonspecific and may include lethargy, hematuria, abdominal discomfort, and shock.
II. Clinical signs may worsen if azotemia, metabolic acidosis, and hyperkalemia occur.
III. With traumatic ureteral rupture, 70% of animals arrive at the clinic in shock or with multiple organ injuries (Weisse et al., 2002).
IV. Concurrent injury to the kidney, surrounding vessels, and other organs may result in a hemoabdomen and signs of acute anemia.

Diagnosis and Differential Diagnosis

I. Ureteral obstruction, renal failure, bladder rupture, and proximal urethral rupture have similar clinical signs.

II. Abdominal radiographs may show loss of abdominal detail or increased opacification of the retroperitoneal space, but are not specific for uroabdomen or uroretroperitoneum.
III. Abdominocentesis is performed if uroabdomen is suspected.
  A. A fluid: serum creatinine ratio >2 hr : 1 hr or a fluid: serum potassium ratio >1.4 hr : 1.0 hr indicates uroabdomen (Schmeidt and Tobias, 2001).
  B. If hemorrhagic fluid is obtained, compare the abdominal fluid packed cell volume (PCV) with peripheral blood PCV (a higher fluid PCV indicates hemoabdomen).
IV. Excretory urography may localize the lesion.
  A. A retrograde cystourethrogram is performed first to rule out lower urinary tract rupture.
  B. Excretory urography is contraindicated if the animal is hypotensive.
    1. The animal must be hemodynamically stable to avoid renal failure, bradycardia, or cardiac arrest after administration of contrast agents.
    2. Poor renal perfusion also results in a nondiagnostic study (see Chapter 4).
  C. Excretory urography may help identify leakage from the ureter, but it does not always identify the location or severity of the tear.

Treatment

I. Fluid resuscitation with IV crystalloid solutions is initiated immediately for hypovolemic shock.
II. Dehydration is corrected over the next 6 to 24 hours with IV crystalloid solutions.
  A. Fluid rate is adjusted to maintain urine output at 1 mL/kg/hr.
  B. Ongoing losses from a peritoneal drainage catheter must be compensated for in the fluid rate.
III. Treat hyperkalemia and other metabolic disorders.
  A. Many abnormalities are corrected with fluid therapy.
  B. Hyperkalemia-associated cardiac disturbances are treated immediately.
    1. Regular insulin 0.25 to 0.5 U/kg and dextrose 1 to 2 g/U of insulin may be given as IV boluses.
    2. A 2.5% dextrose solution is also started as a constant rate infusion to prevent hypoglycemia.
    3. Alternatively, calcium gluconate 50 to 100 mg/kg is administered IV over 2 to 3 minutes, with continuous electrocardiographic monitoring.
IV. Establish abdominal drainage with a temporary peritoneal catheter.
V. Place a urethral catheter to monitor urine output if the opposite ureter is intact.
VI. Bilateral temporary nephrostomy tubes may be placed if bilateral ureteral trauma is suspected (Nwadike et al., 2000).
VII. Definitive surgical repair is not performed until the animal is stable.
  A. Surgical correction of the injury depends on its severity and location.
  B. Neoureterocystostomy or ureteral resection and anastomosis are options for surgical correction of ureteral tears.
    1. These techniques are difficult to perform and magnification is necessary in small dogs and cats.
    2. Tension on the ureteral repair is detrimental; relieve tension by psoas muscle pexy or renal descensus.
    3. Possible complications include ureteral obstruction, avulsion, stricture, and leakage.
  C. Neoureterocystostomy is used for injuries in the middle to distal one third of the ureter.
  D. Ureteral anastomosis is used for injuries in the middle to proximal one third of the ureter.
  E. Ureteronephrectomy is necessary if severe damage to the kidney and ureter occurs or if tension on a ureteral repair cannot be alleviated; however, the opposite kidney and ureter must be intact and functioning normally.

Monitoring of the Animal

I. Monitor urine output, serum blood urea nitrogen (BUN), creatinine, and potassium at least every 24 hours for 3 days postoperatively.
II. A decrease in urine output and increased serum potassium or azotemia may indicate renal failure, ureteral obstruction, or uroabdomen.
III. Abdominal ultrasonography is useful to assess for hydronephrosis or hydroureter related to a stricture or obstruction after surgery.

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CHAPTER 50

Diseases of the Urinary Bladder

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CONGENITAL DISORDERS

See Table 50-1.

INFECTIOUS DISORDERS

Bacterial Cystitis

Definition

I. Infection by bacteria causes secondary inflammation of the bladder mucosa.
II. Bacterial urinary tract infections (UTIs) are the most common infectious diseases of the bladder.
III. Recurrent UTIs may arise from reinfection or relapsing infections.
IV. Reinfection occurs from different bacteria, after appropriate antibiotic therapy has been instituted.
V. A relapse is a bladder infection from the same bacteria, with the same or slightly different antibiotic susceptibility patterns, that develops after appropriate antibiotic therapy has been instituted.
   A. The clinician should determine if the UTI is caused by a relapse or by reinfection.

TABLE 50-1

Congenital Abnormalities of the Bladder

CONDITION	DEFECT/CAUSE	CLINICAL SIGNS	DIAGNOSIS	TREATMENT
Persistent (patent) urachus	Urachus (conduit from bladder to the umbilicus) did not close	Urine leakage in the area of the umbilicus (may only see damp hair) Signs present from birth Urine spotting when laying down	Physical examination findings Contrast radiography: contrast cystourethrogram or inject contrast directly into opening	Surgical resection of patent urachus
Urachal diverticulum (vesicourachal diverticulum)	Small outpouching of tissue at the bladder apex from incomplete closure of the fetal urachus Secondary diverticula can occur secondary to severe urethral obstruction or feline sterile idiopathic cystitis	Signs of secondary UTI: diverticula provide an area for bacterial colonization in bladder May contribute to signs of idiopathic cystitis	Survey radiography or abdominal ultrasonography (uncommon) Contrast radiography Cystoscopy	Diverticulectomy if the animal has clinical signs No treatment if no clinical signs
Pelvic bladder	Bladder >10% within the pelvic canal rather than in the abdomen Most common bladder anatomical abnormality	± Urinary incontinence ± Incidental finding	Survey radiography May be palpable on rectal examination Cystoscopy may be suggestive	Treat with colposuspension if clinical signs are present
Urachal cyst	Secreting urachal epithelium persists in isolated segments of the urachus after birth	Incontinence UTI	Contrast radiography	Surgical removal of cyst
Bladder duplication	Very rare, occasionally reported in dogs	Incontinence UTI	Survey and contrast radiography	Surgery

UTI, Urinary tract infection.

B. A relapse is more often associated with treatment failure, whereas reinfection is usually associated with proper treatment in the presence of an underlying problem that predisposes the animal to a new UTI.

Causes

I. Bacterial UTIs are commonly associated with other primary abnormalities that increase the bladder's susceptibility to infection.
   A. Recessed vulva
      1. The vulva is partially hidden by overhanging skin and is not readily visible.
      2. This leads to a warm, moist environment for bacteria to grow and ascend to the bladder.
   B. Urinary cystoliths
   C. Bladder catheterization
   D. Urinary incontinence, with wicking of bacteria through the urethra from decreased midurethral pressure
   E. Diseases that decrease urine specific gravity
      1. Hyperadrenocorticism
      2. Chronic renal failure
      3. Diabetes mellitus
      4. Diabetes insipidus
   F. Anatomical abnormalities of the bladder and ureters
      1. Urachal diverticulum
      2. Ectopic ureter
      3. Patent urachus
      4. Urachal cyst
   G. Detrusor areflexia and hyporeflexia or other neurological abnormalities of the bladder

II. Bacteria commonly associated with UTI include the following:
   A. *Escherichia coli:* 40% to 50% of cases (Ling et al., 2001)
   B. *Staphylococcus* spp.
   C. *Proteus* spp.
   D. *Streptococcus* spp.
   E. *Enterobacter* spp.

III. Bacterial UTIs are not commonly seen in cats <10 years of age that can concentrate their urine well.

IV. In cats >10 years of age, the incidence of bacterial UTI increases to >50% for those with lower urinary tract signs (Lekcharoensuk et al., 2001).

Pathophysiology

I. Bacteria can be introduced via four mechanisms.
   A. Hematogenous route: secondary to a bloodborne bacteria
   B. Iatrogenic: secondary to urinary catheterization
   C. Local infections: secondary to a pyometra, an infected surgical sponge in the area of the bladder
   D. Ascending infections
      1. Most common route of infection
      2. Associated with ascending bacteria from the skin or the gastrointestinal (GI) tract

II. Almost all animals with a UTI have a suboptimal host defense system.

III. Normal host defense mechanisms consist of many parts.
   A. Normal voiding of urine (hydrokinetic washout)
   B. Increased urea in the urine
   C. Increased acidity of the urine
   D. Increased osmolality of the urine (especially in cats)

Clinical Signs

I. Clinical signs often include pollakiuria, stranguria, hematuria, and periuria (urinating in abnormal areas, such as outside the litter box).

II. Signs may be misconstrued as urinary incontinence.

III. Evidence of systemic disease (e.g., fever, leukocytosis) is usually indicative of an upper UTI.

IV. If the bacteria involved are *Escherichia coli*, then polyuria and polydipsia (PU/PD) may be noted.
   A. *E. coli* can interfere with the action of antidiuretic hormone (ADH), even when infection is not in the kidneys (because of distant effects of its endotoxin).
   B. Other bacterial infections are not associated with PU/PD, unless organisms are within the kidneys.

V. Up to 10% of dogs with no clinical signs have a positive urine culture when urine cultures are submitted as a routine data base (Ling, 1995).

Diagnosis

I. Urinalysis often reveals pyuria, hematuria, and bacteriuria.
   A. Bacteriuria in the absence of pyuria can indicate contamination, unless the animal is immunosuppressed.
      1. Many things in the urine sediment resemble bacteria, especially cocci.
      2. Clumps of white blood cells (WBC) are compelling evidence of the presence of bacteria.
   B. Sediment is examined as soon as possible, because cellular degeneration can occur rapidly and identification of cells may become more difficult with time.

II. A quantitative urine culture (reported in colony-forming units/mL [cfu/mL]) is indicated in possible cases of bacterial UTI.
   A. Urine is collected via cystocentesis.
   B. Catheterized urine samples are useful in cats and in male dogs, but the degree of contamination in female dogs is too high to justify its routine use.
   C. Voided urine is usually of no value unless nothing grows, because the presence of organisms may reflect contamination.
   D. Culture allows organism identification and testing for susceptibility to antimicrobials.
      1. Growth of >1000 cfu/mL (cystocentesis sample) of a single organism is diagnostic of UTI.
      2. Most UTIs have results >10,000 cfu/mL and many have >30,000 cfu/mL.
   E. Culture and susceptibility testing are imperative with recurrent UTIs, because organisms may become resistant to multiple antibiotics.

Differential Diagnosis

I. Urinary incontinence

II. Other causes of PU/PD: endocrine diseases, diabetes insipidus, psychogenic polydipsia

III. Other causes of cystitis: fungal, idiopathic (sterile)

TABLE 50-2

Common Antibiotics Used to Treat Bacterial Cystitis in Dogs

DRUG	DOSE (mg/kg)	ROUTE	FREQUENCY	MEAN URINE CONCENTRATION (µg/mL)
First-Choice Antibiotics				
Ampicillin	22	PO	TID	309
Amoxicillin	11	PO	TID	201.5
Trimethoprim-sulfonamide	13	PO	BID	26/79
Cephalexin	8	PO	TID	225
Second-Choice Antibiotics				
Chloramphenicol	33	PO	TID	124
Nitrofurantoin	4.4	PO	TID	100
Gentamicin	6	SC	SID	107
Amikacin	15	SC	SID	342
Enrofloxacin	5-10	PO	SID	40
Tetracycline	18	PO	TID	138

Adapted from Greene CE (ed): Infectious Diseases of the Dog and Cat. 3rd Ed. Elsevier Saunders, St. Louis, 2006; Ling GV: Lower Urinary Tract Diseases of Dogs and Cats. Mosby–Year Book, St. Louis, 1995.

IV. Neurological abnormalities of the bladder with loss of house-training habits
V. Behavioral elimination disorders

Treatment

I. Select an antimicrobial agent based on culture and sensitivity results (Table 50-2).
   A. First-choice antibiotics are used while awaiting culture results.
      1. If the infection is recurring, then use the antibiotic that was appropriate based on the last susceptibility results.
      2. Good initial antibiotics reach high enough concentrations in the bladder to be effective and have few side effects.
   B. Second-choice antibiotics are not considered initially because of their toxicity, low mean urine concentration, or high potency, and they are reserved for resistant infections.
   C. Nitrofurantoin is used more commonly to prevent rather than treat UTIs, and some dogs may develop myasthenia-like signs when on the drug.
   D. The side effects associated with the aminoglycosides (amikacin and gentamicin) preclude their use in all but the most resistant bacterial cystitis.
   E. Although enrofloxacin reaches good concentration in the urine, the medication is considered too broad spectrum and potent to be used as a first line of defense for bacterial cystitis.
      1. Enrofloxacin is used with caution in cats because of the possibility of acute blindness.
      2. Some infections with *Pseudomonas* spp. require 20 mg/kg/day PO to be effective.
II. Treat uncomplicated cases of bacterial cystitis for 10 to 14 days.
   A. Culture the urine 3 to 7 days after antibiotic therapy has been discontinued to document eradication of organisms.
   B. If the culture remains positive, then use appropriate antibiotics for a longer period of time.
III. In complicated or recurrent cystitis (or in dogs with cystoliths), give antibiotics for 3 to 4 weeks.
   A. Urine is recultured 5 to 7 days after beginning therapy to document in vivo susceptibility to the antibiotic therapy chosen.
   B. Urine is recultured 7 days after stopping therapy to document treatment efficacy.
   C. If the culture is positive while on therapy, then a different antibiotic is chosen.
   D. If the culture remains positive after completing therapy, then a different antibiotic is chosen or the same antibiotic is used for a longer period of time.
IV. In animals with frequent, new infections, consider long-term, low-dose prophylactic antibiotic therapy after the active UTI has been eradicated.
   A. Administer 33% to 50% of the recommended therapeutic dose of the antimicrobial SID.
   B. The antibiotic is given in the evening to increase the amount of time it comes in contact with urine.
V. Also treat any predisposing factors, such as diabetes mellitus, hyperadrenocorticism, hyperthyroidism, recessed vulva, ectopic ureter, or urinary incontinence.

Monitoring of Animal

I. In animals with predisposing factors, urine cultures are indicated every 3 to 4 months regardless of the presence of clinical signs.
II. Monitor animals with recurrent UTIs for the development of cystoliths and pyelonephritis via radiography, ultrasonography, and evaluation of urine sediment for casts (indicative of kidney damage).
III. Sequelae of bacterial UTIs include the following (Table 50-3):
   A. Emphysematous cystitis
   B. Cystoliths, especially struvite from urease producing bacteria
   C. Pyelonephritis
   D. Encrusting cystitis
   E. Polyploid cystitis

Fungal Cystitis

Definition

I. Fungal cystitis is a rare inflammation of the bladder secondary to a fungal infection.
II. A confirmed fungal infection is treated whether or not the animal is symptomatic; however, fungal agents in the urine may also represent contamination of the sample rather than true infection.

TABLE 50-3

Uncommon Forms of Cystitis

TYPE OF CYSTITIS	CAUSES	SIGNS	DIAGNOSIS	TREATMENT
Emphysematous	Usually associated with diabetes mellitus Infection of bladder wall with gas produced in the bladder wall	Recurrent UTI Painful urination	Survey radiography Abdominal ultrasonography	Appropriate antibiotic therapy Rarely, surgical stripping of bladder wall
Encrusting	*Corynebacterium urealyticum*	Recurrent UTI Painful urination	Urine culture Abdominal ultrasonography Contrast radiography Cystoscopy	Long-term antibiotics Bladder wall submucosal resection often needed
Polypoid	Inflammatory response to UTI Benign condition	Recurrent UTI	Contrast radiography Ultrasonography Cystoscopy	Treatment of underlying UTI Surgery to remove polyps (partial cystectomy or submucosal resection)
Parasitic	Most common cause is *Capillaria* spp.	Dysuria, pollakiuria, periuria May be asymptomatic	Urine sediment examination	Only if symptomatic: Fenbendazole 50 mg/kg PO SID for 5-10 days Levamisole 2.5 mg/kg SID PO for 5 days Ivermectin 0.2 mg/kg PO once in dogs (avoid in collie type of dogs)
Drug-induced	Sterile cystitis caused by cyclophosphamide or ifosfamide May be caused by metabolite (acrolein) that is a local irritant	Hematuria is primary sign (can be severe) Stranguria Pain on palpation of bladder	History of drug administration Exclusion of other causes of cystitis	Discontinue drug Institute diuresis Treat blood loss

UTI, Urinary tract infection.

Causes

I. Infection with *Candida* spp. is the most common cause.
II. Other systemic fungi and algae may disseminate to the bladder, including *Blastomyces* spp., *Cryptococcus* spp., *Aspergillus* spp., *Prototheca* spp., and *Trichosporum domesticum*.

Pathophysiology

I. Fungal cystitis occurs primarily in animals that are immunosuppressed or have other predisposing factors (e.g., bladder neoplasia, cystostomy tubes, prolonged use of antibiotics).
II. Animals with urinary tract disorders, neoplasia, or renal failure are at increased risk for fungal infections (Jin and Lin, 2005).

Clinical Signs

I. Animals may be asymptomatic.
II. Clinical signs may include stranguria, pollakiuria, and periuria.
III. Animals with disseminated fungal infections often have systemic signs.

Diagnosis

I. Fungal organisms are noted in the urine sediment.
II. To avoid treating simple contamination, only treat if two positive samples are obtained.
III. If a fungal infection is documented, then examine the animal for evidence of systemic fungal disease.
IV. Examine the animal thoroughly for predisposing factors.

Differential Diagnosis

I. Bacterial cystitis
II. Sterile cystitis
III. Contamination of the urine sample

Treatment

I. Treat any underlying condition.
II. If possible, discontinue any immunosuppressive therapy (e.g., corticosteroids).
III. Selection of an oral antifungal agent is based on the organism that is identified and susceptibility testing.
   A. Ketoconazole: 10 to 20 mg/kg PO SID or divided BID (dogs); 10 mg/kg PO BID (cats)

B. Itraconazole: dogs and cats 5 mg/kg PO SID, BID
C. Fluconazole: 3.5 to 7 mg/kg PO BID (dogs); 3.5 to 6 mg/kg PO BID (cats)
D. Amphotericin B: various IV doses

IV. Bladder infusion of clotrimazole has been reported for *Candida* spp. (Toll et al., 2003).
V. Altering urine pH as a means of treating fungal infection has not been effective.

Monitoring of Animal

I. Routine urine cultures and examination of urine sediment are performed every 2 to 4 weeks until the animal is negative for the fungal organism.
   A. Continue antifungal agents for an additional 7 to 14 days after negative results.
   B. If a second urine culture and sediment are negative for the organism, then the antifungal agents are discontinued.
II. Once the infection has been successfully cleared, examine the urine sediment and culture every 1 to 2 months until three negative examinations are obtained.
III. Animals with predisposing factors must be monitored closely for recurrences.

INFLAMMATORY DISORDERS

Feline Idiopathic Cystitis

Definition and Causes

I. Feline idiopathic cystitis is inflammation (nonobstructive) of the bladder in which no infectious pathogen is identified.
II. In cats, it is considered an idiopathic disease.
III. Idiopathic cystitis is a diagnosis of exclusion.
IV. The terms *feline urologic syndrome* and *feline lower urinary tract* disease are nonspecific and do not indicate a diagnosis.

Pathophysiology

I. It may be induced or maintained by activation of neurogenic inflammation.
   A. Increased sensory neural input from the bladder
   B. Increased catecholamine outflow from the brainstem
   C. Altered uroepithelial structure and function
   D. Altered dynamics of urinary glycosaminoglycan
   E. Increased bladder permeability
   F. Mast cell infiltration
   G. Local axon reflex discharges in the bladder
II. Other contributing factors include the following:
   A. Gender: males affected more commonly
   B. Urethral disease: spasms, stricture, inflammation
   C. Stress: believed to play an important role
   D. Dry foods: low urinary output

Clinical Signs

I. Dysuria, stranguria, pollakiuria, periuria
II. Hematuria
III. Licking at the prepuce
IV. Can progress to urinary obstruction in males

Diagnosis

I. Clinical signs are often suggestive in cats.
   A. Presence of hematuria in young to middle-aged cats is highly suggestive.
   B. Recurrent episodes occur in about 50% of cats (Westropp and Buffington, 2003; Kruger et al., 2003).
   C. Episodes may be related to stressful events in the cat's life.
   D. Regardless of treatment, most acute episodes resolve within days.
II. Bacterial culture of the urine is negative.
III. Urinalysis shows a preponderance of red blood cells (RBCs), few WBCs, occasional transitional epithelial cells, and no bacteria.
   A. Hematuria and proteinuria may wax and wane in chronic cases.
   B. Urine pH is usually <7.0.
   C. Crystals are often absent or few in number.
      1. Crystals are thought to have no pathophysiological importance with nonobstructive cystitis.
      2. Significance of crystals in sterile cystitis is difficult to interpret (see Urolithiasis).
         a. Struvite crystals may occur in sterile urine, but urine pH is usually alkaline.
         b. Calcium oxalate crystals and uroliths usually develop in acidic urine.
         c. Crystalluria does not correlate well with urolith formation.
IV. Radiography is indicated to rule out the presence of cystoliths.
   A. Some animals (33%) have focal or diffuse bladder wall thickening on survey or contrast radiography (Figure 50-1) (Scrivani et al., 1998).
   B. Usually the bladder appears normal on double-contrast radiography.

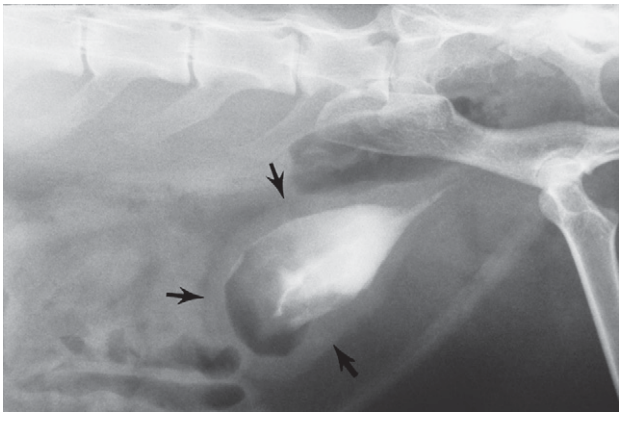

FIGURE 50-1 Double-contrast cystogram of a cat with chronic idiopathic cystitis. Note the diffusely thickened bladder wall *(arrows)* and filling defects within the central contrast pool. *Courtesy Paul Barthez.*

C. Rarely, contrast material diffuses through the layers of the bladder wall.

V. Examination of the bladder may reveal mucosal edema, glomerulations (submucosal petechiations), and increased vascularity.

Differential Diagnosis

I. Bacterial cystitis
II. Fungal cystitis
III. Renal hematuria
IV. Urethral obstruction
V. Urolithiasis
VI. Neoplasia: transitional cell carcinoma (rare in cats)
VII. Behavioral elimination abnormalities

Treatment

I. Episodes of idiopathic cystitis usually resolve within 4 to 7 days regardless of treatment.

II. Symptomatic treatment includes environmental enrichment, increasing water intake, and medical therapy.

A. A recent study showed an 80% decrease in recurrence of feline idiopathic cystitis when environmental enrichment was initiated (Buffington et al., 2006).

1. Provide stimulation (e.g., toys, windows for outside viewing, increasing time spent with the owner) to help affected cats.
2. Increase the number of litter boxes to equal the number of cats in the household plus one.
3. Remove dirty litter at least SID and clean the box at least monthly using water and mild detergents.
4. Use unscented litter.
5. Note that some cats show an aversion to or preference for certain types of litter (see Chapter 119).

B. Increasing water intake and decreasing urine specific gravity may reduce noxious irritants in the bladder.

1. Provide affected cats with plenty of fresh water.
2. Circulating water fountains, adding water to food, or providing the cat with ceramic water bowls may increase their proclivity to drink.
3. Feed canned food to decrease urine specific gravity.
4. Subcutaneous fluids may be helpful in some cats.

C. Medical therapy for acute episodes includes medications to decrease stress, provide pain relief, and combat inflammation of the bladder.

1. Acepromazine is given at 0.05 to 0.1 mg/kg SC every 4 to 6 hours or 0.25 to 1.0 mg/kg PO BID.
   a. Tranquilizing effects reduce stress associated with the episode and helps to relieve urethral spasms.
   b. The drug is given to the point where the cat is mildly sedated and the third eyelid is elevated.
2. Oral diazepam is avoided because of the possibility of acute hepatocellular necrosis.
3. Butorphanol (0.2 to 0.4 mg/kg SC every 4 to 6 hours or 1.0 to 2.5 mg PO SID-BID) or buprenorphine (0.005 to 0.01 mg/kg SC, PO TID to QID) is given for pain.
   a. Buprenorphine may be preferable, because it can be given less frequently.
   b. The injectable form of buprenorphine can be given orally and is well tolerated by cats.
4. Tricyclic antidepressants are not recommended for acute episodes, because their maximal effect may take weeks.
5. Antibiotics are not usually warranted, especially in young cats.
6. Glucocorticoids are contraindicated after any recent urinary obstruction because of the increased susceptibility to bacterial UTI and pyelonephritis (Barsanti et al., 1992).
7. For more information, see treatment of associated urethritis and urethral spasms in Chapter 52.

III. Medical therapy for chronic idiopathic cystitis may include medications to modify behavior or inflammation.

A. Tricyclic antidepressants are used for their antiinflammatory effects (Chew et al., 1998).

1. They are not used in recently obstructed cats because of their anticholinergic effects on the detrusor muscle of the bladder, which is adversely affected from overdistension.
2. Amitriptyline is given at 2.5 to 12.5 mg PO SID.
3. Clomipramine is given at 0.5 mg/kg PO SID and affects norepinephrine reuptake less than amitriptyline (Dell and Butrick, 2006).
4. Abrupt withdrawal can lead to exacerbation of clinical signs.

B. Buspirone (5 to 10 mg PO BID to TID) maybe useful in some cats.

C. Feline pheromone (Feliway) may be beneficial in some cases (Gunn-Moore and Cameron, 2004).

1. Use with caution around people with asthma.
2. Effects on cats with asthma are unknown.

D. Other therapies with no proven benefit include the following:

1. Pentosan polysulfate sodium (*Elmiron,* Cartrophen Vet) 50 mg PO BID on food for a minimum of 4 weeks
2. Glucosamine-chondroitin sulfate (*Cosequin* for cats) 1 capsule PO SID
3. Polysulfated glycosaminoglycans 1.1 to 4.8 mg/kg IM every 4 days for six doses

Monitoring of Animal

I. Once idiopathic cystitis is diagnosed in a cat, institute preventative measures.

A. This includes environmental enrichment, long-term medical management, and reducing stress.

B. Treating cats prophylactically with acepromazine, butorphanol, and/or buprenorphine before a known stressful event may prevent recurrent episodes (Buffington et al., 2006).

C. Note that the stress of a visit to the veterinarian's office may exacerbate the signs.

D. See www.vet.ohio-state.edu/indoorcat for further information regarding environmental enrichment.

II. Despite preventative measures, recurrences are common and the time between episodes is variable (weeks to years).

III. Male cats must be closely monitored for the development of urethral obstruction (see Chapter 52).

Urinary Cystolithiasis

Definition

I. Uroliths (calculi) are concretions of minerals and matrix proteins that form in the urinary tract, especially the bladder.

II. Uroliths often form when urine is oversaturated with minerals.
   A. Supersaturation occurs when the concentration of calculogenic minerals is increased.
   B. An increase in concentration of minerals can occur in animals without formation of uroliths.
   C. Urine pH and promoters or inhibitors of crystal formation may affect the solubility of calculogenic minerals.

Causes and Pathophysiology

I. Crystals or microscopic precipitates in urine are not always evidence of urolith formation.
   A. Uroliths may be present without crystals, and crystals may be present without forming uroliths.
   B. The type of crystals present may be different from the type of calculi found.

II. Struvite uroliths are the most common uroliths found in dogs.
   A. Struvites are formed from magnesium, ammonium, and phosphate ions.
   B. In both dogs and cats, struvite uroliths are more likely to form in alkaline and infected urine.
   C. In dogs, UTIs with urease-producing bacteria predispose to struvite formation.
      1. Calculi can form in the absence of infection, which is more common in cats (95% of cat struvite uroliths are sterile) (Houston et al., 2004b).
      2. Urease-producing organisms include *Staphylococcus* spp., *Proteus* spp., *Streptococcus* spp., *Klebsiella* spp., and *Ureaplasma* spp.
      3. Urease-producing bacteria alkalinize the urine and increase concentrations of ammonium and trivalent phosphate ions in the urine.
   D. Predisposed canine breeds include the miniature schnauzer, shih tzu, bichon frisé, Lhasa apso, and miniature poodle.
      1. American cocker spaniels are predisposed to sterile struvite urolithiasis.
      2. Predisposed feline breeds include the ragdoll, British shorthair, domestic shorthair, Oriental shorthair, Chartreux, and Himalayan.
      3. Devon Rex, Burmese, Abyssinian, Russian blue, Siamese, and Birman cats are at decreased risk.
   E. Other risk factors include diets high in protein, magnesium, and phosphorous, with increased urine excretion of magnesium and phosphorous.

III. Calcium oxalate uroliths are more likely to occur in acidic urine.
   A. Their formation is related to systemic acid-base effects rather than the physicochemical effects of pH in the urine.
   B. Hypercalcemia and calciuretic medications (e.g., saline, furosemide, prednisone) can increase formation of calcium oxalate uroliths.
   C. A familial defect causing primary hyperoxaluria has been reported.
   D. Pyridoxine deficiency and fat malabsorption theoretically may predispose to calcium oxalate stones, but no clinical cases have been observed.
   E. Male dogs are more commonly affected than female dogs.
   F. Predisposed breeds include the miniature schnauzer, shih tzu, bichon frisé, Lhasa apso, Yorkshire terrier, and miniature poodle.
   G. Calcium oxalate uroliths are the most common type seen in cats.
      1. Predisposed feline breeds include the Persian, Himalayan, ragdoll, British shorthair, exotic shorthair, Havana brown, and Scottish fold.
      2. Birman, Abyssinian, and Siamese cats are at decreased risk.

IV. Ammonium urate uroliths form when increased amounts of urates build up in the urine, usually from increased intake of purines (precursors of uric acid) in the diet.
   A. These uroliths are more likely to form in acidic urine.
   B. They also occur secondary to impaired ability to convert uric acid to allantoin, which is more soluble (especially in Dalmatians).
   C. They are associated with portosystemic shunts or hepatic microvascular dysplasia.
   D. Besides the Dalmatian, English bulldogs may be predisposed.

V. Calcium phosphate uroliths (hydroxyapatite) occur very infrequently in dogs and cats.
   A. Calcium phosphate is more commonly a component of other stones.
   B. Alkaline urine increases the precipitation of hydroxyapatite in urine.
   C. Hyperparathyroidism is the most common clinical disease associated with these calculi.
   D. Predisposed breeds include the miniature schnauzer, bichon frisé, shih tzu, and Yorkshire terrier.

VI. Cystine uroliths are uncommon in dogs and cats.
   A. The solubility of cystine crystals decreases in acidic urine, thereby increasing the likelihood of calculi formation.
   B. Predisposed breeds include the English mastiff, Newfoundland, English bulldog, dachshund, Tibetan spaniel, and basset hound.
   C. Siamese cats are also predisposed.

D. Male dogs and cats are more likely to develop these calculi.

VII. Xanthine uroliths are also uncommon in dogs and cats.
A. They usually occur secondary to allopurinol treatment, especially if the animal continues to eat a high-purine diet.
B. Breed predisposition includes any dog on allopurinol (especially Dalmatians), as well as the Cavalier King Charles spaniel and dachshund.

VIII. Silica uroliths are very rare in dogs and cats.
A. They occur in dogs and cats on diets high in corn gluten or soybean hulls.
B. The German shepherd dog and Old English sheepdog have an increased incidence.
C. Males are affected more frequently than females.

Pathophysiology

I. Urethral obstruction can occur if stones are small enough to move out of the bladder but too large to move through the urethra.
II. Calculi can cause irritation to the bladder mucosa, leading to inflammation and cystitis.
III. Calculi can also serve as substrate for bacteria, leading to persistent bacterial UTI.

Clinical Signs

I. Clinical signs are similar regardless of the type of urolith present.
II. Hematuria, stranguria, dysuria, and pollakiuria may be noted.
III. Bacterial infections associated with the uroliths may worsen the clinical signs.
IV. Some dogs and cats exhibit no clinical signs related to the uroliths.
V. Some uroliths may be passed in the urine.
VI. If the animal becomes obstructed from the stone moving into the urethra, then it has difficulty urinating.

Diagnosis

I. Uroliths are considered in animals that have predisposing factors (e.g., systemic disease, history of stone formation).
II. Physical examination may be unremarkable, but occasionally stones are palpable in the urinary bladder or the urethra.
III. Urinalysis may reveal hematuria, bacteriuria, and changes in pH typical for the type of stone present.
IV. Crystalluria may be present without stones, and stones may be present without crystalluria; therefore crystalluria is not very helpful in the diagnosis of calculi.
V. Urine culture is indicated to identify primary and secondary UTI.
VI. A complete blood count and biochemistry profile may be normal; however, hypercalcemia is observed in approximately 4% of dogs and 35% of cats with calcium oxalate uroliths (Bartges et al., 2004).
VII. Abdominal radiography may reveal stones that are radiopaque.
A. Radiopaque uroliths include struvite, calcium oxalate, and calcium phosphate.
B. Stones must be ≥3 mm in diameter to be seen on radiographs.
C. The entire urethra is radiographed to look for calculi that may cause obstruction.
D. Double-contrast radiography may be needed to demonstrate urate and cystine uroliths, which are radiolucent.
E. Ultrasonography is helpful in identifying calculi in the bladder and proximal urethra, regardless of their radiodensity; however, it cannot examine the distal portions of the urethra.

Differential Diagnosis

I. Any form of cystitis
II. Bladder neoplasia

Treatment

I. Surgical removal of calculi is often necessary, especially if the animal is obstructed or has had multiple episodes of urolithiasis.
A. If medical therapy is attempted and no improvement is seen after 4 to 6 weeks, then surgery is indicated.
B. Postoperative radiographs are taken to document that all calculi have been removed.
C. Submit all calculi for analysis (dry, not in formalin).

II. Voiding urohydropulsion may be used to retrieve stones that are smaller than the diameter of the urethra (Figure 50-2).
A. Approximate sizes are 5 mm in male dogs, 7 mm in female dogs, 1 mm in male cats, and 5 mm in female cats.
B. An alternative method is to insert a urinary catheter in the bladder and distend the bladder with saline, which dilates the urethra and helps the calculi pass.
C. Voiding urohydropulsion is less successful in male dogs and cats than in female dogs.

III. Indications for medical treatment include animals that are poor candidates for general anesthesia and the presence of dissolvable calculi (struvite, cystine, possibly xanthine).
A. Struvite uroliths may be treated as follows:
1. Infection-associated struvite stones are dissolved using appropriate antimicrobial therapy (based on culture and sensitivity testing) and dietary changes.
2. The average time for dissolution is 12 weeks in dogs and 11 weeks in cats (Osborne et al., 1999).
3. Diets formulated for struvite dissolution are protein and magnesium restricted and cause the urine pH to become acidic.
a. These diets are also supplemented with salt to induce diuresis.
b. Blood urea nitrogen (BUN) and urine specific gravity are monitored during dietary modification to ensure that the animal is receiving this diet exclusively.

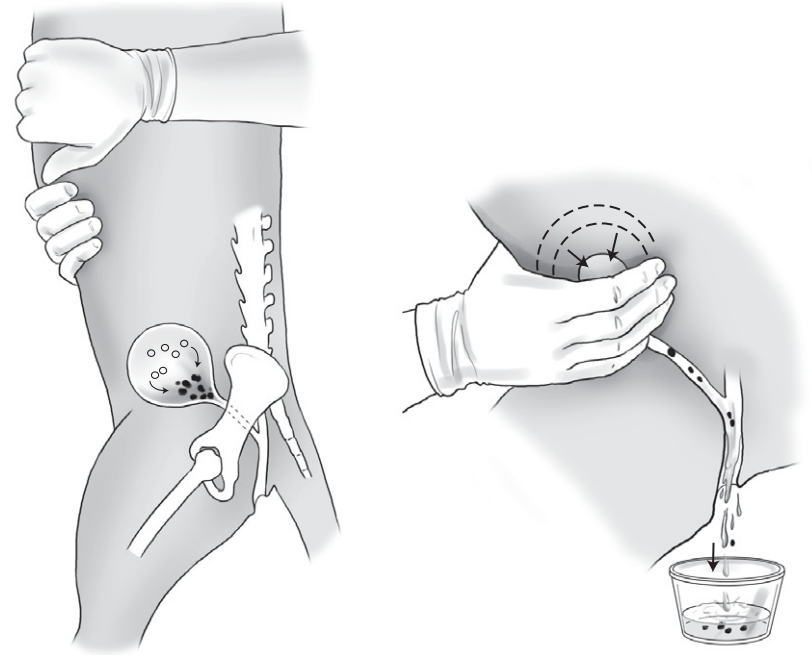

FIGURE 50-2 Technique for voiding urohydropulsion in a female dog. **A,** The animal is held so that the head points upward and the spine is relatively vertical to the floor. **B,** After the bladder has been filled to moderate distension, the urethral catheter is removed and the bladder is expressed to expel small stones *(black dots)*. The procedure is repeated several times until all stones have been expelled. *Arrows* indicate direction of bladder compression.

(1) Dogs should have low normal BUN owing to low protein in the diet.
(2) Cats should have normal BUN, because calculolytic diets in cats are not protein-restricted.
(3) Treated animals should have a urine specific gravity lower than before starting the diet, usually in the range of 1.006 to 1.017.

c. Feeding anything other than the prescribed diet (e.g., treats, other commercial pet foods, table scraps) dramatically decreases the success of dietary modification.

4. In sterile struvite urolithiasis, antimicrobial therapy is not needed; these uroliths may dissolve more quickly (4 to 6 weeks in dogs, 5 weeks in cats) (Osborne et al., 1999).

B. Calcium oxalate uroliths cannot be dissolved medically.

C. Treatment of ammonium urate uroliths varies.
1. Uroliths associated with portosystemic shunts are not amenable to medical dissolution.
a. Surgical removal is indicated and maybe done at the time of ligation of the shunt.
b. Uroliths may dissolve once the shunt is ligated if they are not removed at the time of ligation (because of surgical or anesthetic difficulties).
2. Urate calculi not associated with portosystemic shunts may often be dissolved medically.
3. Allopurinol may be tried in dogs at 10 to 15 mg/kg PO BID.
4. Allopurinol must be used cautiously in cats (9 mg/kg PO SID) because of limited data on its safety and efficacy.
5. Alkalinizing the urine through dietary changes may also be beneficial.
6. Diets low in purine, such as Hill's u/d, may be beneficial in the short term, but are not used long term.
7. Medical dissolution (successful in 50% of cases and usually takes 4 weeks) (Osborne et al., 1999).

D. Cystine uroliths may respond to the following:
1. 2-Mercatopropionol glycine (2-MPG) is given at 15 to 20 mg/kg PO BID in dogs
a. No feline dose identified.
b. Reported side effects include behavioral changes in dogs.
2. Dissolution takes approximately 4 to 12 weeks.
3. Feed a low-protein, alkalinizing diet.

E. For xanthine uroliths treatments of choice are discontinuation of allopurinol and feeding a low-purine diet.

IV. Calcium oxalate, calcium phosphate, and silica uroliths cannot be dissolved medically.

V. Other measures that may be beneficial regardless of type of urolith include the following:
A. Most dogs and cats are placed on a canned diet (higher moisture content) to decrease urine specific gravity, and attempts are made to increase water intake.
B. Treat any underlying disease, such as hyperadrenocorticism or hyperparathyroidism, appropriately.
C. Treat any associated bacterial UTI appropriately.

Monitoring of Animal

I. Monitoring for recurrence is essential.
II. Serial radiographs are performed for all radiopaque stones during dissolution, at least 3 to 4 months after dissolution and every 6 to 12 months thereafter.
III. Medical therapy is continued for at least 1 month after radiographic resolution.
IV. With struvite uroliths, preventing recurrence of infections is essential.
  A. Repeat urine cultures every 3 to 4 months.
  B. Treat any underlying cause of the infections (e.g., hyperadrenocorticism, recessed vulva).
  C. Low-dose antibiotic therapy may be used to prevent recurrent UTI.
  D. In those dogs with infection-induced struvite uroliths, changing the diet may not be needed, except to increase water intake.
  E. For those animals with sterile struvite uroliths, permanently changing to an acidifying diet can help to prevent recurrence.
    1. Avoid excessive acidification of the urine (<6.0 pH).
    2. Restrict dietary magnesium.
V. For calcium oxalate uroliths, no treatment has been shown to definitively prevent recurrence.
  A. Treating any underlying calcium abnormality may decrease recurrences.
  B. In dogs, a protein- and sodium-restricted diet may be helpful.
    1. Less acidifying diets may decrease calciuresis.
    2. Choose a diet that promotes a neutral pH (6.5 to 7.0).
    3. Alkalinizing diets may promote struvite formation in susceptible individuals.
  C. Adding potassium citrate to the diet may alkalinize the urine if diet alone does not prevent recurrence.
    1. Potassium citrate increases concentration of citrate in urine, facilitating interaction of urinary calcium with citrate.
    2. Calcium citrate is more soluble than calcium oxalate.
    3. Dose in dogs is 50 to 75 mg/kg PO BID.
    4. Efficacy is uncertain in dogs and cats.
  D. Cats are encouraged to increase their water intake by feeding a canned diet or adding water to the diet.
  E. Hydrochlorothiazide reduces urinary calcium excretion in normal dogs and may be tried in dogs with multiple recurrences at 2 mg/kg PO BID (Lulich et al., 2001).
  F. Serial radiographs are essential to document recurrence before clinical signs develop.
VI. If ammonium urate uroliths are associated with portosystemic shunts and the shunt is not treatable, then feeding a low-protein, alkalinizing diet may help prevent recurrences.
  A. Diets high in vegetable or dairy proteins have lower purine levels than those derived from other protein sources.
  B. Dry formulations of low-purine diets are less effective than canned diets.
  C. If calculi arise from other causes (e.g., feeding a low-protein diet), then feeding an alkalinizing diet prevents recurrence in 80% of dogs (Bartges, 1993).
  D. Cats may also benefit from a low-protein, alkalinizing diet.
  E. Allopurinol can be used in dogs without portosystemic shunts at 5 to 10 mg PO BID to help prevent recurrences.
VII. Maintaining neutral pH of urine can prevent calcium phosphate uroliths.
VIII. To prevent cystine uroliths, animals are fed a low-protein, alkalinizing diet.
  A. Potassium citrate (50 to 75 mg/kg PO BID) is given, with the dose adjusted to maintain a urine pH ≥7.5.
  B. In dogs, 2-MPG (15 to 20 mg/kg PO BID) can be given with alkalinizing therapy, if dietary modification is not possible.
    1. Regenerative anemia and myopathy have been reported with 2-MPG.
    2. Behavioral aggression has also been associated with 2-MPG.
IX. Discontinuing use of allopurinol and changing to a low-purine diet can prevent xanthine uroliths.
X. Avoiding diets high in plant proteins can prevent silica uroliths.

NEOPLASIA

Definition and Causes

I. Bladder tumors occur more often in dogs than in cats.
II. Bladder tumors account for <1% of all canine neoplasms (Mutsaers et al., 2003).
III. Bladder tumors are more common in older animals, and females may be predisposed (Mutsaers et al., 2003).
IV. Transitional cell carcinoma (TCC) is the most frequently identified tumor.
  A. The Scottish terrier, Shetland sheepdog, collie, Airedale terrier, and beagle are predisposed.
  B. The German shepherd dog is resistant to bladder neoplasia.
V. Other identified bladder tumors include the following:
  A. Rhabdomyosarcomas: most common in young, large-breed, male dogs
  B. Lymphoma
  C. Squamous cell carcinoma
  D. Adenomas
  E. Adenocarcinomas

Pathophysiology

I. Previous exposure to lawn herbicides, flea products, and cyclophosphamide has been associated with increased risk of developing TCC (Raghavan et al., 2004).
II. Approximately two thirds of bladder tumors involve the trigone region.

Clinical Signs

I. Clinical signs are similar regardless of tumor type and are related to secondary cystitis or urinary outflow tract obstruction.
II. The most common clinical signs are hematuria, pollakiuria, and stranguria.
III. The index of suspicion is highest in older dogs with stranguria.
IV. Uremia may occur if the tumor is obstructing the ureters or urethra.

Diagnosis

I. The bladder tumor may be palpable on rectal examination.
II. Fresh urine cytology on voided urine may reveal clumps of epithelial cells associated with RBCs and few WBCs.
  A. Cellular atypia and mitotic figures in the epithelial cells are evidence of neoplasia and are highly suggestive of TCC.
  B. Avoid taking cystocentesis samples because of the possibility of seeding tumor cells along the cystocentesis tract (Nyland et al., 2002).
III. Survey abdominal radiography may be normal, but contrast radiography or abdominal ultrasonography often reveals a mass in the bladder.
  A. Ultrasonography may detect the presence of a bladder mass, but double contrast-cystography is more sensitive for detecting small masses.
  B. Survey radiographs are examined closely for alterations in adjacent organs and regional lymph nodes.
  C. Thoracic radiographs are examined for signs of metastasis.
IV. Cystoscopy is more sensitive than imaging modalities in diagnosing and staging a mass and determining the extent of bladder involvement, and it can also be used to biopsy the tumor.
V. Traumatic catheterization (blind or ultrasound-guided) may be helpful to obtain cells from the tumor.
  A. It must be performed under heavy sedation or general anesthesia.
  B. The largest catheter that can be passed is used for the procedure.
  C. After obtaining urine, the catheter is rigorously moved back and forth while applying negative pressure.
VI. The bladder tumor antigen test (V-BTA Test; Polymedco, Cortlandt Manor, N.Y.) detects the presence of tumor antigens in urine.
  A. It has a high negative predictive value (98.6%), but its positive predictive value is poor (31%) (Billet et al., 2002; Henry et al., 2003).
  B. False-positives occur in the presence of proteinuria, pyuria, hematuria, and glucosuria.

Differential Diagnosis

I. Any cause of cystitis
II. Polypoid cystitis
III. Tumors of adjacent structures: vagina, prostate, urethra

Treatment

I. Surgical excision offers the best chance for a good outcome if the tumor is not in the area of the trigone.
  A. Urethrocystoscopy often shows multiple areas of seeding of malignant sites throughout the bladder (not just in the area of the obvious tumor mass).
  B. Complete excision is often impossible.
  C. Small apical tumors have the best chance for complete excision.
II. Some neoplasms, such as lymphoma, are sensitive to chemotherapy (see Chapter 69).
III. Piroxicam is recommended in all dogs for its antiinflammatory and antitumor properties.
  A. The dose in dogs is 0.3 mg/kg PO SID to QOD.
  B. Side effects include anorexia, vomiting, diarrhea, and GI ulceration.
  C. Secondary renal toxicity is possible but uncommon.
IV. Diverting urine from the bladder through a tube cystostomy may be considered in animals with tumors that are inoperable and obstructing the urethra.
  A. Urine scald and recurrent UTIs have been associated with tube cystostomy.
  B. Other surgical procedures that divert urine (e.g., urethral-colonic anastomosis) are not advised because of their side effects.
V. Radiation therapy has not been used successfully in TCC in dogs.
VI. Treat any secondary UTI with appropriate antibiotics.

Monitoring of Animal

I. Prognosis for long-term survival with bladder neoplasia is poor.
II. Monitoring the animal's quality of life is important.
  A. Special regard must be paid to the animal's ability to urinate.
  B. Many animals respond positively to piroxicam, including those with urinary outflow obstruction.
III. Frequent rechecks (at least monthly) are performed.
IV. Monitor urine cultures at least every 2 to 3 months.

TRAUMA

Definition and Causes

I. Injury to the bladder can be caused by surgery, blunt (e.g., automobile crash), or penetrating (e.g., knife, stick, gunshot wound) trauma to the abdomen.
II. Occasionally, overzealous palpation of the bladder, especially if the bladder is distended or diseased, may lead to bladder rupture.
III. Bladders can also be traumatized by cystocentesis, improper placement of urinary catheters, improper abdominocentesis techniques, or overdistention during cystoscopy or contrast radiography.
IV. Rupture may occur with prolonged urethral obstruction.

Pathophysiology

I. Small rents in the bladder wall usually heal spontaneously, without incident.

II. Transient leakage of sterile urine into the abdomen after cystocentesis or a small rent is usually self-limiting and resolves quickly.
III. Larger rents or tears in diseased bladders may not heal and the animal may develop clinical signs of bladder rupture.
IV. The fundus of the bladder is the most frequent site of rupture.

Clinical Signs

I. Hematuria is common.
II. Difficulty urinating may be noted; however, normal urination does not rule out bladder trauma.
III. A decrease in urine output and an increase in abdominal distention may be seen with a ruptured bladder.
IV. Occasionally, a urinary catheter still drains urine from a ruptured bladder, therefore urine output may remain stable and it may appear as though the animal is passing urine normally.
V. Sterile peritonitis may occur from exposure to urine; if the urine is infected, then the peritonitis is more severe.
VI. Anorexia, depression, fever, abdominal pain, and azotemia can occur secondary to bladder rupture.
VII. Systemic signs are secondary to absorption of waste products across the peritoneum into the circulation.

Diagnosis

I. A history of trauma and compatible clinical signs raises the index of suspicion.
II. Survey radiographs may show loss of serosal detail and/or displacement of the bladder.
III. Pelvic bone fractures are highly associated with bladder rupture.
IV. Ultrasonography may reveal free fluid in the abdomen.
V. Abdominocentesis reveals bloody fluid with creatinine concentrations higher than the serum creatinine concentration.
   A. Culture the fluid if bacterial peritonitis is suspected.
   B. Examine the abdominal fluid microscopically for the presence of blood and/or degenerative neutrophils.
VI. BUN and creatinine are usually increased early in the course, with BUN more elevated than creatinine because of differences in their diffusion characteristics.
VII. Decreases in serum sodium and chloride and increases in potassium may occur as the effects of urine in the abdomen equilibrate with extracellular fluid.
VIII. Positive contrast radiography is the diagnostic test of choice (see Chapter 4).

Differential Diagnosis

I. Urine leakage from other sites of trauma: urethra, ureters
II. Other causes of ascites and abdominal effusions
III. Urinary obstruction from uroliths, neoplasia
IV. Ruptured paraprostatic (males) or perinephric pseudocyst
V. Other causes of peritonitis

Treatment

I. Treatment depends on the extent, location, and cause of the trauma.
II. The animal is assessed for more life-threatening injuries first.
III. If the rupture is small, then a urinary catheter (preferably flexible) is inserted and continuous drainage using a closed system is performed for 3 to 10 days, so the bladder is allowed time to heal.
IV. If the bladder rupture is large, then surgical repair is attempted once the animal is stabilized.
V. Antibiotics can be used if a high possibility of infection exists.
VI. Short-term peritoneal dialysis or peritoneal drainage may be needed if the animal is in poor condition and urine flow cannot be established adequately with catheterization.

Monitoring of Animal

I. Urinations are monitored after removal of the urinary catheter to make sure no obstruction develops secondary to surgical repair (stricture).
II. The urine is often cultured after removal of the urinary catheter to rule out a nosocomial UTI.
III. Serum electrolyte abnormalities and azotemia usually resolve within days.
IV. If clinical signs recur or persist, then contrast radiography is repeated.

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CHAPTER 51

Micturition Disorders

Joan R. Coates | Marie E. Kerl

GENERAL INFORMATION

Definition and Classifications

I. The lower urinary tract stores and allows periodic elimination of urine.
II. The process of micturition includes both storage and emptying of the urinary bladder.
III. *Urination* refers to the voiding process.
IV. The storage phase includes passive filling of the urinary bladder and mechanisms to maintain continence.
V. The emptying phase requires sphincter relaxation with coordinated voluntary bladder contraction.
VI. Urinary continence requires a normal, compliant bladder and an active, competent urethral sphincter.
VII. The micturition process is under control of the central nervous system (CNS), which integrates the autonomic and somatic nervous systems.
VIII. Micturition dysfunction includes retention of urine or incontinence.
IX. Neurogenic bladder describes bladder dysfunction caused by an underlying nervous system dysfunction.
X. Classification of micturition disorders is as follows:
   A. Neurogenic versus nonneurogenic
      1. Neurogenic disorders result in mechanical dysfunction of the urethra and urinary bladder secondary to underlying pathology in the nervous system.
         a. Upper motor neuron (UMN): suprasacral spinal cord lesion (lumbar [L] segment 7 to brainstem)
         b. Lower motor neuron (LMN): sacral spinal cord lesion, peripheral neuropathy, myopathy, neuromuscular junctionopathy, dysautonomia
      2. Nonneurogenic lesions may be anatomical or functional.
         a. *Anatomical* refers to a structural lesion in the lower urinary tract causing dysfunction.
         b. *Functional* refers to nonstructural lesions causing mechanical dysfunction of the urinary bladder and urethra, as well as to neurogenic disorders.
   B. Failure to empty versus failure to retain urine
      1. Urinary retention
         a. Incomplete or absent detrusor muscle contraction (detrusor hyporeflexia and areflexia)
         b. Urethral obstruction
      2. Urinary incontinence
         a. Inappropriate urination
         b. Bladder storage dysfunction
         c. Urethral dysfunction
      3. Anatomical and functional causes

Functional Neuroanatomy

I. The urinary bladder is divided into a neck (trigone) and body, and it serves as a low-pressure reservoir.
   A. Urinary bladder musculature, or the detrusor muscle, is composed of three interwoven layers of smooth muscle.
   B. Smooth muscle fibers form a syncytium via tight junctions that propagate excitatory transmission from a pacemaker cell throughout the detrusor muscle.
   C. Adrenergic and muscarinic cholinergic receptors lie within the detrusor smooth muscle.
II. The urethral musculature consists of two sphincters that are considered outlets for urine from the urinary bladder.
   A. The internal smooth muscle (internal urethral sphincter) is composed of outer and inner longitudinal and middle circular layers, and it begins at the bladder neck and extends distally.
   B. The external striated muscle (external urethral sphincter) is interwoven with the proximal urethral smooth muscle but is more prominent in the distal half of the urethra.
   C. The adrenergic and nicotinic cholinergic receptors are located on the internal smooth and external striated muscles, respectively.
III. Bladder receptors are as follows:
   A. β-Adrenergic receptors predominate in the body of the detrusor muscle.
      1. They mediate information conveyed by postganglionic sympathetic fibers of the hypogastric nerve.
      2. Stimulation causes detrusor muscle relaxation and allows bladder filling at constant pressures.
   B. Muscarinic cholinergic receptors are located within the body (at the base of the detrusor muscle).
      1. They mediate information conveyed by postganglionic parasympathetic fibers of the pelvic nerve.
      2. Stimulation causes detrusor muscle contraction and bladder emptying.
   C. Sensory receptors lie within muscle fascicles and connective tissue of the smooth muscle layers.
      1. They mediate sensory information arising from distention (stretch) and pain of the detrusor muscle.

2. The pelvic nerve innervates all regions of the bladder and relays information from the receptors.
3. The filling threshold triggers the micturition reflex.
4. Pain receptors within the submucosa are innervated by hypogastric nerve terminations located near the base of the bladder.

IV. Urethral receptors are as follows:
- A. α-Adrenergic receptors predominate at the base of the detrusor muscle and internal sphincter of the proximal urethra.
  1. They mediate information relayed by postganglionic sympathetic fibers of the hypogastric nerve.
  2. Stimulation causes contraction of smooth muscles of bladder neck and proximal urethra to counter urine flow and facilitate bladder filling.
- B. Nicotinic cholinergic receptors are located within the striated muscle fibers of the external urethral sphincter.
  1. These somatic receptors mediate information relayed by the pudendal nerve.
  2. Stimulation causes external sphincter muscle contraction to counter urine flow and to facilitate bladder filling.
- C. Sensory receptors mediate information about stretch, pain, and urine flow.

Neurophysiology

I. Storage phase of micturition (Figure 51-1)
- A. The pelvic nerve conveys information from stretch receptors in the detrusor muscle (generated during bladder filling) to a sacral and thoracolumbar intersegmental spinal reflex pathway.
  1. Activation of preganglionic sympathetic neurons mediates relaxation of the detrusor muscle and contraction of the proximal urethral sphincter.
  2. Activation of the pudendal motor neurons mediates contraction of the striated external urethral sphincter muscle.
- B. Reticulospinal fibers descend from the lateral cell group of the brainstem micturition center within the pons to activate pudendal motor neurons.

II. Emptying phase of micturition (Figure 51-2)
- A. Urinary bladder capacity exceeds threshold and stimulates mechanoreceptors to trigger the micturition reflex.
  1. Signals from stretch receptors are relayed via the pelvic nerve.
  2. Inhibition of preganglionic sympathetic neurons, and pudendal motor neurons result in relaxation of smooth and striated sphincter muscles, respectively.
  3. Fibers ascend cranially to the brainstem micturition center in the pons.
  4. Reticulospinal fibers descend from the medial cell group of the brainstem micturition center to activate preganglionic parasympathetic neurons of the pelvic nerve.
  5. The detrusor muscle contracts and the urethral sphincters relax, resulting in coordinated emptying of bladder.
     - a. Detrusor muscle contraction pulls the bladder neck open.
     - b. Sensory receptors within the urethra detect urine flow.
     - c. The pudendal nerve conveys the sensation of urine flow.
- B. Sensory information ascends the spinal cord to the cerebral cortex.
- C. Descending fibers from the cerebral cortex then activate the brainstem micturition center for voluntary control of urination and continued urine flow until bladder emptying is complete.

III. Reflexes
- A. The detrusor reflex is a pathway for urination via a brainstem and spinal cord reflex arc (see Figure 51-2).
- B. The micturition reflex is a pathway that involves the integration of bladder filling, storage, and emptying of the bladder with urethral sphincter contraction and relaxation (see Figure 51-2).

Diagnosis of Micturition Dysfunction

I. Historical findings
- A. Neutering or other urogenital surgeries
- B. Failure of housebreaking behavior
- C. Onset and progression of signs
- D. Urination attempts and awareness
- E. Frequency of urination
- F. Volume of urine
- G. Presence of urine leakage
- H. Behavioral changes

II. Physical examination findings
- A. Observe voiding patterns.
  1. Stream size is evaluated as normal or thin.
  2. Evidence of dysuria or stranguria is common with voiding disorders.
  3. Duration of voiding provides evidence of urine retention and dyssynergia.

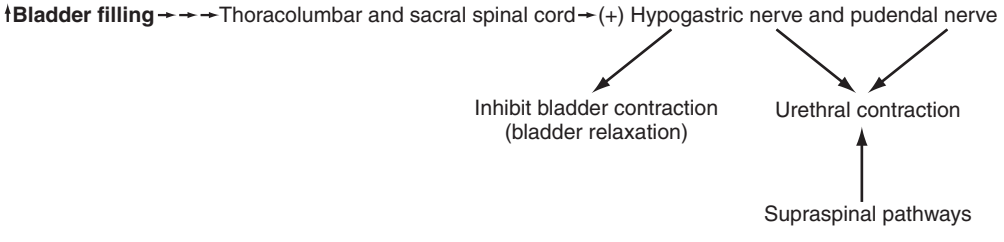

FIGURE 51-1 Neurophysiologic aspects of the storage phase of micturition.

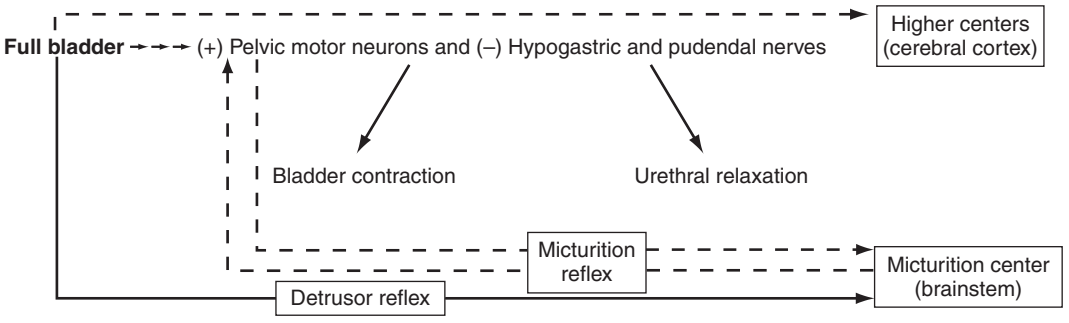

FIGURE 51-2 Neurophysiologic aspects of the emptying phase of micturition, showing the micturition *(dotted lines)* and detrusor *(solid line)* reflexes.

4. Urine color may reveal evidence of hematuria.

B. Examine external genitalia for masses, abnormal conformation, strictures, and urine scalding.
C. Palpate abdomen to reveal bladder size and presence of other masses.
D. Palpate urinary bladder before and after urination.
   1. Assess tone and flaccidity.
   2. Normal bladder is firm on palpation and difficult to manually express.
   3. Ease of manual bladder expression may reflect urethral tone.
E. Palpate urethral papilla and vaginal vault in female dogs for masses.
F. Palpate rectum and pelvic urethra for masses and to assess anal tone.
G. Use urethral bladder catheterization to assess for obstructive lesions.
H. Measure residual volume when emptying phase is in question.
   1. Residual volume is defined as the amount of urine remaining in the bladder after voiding is complete.
      a. Normal residual volume: 0.2 to 0.4 mL/kg
      b. Normal dog: <10 mL
      c. Normal cat: <2 mL
   2. Large residual volume indicates a urine retention disorder.

III. Presence of neurologic disease
   A. Anal and urethral tone is assessed during rectal palpation.
   B. Tail function, position, and tone are observed because they reflect coccygeal nerve function.
   C. The perineal reflex is contraction of the anal sphincter when the anal sphincter is pinched, with simultaneous assessment of sensation of the perineum.
   D. The bulbocavernosus reflex is contraction of the anal sphincter when the bulb of penis or clitoris is pinched.
   E. Low lumbar paraspinal hyperesthesia is commonly associated with pathology of the bones and nerve roots.

IV. Localization of neurologic disease
   A. UMN signs localize as suprasacral (L7 to brainstem).
      1. Reflexes are normal to increased.
      2. Postural reaction deficits are present.
   B. LMN signs localize as sacral (sacral [S]1 to 3), peripheral neuropathy, or dysautonomia.
      1. Reflexes are decreased to absent.
      2. Loss of muscle tone occurs.
      3. Postural reaction deficits may be present if the sciatic nerve is affected.

V. Clinicopathologic findings
   A. A complete blood count (CBC) and chemistry profile are done to assess the presence of inflammatory disease, renal insufficiency, and underlying metabolic causes of polyuria.
   B. Urinalysis is performed to evaluate for urinary tract infection (UTI), which is a common sequela to neurogenic bladders and urine retention.
   C. Urine culture also can be performed to screen for underlying UTI.
   D. Serology is used to detect infectious diseases.

VI. Plain radiography
   A. Survey abdominal and pelvic radiography (including entire urethra) assesses bony or soft tissue abnormalities of the lumbosacral spine and pelvis and detects radiodense urinary calculi.
   B. Thoracic radiography may detect metastatic disease.

VII. Contrast urography
   A. Contrast cystography and urethrography evaluate for anatomical obstructions.
   B. IV pyelogram evaluates renal architecture.

VIII. Advanced imaging
   A. Computed tomography gives anatomical detail on bony structures of the lumbosacral spine and pelvis.
   B. Magnetic resonance imaging provides detail on soft tissue structures associated with the spinal cord and pelvic region.
   C. Myelography is used to assess compressive spinal cord disease cranial to L7.
   D. Ultrasonography assesses integrity of the bladder wall and lower urinary tract anatomy.

IX. Cystoscopy and urethroscopy: identify masses, obtain biopsies, remove small calculi

X. Cerebrospinal fluid analysis: presence of spinal cord disease

XI. Electrodiagnostic testing

A. Electromyography (EMG) of perineum and urethra assesses innervation status.
B. Nerve conduction velocity of sciatic nerve evaluates axon and myelin pathology associated with peripheral neuropathy.
C. Somatosensory and spinal-evoked potential studies evaluate sensory pathways and nerve root function.

XII. Urodynamic testing
A. Cystometry measures bladder pressure during filling and emptying, and it detects the presence of a detrusor reflex.
B. Urethral pressure profilometry measures urethral length and assesses urethral tone.
1. A catheter is connected to a pressure transducer and fluid is infused at a constant rate as the catheter is withdrawn.
2. Maximum urethral pressure and functional urethral profile length are recorded.
C. Leak point pressure testing is a functional technique used to simulate urethral compliance associated with an external abdominal press.
D. Sphincter muscle EMG is used to assess pudendal nerve function.

DISORDERS OF URINE RETENTION

Definition

I. Urine retention is associated with incomplete or absent detrusor muscle contraction or urine outflow obstruction from either an anatomical or a functional cause.
II. Disorders associated with voiding usually involve abnormalities of the lower urinary tract and cause outflow obstruction of urine.
III. Secondary overflow incontinence may occur when urinary bladder pressure exceeds urethral resistance.

Clinical Signs

I. Incomplete or absent detrusor muscle contraction
A. The animal's attempt to void depends on the integrity of the pelvic nerve and spinal cord.
B. An animal with dyssynergia may attempt to void in small amounts or without success.
1. Dyssynergia is the simultaneous contraction of muscles with actions in opposite directions.
2. The disorder is usually associated with contraction of the detrusor muscle without relaxation of the sphincter muscle.
C. Urine scald may be evident with secondary overflow incontinence.
D. Physical examination findings with an UMN bladder (suprasacral lesion) are as follows:
1. No attempt is made to void.
2. The bladder is large and firm on palpation and difficult to express manually.
3. Sphincter tone is hypertonic or normal.
4. A large amount of residual urine is present.
5. The perineal reflex is present.
6. Evidence of secondary overflow incontinence may be noted.
E. Physical examination findings with a LMN bladder (sacral spinal cord or peripheral nerve lesion) are as follows:
1. No attempt to void is noted, and urine leakage is continuous.
2. The bladder is large and flaccid, with leakage on manual expression.
3. The bladder may be difficult to express manually because the internal urethral sphincter is still innervated by the hypogastric nerve.
4. Sphincter tone is normal to hypotonic.
5. A large amount of residual urine is present from secondary overdistension.
6. Presence of other LMN signs (loss of perineal reflex and sensation and/or tail tone and sensation) may be noted.
7. In dysautonomia the bladder is overdistended, flaccid, and easy to express manually.
8. Urine scald is present from overflow incontinence.
F. Physical examination findings with primary detrusor muscle dysfunction from overdistension are as follows:
1. Attempts are made to void but are unsuccessful.
2. The bladder is difficult to express manually.
3. Sphincter tone varies with the underlying disorder.
4. A large amount of residual volume is present.
5. The perineal reflex is normal.
G. A dyssynergic-like syndrome associated with LMN dysfunction occurs when incomplete detrusor muscle contraction is unable to override urethral sphincter tone.
1. Attempts are made to void, but the stream is thin and intermittent (small spurts).
2. The bladder is difficult to express manually.
3. Sphincter tone is normal.
4. Large or variable amounts of residual volume are present.
5. The perineal reflex is decreased.
H. The animal may have other neurologic signs.
1. UMN bladder dysfunction is common with thoracic (T)3 to L3 myelopathies.
2. LMN bladder dysfunction occurs with sacral myelopathies, neuromuscular disease, and dysautonomia.

II. Urethral obstruction
A. The animal may sense bladder fullness and seek an appropriate place to void.
B. The animal makes multiple attempts to void without success.
C. Physical examination findings with an anatomical and functional urethral obstruction are as follows:
1. A urination posture is assumed.
2. The urine stream is thin or interrupted as spurts.
3. The bladder is difficult to manually express.
4. Urethral catheterization is difficult or impossible.
5. The perineal reflex is intact.

D. Reflex dyssynergia (detrusor-sphincter dyssynergia) is associated with recovery from spinal cord injury and manifests as the following:
   1. Attempts to void are made, but the stream is thin and intermittent (small spurts).
   2. The bladder is large, firm, and difficult to express manually.
   3. Sphincter tone is hypertonic.
   4. A large or variable amount of residual volume is present.
   5. The perineal reflex is normal.

Differential Diagnosis

I. Incomplete or absent detrusor muscle contraction (detrusor hypoflexia or areflexia, bladder atony) (Table 51-1)
   A. Primary diseases of the urinary bladder may cause enough damage to disrupt detrusor muscle contraction and result in secondary bladder storage dysfunction.
      1. Infiltrative neoplasms cause primary damage to the detrusor muscle.
      2. Chronic cystitis may cause secondary muscle fibrosis.
      3. Chronic LMN disease may cause neurogenic atrophy of the detrusor muscle.
   B. Suprasacral lesions involving the spinal cord and brainstem micturition center disrupt coordination of micturition, cause loss of the detrusor reflex or deficient detrusor muscle contraction, and produce hypertonic to normal urethral sphincter tone.
      1. Loss of micturition function occurs with loss of voluntary motor and sensory nerve function.
      2. Loss of inhibitory pathways alters urethral sphincter relaxation mechanisms.
      3. UMN bladder dysfunction is common with T3 to L3 myelopathies (see Chapter 24).
      4. Secondary overflow incontinence occurs when bladder pressure exceeds urethral sphincter tone.
   C. Lesions of the sacral spinal cord and pelvic plexus, neuromuscular disease, and dysautonomia alter pelvic nerve function, abolish the detrusor reflex, and produce normal to hypotonic urethral sphincter tone (see Chapters 24 and 25).
      1. Absent detrusor muscle contraction causes secondary overdistension and bladder flaccidity (detrusor areflexia, bladder atony).
      2. External urethral sphincter tone is lost from pudendal nerve dysfunction.
      3. The internal sphincter muscle may still remain innervated by the hypogastric nerve and may make expression of the bladder difficult.
      4. Dysautonomia usually causes an overdistended bladder that is flaccid and easily expressed from loss of innervation to the detrusor and sphincter smooth muscles, respectively.
   D. Cauda equina syndrome and pelvic plexus injury affect the pelvic nerve, resulting in weakened detrusor muscle contraction (detrusor hyporeflexia and areflexia) and failure to override normal urethral sphincter tone (dyssynergic-like conditions).
   E. Nonneurogenic disorders cause bladder atony (hypotonia) as a result of overdistention of the detrusor muscle and disruption of tight junctions between the myofibers.
      1. Anatomical obstructive diseases preventing urine outflow
      2. Painful disorders of the pelvic region
      3. Opioids and epidural anesthesia: incomplete micturition, with urge to urinate
      4. Prolonged recumbency, reluctance to urinate in cage

TABLE 51-1

Disorders of Urine Retention Associated with Bladder Dysfunction

	FUNCTIONAL ABNORMALITIES	
ANATOMIC LESIONS	**NEUROGENIC DISORDERS (DETRUSOR HYPOREFLEXIA AND AREFLEXIA)**	**NONNEUROGENIC DISORDERS (OVERDISTENSION CAUSING DETRUSOR AREFLEXIA)**
Chronic cystitis Infiltrative neoplasms Neurogenic atrophy of detrusor muscle Overdistension secondary to obstructive disease	UMN (sphincter tone hypertonic or normal) T3-L3 myelopathies that are severe enough to cause loss of voluntary motor and sensory function Reflex dyssynergia Disorders that affect the brainstem micturition center LMN (sphincter tone normal or hypotonic/atonic) Sacral spinal cord lesion Pelvic plexus lesion Generalized severe peripheral neuropathy Myopathy Neuromuscular junction lesion Dysautonomia	Secondary to urethral obstruction Disorders associated with pain in pelvic region Drugs (opioids, epidural anesthesia) Prolonged recumbency

UMN, Upper motor neuron; *LMN,* lower motor neuron; *T,* thoracic; *L,* lumbar.

II. Urethral obstruction (Table 51-2)
  A. Anatomical obstructive diseases mechanically prevent urine outflow and limit ability of the urethra to dilate during urination.
    1. Intraluminal diseases include urolithiasis, blood clots, tissue blockage, neoplasia, and urethritis.
    2. Intramural diseases include neoplasia, inflammation, edema, and strictures.
    3. Extraluminal diseases include prostatic disease, strictures, urethral granuloma, and bladder neck and pelvic neoplasms.
  B. Functional obstructive diseases are neurogenic or nonneurogenic disorders that result in failure of urethral sphincter relaxation.
    1. Neurogenic disorders include those that affect the LMN or UMN pathways and prevent relaxation of the internal or external urethral sphincter.
    2. Urethral hypertonia (spasticity) results from UMN lesions that cause increased resistance.
      a. Urethral sphincter tone is uninhibited because of loss of descending inhibition.
      b. It is often associated with detrusor areflexia.
    3. Reflex dyssynergia (detrusor-sphincter dyssynergia) is associated with partial UMN spinal cord disease and loss of inhibition of pudendal nerves during the detrusor reflex, which prevents coordinated urinary bladder contraction and urethral sphincter relaxation.
      a. Initiation of voiding is normal, but involuntary contraction of urethral sphincter causes interruption of urine stream.
      b. It is more often observed in male dogs.
      c. Diagnosis is made by exclusion of other more common disorders.
    4. Nonneurogenic disorders are those for which an anatomical or underlying neurologic cause is not identified.
      a. Idiopathic detrusor-urethral dyssynergia
      b. Urethral irritation after relief of urethral obstruction

Diagnosis

I. The residual volume is usually large.
II. Urethral bladder catheterization determines the presence or absence of urethral obstruction.
III. Urinalysis and urine culture ascertain the presence of a UTI, which is a common sequela of urine retention disorders.
IV. Abdominal radiography, ultrasonography, and contrast cystourethrography delineate obstructive or mass lesions.
V. Cytoscopy is useful to visualize small obstructions in urethra.
VI. Urodynamic testing evaluates detrusor muscle function and urethral tone.
  A. Cystometry may demonstrate lack of a detrusor reflex on volume threshold stimulation.
  B. Urethral pressure profilometry can detect areas of higher than normal pressure, suggesting a stricture or spasm.

Treatment

I. Stimulate detrusor muscle contraction.
  A. Cholinergic agonists enhance detrusor muscle contraction.
    1. Bethanechol chloride is a direct-acting cholinergic.
      a. Dogs: 5 to 25 mg PO TID
      b. Cats: 1.25 to 5.0 mg PO TID
      c. Side effects: salivation, diarrhea, bronchoconstriction
    2. Cisapride is an indirect-acting cholinergic that enhances presynaptic release of acetylcholine.
      a. Dogs: 0.5 mg/kg PO TID or 2.5 to 10 mg PO TID (dose varies with body size)
      b. Cats: 1.25 to 5.0 mg PO TID
      c. Side effect: diarrhea
  B. β-Adrenergic blockade with propranolol enhances detrusor contractility.
    1. Dogs: 2.5 to 20 mg PO BID to TID (dose varies with body size)
    2. Cats: 2.5 to 5.0 mg PO BID to TID

TABLE 51-2

Disorders of Urine Retention Associated with Urethral Obstruction

	FUNCTIONAL ABNORMALITIES	
ANATOMIC LESIONS	**NEUROGENIC DISORDERS (URETHRAL HYPERTONIA)**	**NONNEUROGENIC DISORDERS (URETHRAL HYPERTONIA)**
Intraluminal disease Intramural disease Extraluminal disease	UMN (sphincter tone hypertonic or normal) T3-L3 myelopathies that are severe enough to cause loss of voluntary motor and sensory function Spasticity Reflex dyssynergia Disorders that affect the brainstem micturition center	Idiopathic detrusor-urethral dyssynergia Urethral irritation after relief of obstruction

UMN, Upper motor neuron; *T,* thoracic; *L,* lumbar.

3. Side effects: bradycardia, lethargy, hypotension, bronchoconstriction

II. Decrease urethral sphincter tone.
   A. α-Adrenergic antagonists decrease internal urethral smooth muscle sphincter tone.
      1. Phenoxybenzamine is a nonspecific α-antagonist.
         a. Dogs: 0.5 mg/kg PO BID or 2.5 to 15 mg PO TID
         b. Cats: 1.25 to 5.0 mg PO SID to BID
         c. Side effects: hypotension, tachycardia, gastrointestinal (GI) disturbance
      2. Prazosin is an α-1 antagonist.
         a. Dogs: 1 mg/15 kg PO BID to TID
         b. Cats: 0.25 to 0.5 mg PO SID to BID
         c. Side effects: hypotension, sedation, salivation
      3. Acepromazine is a nonspecific α-antagonist.
         a. Dogs: maximum dose 3 mg IV
         b. Cats: 0.1 mg/kg SC, IV SID to BID; 1 to 2 mg/kg PO SID to BID
         c. Side effects: hypotension, sedation
   B. Skeletal muscle relaxants decrease external urethral striated muscle tone.
      1. Diazepam is centrally acting.
         a. Dogs: 2 to 10 mg PO TID
         b. Cats: 0.2 to 0.5 mg/kg IV TID; 2 to 5 mg PO TID
         c. Side effects: sedation, excitation, acute hepatocellular necrosis (cats)
      2. Dantrolene is direct-acting.
         a. Dogs: 3 to 15 mg/kg PO TID
         b. Cats: 0.15 to 0.6 mg/kg PO TID
         c. Side effects: weakness, hepatotoxicity, vomiting, hypotension
      3. Methocarbamol is centrally acting.
         a. Dogs: 15 to 20 mg/kg PO TID
         b. Cats: initial dose 33 mg/kg PO TID, then 20 mg/kg PO TID
         c. Side effects: sedation, lethargy, salivation, vomiting, weakness

III. Prevent bladder overdistension.
   A. Urinary bladder catheterization
      1. Continuous, closed-system, indwelling catheter may be used.
      2. Intermittent catheterization has a lower risk of inducing UTI.
   B. Manual bladder expression
      1. Female dog has shorter urethra and less resistance than male dog
      2. Less likely to induce a UTI
   C. Treatment for secondary UTI
      1. Periodically perform a urinalysis and urine culture.
      2. Avoid use of prophylactic antibiotics in animals with indwelling catheters because they can predispose to resistant UTI.

Monitoring of Animal

I. Recheck examinations
   A. Monitor for bladder size and changes in residual volume.
   B. Perform urinalysis and urine culture to monitor for UTI.
   C. Follow up with owner to determine compliance.
   D. Consider periodic adjustment of medication dosing to increase efficacy.
   E. Remember that side effects are limited if drug administration is started at a low dose and gradually increased.

II. Expected outcome
   A. Micturition function improves with recovery of neurologic status in most cases.
   B. Intermittent catheterization or bladder expression may be required for life in animals that are paraplegic.
   C. A reflex bladder may develop in animals with severe UMN dysfunction.

III. Prognosis
   A. The prognosis for underlying neurogenic causes is dependent on recovery of neurologic functions (presence of sensation and voluntary motor movement).
   B. Chronic cases of urinary retention refractory to medical management have a guarded prognosis.
   C. The prognosis for return of function in chronic cases of bladder atony is poor.
   D. Detrusor atony is often reversible in animals with acute overdistention.
   E. The prognosis is good with resolution of anatomical or nonneurogenic functional obstructions.

DISORDERS OF URINE STORAGE (URINARY INCONTINENCE)

Definition

I. Urinary incontinence can result from urinary bladder storage problems or urethral dysfunction.
   A. Bladder storage dysfunction often arises from poor compliance and elasticity or increased bladder contraction (detrusor hyperreflexia).
   B. Urethral dysfunction arises from decreased urethral resistance.
   C. Structural anomalies may disrupt normal urinary bladder or urethral function.

II. Bladder storage disorders often are characterized by involuntary leakage of small amounts of urine.

III. The bladder is usually small to normal in size in animals with no underlying neurologic disease.

IV. Incontinence must be distinguished from inappropriate urination.

V. Neurologic examination is necessary when localizing the cause of incontinence.

VI. Lower urinary tract disease must be considered in incontinent animals that are neurologically normal and have normal residual volume.

VII. Secondary overflow incontinence may occur with urinary retention disorders when urinary bladder pressure exceeds urethral resistance.

Clinical Signs

I. Inappropriate urination
   A. Animals have normal voiding but the time and place are inappropriate.
   B. Physical examination reveals normal bladder size and residual volume.

II. Bladder storage dysfunction (Table 51-3)
   A. This dysfunction is characterized by involuntary voiding at low bladder volume and pressure.
      1. Urinary incontinence
      2. Urine leakage on standing, barking, jumping
   B. Pollakiuria may result from bladder irritation or underlying metabolic causes of polyuria-polydipsia.
   C. The pattern of incontinence is usually intermittent.
   D. Physical examination findings with neurogenic detrusor hyperreflexia are as follows:
      1. Normal or large amount of residual volume depending on the underlying neurologic cause
      2. Small amounts of urine leakage associated with involuntary voiding
   E. With primary urinary bladder disease (poor compliance), the animal may show urge incontinence, with involuntary voiding of small amounts of urine and pollakiuria.
      1. The bladder is not distended, but a thickened wall may be evident on palpation.
      2. A normal to small amount of residual volume is present.

III. Urethral dysfunction (Table 51-4)
   A. A pattern of incontinence may be continuous or intermittent, and severity of incontinence is dependent on the amount of urethral tone lost.
   B. The bladder size and voiding pattern may vary, depending on the presence of underlying neurologic disease.
   C. Physical examination findings with a congenital structural anomaly (ectopic ureter) are as follows:
      1. Normal voiding pattern
      2. Bladder not distended
      3. Normal residual volume
      4. Continuous pattern of incontinence
   D. Neurogenic urethral dysfunction is usually associated with an LMN bladder.
      1. No attempt is made to void.
      2. The bladder may be large and flaccid.
      3. Ease of manual expression is dependent on the amount of urethral tone maintained by the hypogastric nerve.
      4. A large residual volume is present.
      5. The pattern of incontinence is intermittent or continuous, depending on severity.
      6. Neurologic deficits are detected.
   E. Animals with urethral incompetence show the following:
      1. The voiding pattern is normal.
      2. The bladder is not distended and may be easy to express manually.

TABLE 51-3

Disorders of Urinary Incontinence Associated with Bladder Storage Dysfunction

	FUNCTIONAL ABNORMALITIES	
ANATOMIC LESIONS	**NEUROGENIC DISORDERS (DETRUSOR HYPERREFLEXIA)**	**NONNEUROGENIC DISORDERS (BLADDER WALL IRRITATION)**
Chronic cystitis Patent urachus	UMN (sphincter tone hypertonic or normal) Cerebellar disease Reflex bladder Detrusor instability secondary to other neurologic disease	Infiltrative diseases Chronic inflammation Urge incontinence Idiopathic detrusor hypercontractility

UMN, Upper motor neuron.

TABLE 51-4

Disorders of Urinary Incontinence Associated with Urethral Dysfunction

	FUNCTIONAL ABNORMALITIES	
ANATOMIC LESIONS	**NEUROGENIC DISORDERS (URETHRAL SPHINCTER HYPOTONIA AND ATONIA)**	**NONNEUROGENIC DISORDERS (DECREASE URETHRAL SPHINCTER RESISTANCE)**
Ectopic ureter Urethral hypoplasia Prostatic disease	LMN (sphincter tone hypo-/atonic) Sacral spinal cord disorders that altering external urethral sphincter tone Dysautonomia altering internal and external urethral sphincter tone	Polyuria/polydipsia UTI Hormone-responsive urethral incompetence

LMN, Lower motor neuron; UTI, urinary tract infection.

3. The residual volume is normal.
4. The pattern of incontinence is continuous or intermittent, depending on severity.
5. Urine leakage occurs when the animal is at rest or asleep.

Differential Diagnosis

I. Inappropriate urination is the act of voluntarily voiding urine at the wrong time and in the wrong place.
   A. The diagnosis is ascertained by history and observation of the animal.
   B. Differential considerations include senility, forebrain disease, and physical limitations that prevent reaching an acceptable place to urinate.
   C. Animals with forebrain disease may have seizures, behavioral changes, and contralateral response deficits (hemineglect).

II. Bladder storage dysfunction is deficient bladder compliance and elasticity during the filling phase or involuntary voiding at low bladder pressure (detrusor hyperreflexia).
   A. Anatomical causes include infiltrative diseases that alter elasticity of the detrusor muscle and functional storage capacity.
      1. Bladder wall inflammation (cystitis) causing secondary fibrosis
      2. Patent urachus
   B. Functional disorders may be neurogenic or nonneurogenic.
      1. Neurogenic causes include disorders of detrusor hyperreflexia.
         a. Generalized cerebellar disease can result in frequent voiding with normal residual volume.
         b. Reflex bladder occurs in chronic UMN disease (rare) and causes weak uncoordinated contractions with inadequate bladder emptying.
         c. Detrusor instability may occur in cats positive for feline leukemia virus.
      2. Nonneurogenic causes include infiltrative diseases or disease processes that irritate the bladder wall.
         a. Infiltrative diseases include neoplasia and chronic inflammation.
         b. Bladder wall irritation causes the urge incontinence often associated with UTI.
         c. *Idiopathic detrusor instability* is the term used for no identifiable cause for decreased detrusor compliance.

III. Urethral dysfunction results from weakened urethral smooth or striated muscle tone, which causes urine leakage during the storage phase of micturition.
   A. Anatomical lesions
      1. Congenital anomalies (e.g., ectopic ureter, urethral hypoplasia) may alter urethral closure mechanisms and tone.
      2. Prostatic disorders can disrupt urethral closure function in male dogs.
   B. Functional abnormalities
      1. Neurogenic disorders
         a. Sacral spinal cord disorders affect influence of the pudendal nerve on the striated external urethral sphincter muscle (causing decreased tone).
         b. Dysautonomia alters sympathetic nerve function and the influence of the hypogastric nerve on the smooth internal urethral sphincter muscle (causing decreased tone).
      2. Nonneurogenic disorders
         a. Polyuric disorders can intensify an underlying incontinence problem, because an increased urine volume places further stress on an incompetent urethra.
         b. UTIs and inflammation can cause transient urethral incompetence.
         c. Hormone-responsive urethral incompetence is the most common cause of incontinence in female dogs.
            (1) Urine leakage usually occurs when the dog is at rest or asleep.
            (2) The voluntary urination pattern is normal.
            (3) A correlation exists between body weight and incidence of incontinence (incontinence is worse in animals with increased body weight).
            (4) The intrapelvic bladder position may contribute to urethral incompetence.
            (5) The onset after spaying may be immediate or up to 10 years (mean of 3 years after surgery) (Arnold, 1992).

Diagnosis

I. The residual volume is small or normal in animals with no evidence of neurologic disease.
II. An abnormal neurologic examination determines the presence of UMN or LMN disease.
III. A vaginal examination evaluates for strictures causing urine pooling.
IV. Urinalysis and urine culture are performed to ascertain the presence of UTI.
V. Low urine specific gravity indicates poor concentrating ability and necessitates the need for further blood tests to determine the underlying cause.
VI. Imaging studies (abdominal radiography, ultrasonography, and contrast cystourethrography or urethrography) delineate abnormal anatomy, and indications include the following:
   A. Incontinence observed in animals <1 year of age or in male dogs
   B. Incontinence around time of ovariohysterectomy
   C. Continuous pattern of incontinence
   D. Recurrent UTI
VII. Cystoscopy is useful to visualize congenital anomalies and lesions of the bladder and urethra.
VIII. Urodynamic testing is used to detect detrusor hyperreflexia and decreased urethral tone.
   A. Cystometry may demonstrate a low volume threshold associated with detrusor hyperreflexia or decreased

compliance of the bladder associated with urge incontinence.
B. Urethral pressure profilometry may detect areas of lower than normal maximal urethral closure pressures and shortened functional profile length, which suggest decreased resistance and urethral sphincter muscle tone.
C. Leak point pressures can aid the diagnosis of underlying urethral incompetence.

Treatment

I. Decrease detrusor muscle contraction.
A. Direct-acting smooth muscle relaxants
1. Oxybutynin chloride has direct antimuscarinic and spasmolytic effects on smooth muscle.
a. Dogs: 1.25 to 5 mg PO BID to TID
b. Cats: 0.5 mg PO BID
c. Side effects: diarrhea, sedation
2. Propantheline bromide is an antimuscarinic agent with actions similar to atropine, but it does not cross into the CNS.
a. Dogs: 0.2 mg/kg PO TID to QID or 5 to 30 mg PO TID
b. Side effects: similar to atropine, prolonged GI motility
3. Aminopromazine fumarate acts directly to cause smooth muscle relaxation and is used for urge incontinence.
a. Dogs: 2 mg/kg PO BID
b. Cats: 2 mg/kg PO BID
c. Side effects: mild tranquilization or excitability
B. Treatment of underlying bladder inflammation
II. Increase urethral sphincter tone.
A. Direct nonspecific α-adrenergic agonist, such as phenylpropanolamine
1. Dogs: 12.5 to 50 mg PO TID or 1 mg/kg PO TID
2. Cats: 12.5 mg PO TID
3. Side effects: restlessness, irritability, hypertension, anorexia
B. Indirect α-adrenergic agonist
1. Imipramine is a tricyclic antidepressant agent that indirectly acts by increasing norepinephrine and has nonspecific adrenergic and anticholinergic effects.
a. Dogs: 5 to 15 mg PO BID
b. Cats: 2.5 to 5.0 mg PO BID
c. Side effects: sedation, tremors, seizures, excitability, anticholinergic effects, adverse hematologic changes, diarrhea
2. Diethylstilbestrol increases urethral sphincter smooth muscle sensitivity to norepinephrine.
a. Dogs: 0.1 to 1.0 mg PO for 3 to 5 days followed by once-weekly administration of the lowest effective dose
b. Side effects: bone marrow toxicity, blood dyscrasias
c. May be used with phenylpropanolamine
3. Testosterone cypionate has an unknown mechanism of action that increases sphincter sensitivity.
a. Male dogs: 2.2 mg/kg IM every 30 days
b. Cats: 5 to 10 mg IM (testosterone propionate)
c. May be used with phenylpropanolamine
d. Adverse effects: uncommon, behavioral changes, prostatic disease, perineal hernias
C. Surgical methods for urethral incompetence refractory to medical therapy
1. Submucosal urethral polymeric injections (Arnold et al., 1989)
2. Cystourethropexy, urethropexy and colposuspension procedures (Gregory et al., 1994; Rawlings, 2000; White, 2001)
a. Move the bladder neck to an intraabdominal position
b. Restore continence by increasing pressure transmission to the bladder neck and proximal urethra
3. Mesh and sling procedures (Bushby et al., 1980; Dean et al., 1989)

Monitoring of Animal

I. Recheck examinations
A. Animals with urinary incontinence are periodically monitored for UTI.
B. Animals unresponsive to medical management are reevaluated with urinalysis, urine culture, neurologic examination, and imaging procedures.
C. Underlying behavioral disorders often require trial therapy with various drugs.
II. Expected outcome
A. Most affected dogs can be managed with appropriate medical therapies.
B. Medical therapies may require periodic adjustment or adjunctive therapies.
III. Prognosis
A. Success rate is reduced in male dogs, juvenile dogs, and dogs with marked anatomical abnormalities (Lane, 2003).
B. The control of urinary incontinence varies with each animal.
C. Poor control is commonly attributed to UTIs, polyuric disorders, and behavioral disorders.
D. Success rates have been variable for the surgical procedures but may be enhanced with adjunctive medical therapies.
E. The prognosis is guarded in urinary incontinence attributed to underlying neurologic disease that is not recognized early in its disease course.

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CHAPTER 52

Diseases of the Urethra

Nyssa J. Reine

CONGENITAL DISORDERS

Hypospadias

See Chapter 59.

Urethrorectal Fistula

Definition and Cause

I. Failure of complete separation of the fetal cloaca into an anterior urethrovesical segment and a posterior rectal segment by the urorectal septum occurs, resulting in a permanent communication between the urethra and the rectum.
II. The incidence is quite rare and the cause is unknown.

Clinical Signs

I. Signs typically develop shortly after weaning and are associated with abnormal micturition.
II. Passage of urine through the rectal orifice is most common in dogs, although urination may be observed from both the anus and urethra.
III. Cystitis, perianal dermatitis, hematuria, struvite urolithiasis, and diarrhea may also occur.

Diagnosis

I. The defect may be visualized via a speculum or proctoscopic examination of the rectum.
II. If the defect cannot be seen, then a urethral catheter may be used to explore the floor of the rectum.
III. The catheter can usually be passed into the urinary bladder.
IV. Positive-contrast urethrography (normograde or retrograde) can also be used to confirm the diagnosis.

Differential Diagnosis

I. Traumatic rectovaginal fistula
II. Older age and history of previous trauma: suggestive of acquired, traumatic disease

Treatment

I. Surgical correction is undertaken via abdominal laparotomy, perianal exploration, or ventral pubic symphysiotomy (Bjorling, 2003).
II. Concurrent UTIs are also treated (see Chapter 50).

Monitoring of Animal

I. The surgical site is monitored for infection.
II. Urinalysis and urine culture are performed after completion of treatment to ensure resolution of the infection.
III. Follow-up positive-contrast urethrography may be performed 4 to 6 weeks after surgery to confirm fistula closure.

INFLAMMATORY DISEASES

Urethritis

Definition and Causes

I. Inflammation of the urethra
II. Causes
  A. Idiopathic: granulomatous urethritis, proliferative urethritis, inflammatory polyp
  B. Bacterial: cystitis, vaginitis, prostatitis
  C. Traumatic: secondary to calculi or urethral catheterization
  D. Neoplastic

Pathophysiology

I. Breakdown of the urothelial lining secondary to traumatic disruption or neoplastic infiltration of the urethral mucosa may result in erosion and ulceration.
II. Granulomatous urethritis is frequently associated with marked epithelial hyperplasia, probably related to elaboration and release of growth factors by inflammatory cells.
III. Proliferative urethritis may be secondary to chronic bacterial infection or immune-mediated disease.

Clinical Signs

I. Stranguria, hematuria, pollakiuria
II. Vaginal or preputial discharge, possibly bloody
III. Possible partial or complete urinary obstruction

Diagnosis

I. Physical examination findings
  A. A rectal examination is essential and may reveal urethral thickening that is either tubular or masslike.
  B. A digital vaginal examination may reveal an irregularly shaped urethral papilla.

C. Catheterization may help localize the lesion by partial or complete resistance to passage of the catheter.
   1. Procedure must be done under sedation in female dogs.
   2. Attempts may be unsuccessful in cases with luminal compromise.

II. Laboratory results
   A. Urinalysis may reveal pyuria, hematuria, bacteriuria, and/or proteinuria.
      1. Urine specific gravity is variable.
      2. Culture and sensitivity are indicated.
   B. Biochemical profile may reveal azotemia, particularly if urinary is obstruction present.
   C. Increased serum alkaline phosphatase, creatinine kinase, lactate dehydrogenase, cholesterol, and globulin concentrations may also occur.
   D. Complete blood count (CBC) may be normal or reveal leukocytosis.

III. Imaging studies
   A. Survey radiographs may show no abnormalities, the presence of urinary calculi, or a large and distended urinary bladder.
   B. Contrast retrograde cystourethrography may reveal filling defects within the urethral lumen, irregularities of the mucosa, or urethral stricture.
   C. Ultrasonography may reveal diffuse bladder wall thickening with extension into the urethra or masses within the bladder.

IV. Urethral cytology
   A. Urethral scraping for cytology is a noninvasive test that may help establish a diagnosis.
   B. Under sedation a urinary catheter is passed to the most proximal aspect of the lesion (based on rectal palpation).
   C. Inject sterile saline into the catheter using a syringe, and apply negative pressure to the syringe while moving the catheter back and forth through the affected region.

V. Urethral biopsy
   A. Urethroscopy is used to localize the lesion and facilitate biopsy.
   B. Place female dogs in ventral, dorsal, or right lateral recumbency, and use a rigid cystoscope with a 30-degree angle of view and a cystoscopy sheath to enable biopsy through the biopsy channel.
   C. Place male dogs in right lateral or dorsal recumbency, and use a flexible cystoscope.
   D. Attach a fluid source (0.9% saline) to the cystoscope, in addition to a drainage line, if possible.
   E. Clip and aseptically prepare the perivulvar or preputial area.
   F. Apply a liberal amount of sterile lubricant to the cystoscope.
   G. For female dogs, insert the cystoscope in the vestibule; apply firm, gentle traction to the vulva.
      1. Visualize the vagina, urethra papilla, and cingulum.
      2. Orient the cystoscope so that the vagina is at the top of the screen.
      3. Guide the cystoscope into the urethra while the urethra is distended with fluid.
      4. Visualize the lesion and pass the biopsy instrument through the biopsy channel to obtain biopsies.
   H. For male dogs, an assistant is required to extrude the penis from the prepuce.
      1. Pass the scope through the urethra while the urethra is distended with fluid.
      2. Typically, flexible cystoscopy does not enable biopsy acquisition through the scope.
      3. Biopsies can be obtained by passing a biopsy instrument alongside the scope during visualization.
      4. Alternatively, measurement of the distance to the lesion via the cystoscope can guide a blind biopsy.

VI. Interpretation of biopsies
   A. Histopathology of granulomatous urethritis lesions reveals lymphocytes, plasma cells, and macrophages, with low numbers of neutrophils.
   B. Histopathology of proliferative urethritis is characterized by lymphoplasmacytic or suppurative inflammation but no granulomatous changes.
   C. Histopathology of a urethral polyp reveals fibrous connective tissue, with some inflammatory cells.

Differential Diagnosis

I. Urethral neoplasia
II. Urethral calculi
III. Urethral stricture
IV. Cystitis
V. Vaginitis

Treatment

I. Proliferative urethritis in dogs (Hostutler et al., 2004)
   A. Antiinflammatory treatment with piroxicam 0.3 mg/kg PO SID or immunosuppression with azathioprine 2 mg/kg PO QOD to SID and prednisone 2 mg/kg PO BID may be effective.
   B. Antibiotic therapy, either with the previously mentioned drugs or as a single therapy, may also be considered.

II. Granulomatous urethritis in dogs (Moroff et al., 1991)
   A. Prednisolone 1.1 mg/kg PO BID for 14 days, then tapered to 0.07 mg/kg PO BID
   B. Cyclophosphamide 2.2 mg/kg PO SID for 4 days per week
   C. Concurrent antibiotic treatment for up to 6 weeks

III. Neoplasia: see Neoplasia later in this chapter
IV. Urethral polyps: removal via neodymium:yttrium-aluminum-garnet laser (Elwick et al., 2002)
V. Tube cystopexy for long-term management of obstructed dogs

Monitoring of Animal

I. Monitor the animal's ability to urinate or the patency of any urinary tube or catheter.
II. For dogs on piroxicam, monitor a biochemical profile 1 week after initiation of therapy, then every 1 to 6 months.
III. For dogs taking azathioprine, a CBC and platelet count are done initially every 1 to 2 weeks, then every 1 to 2 months, with a decrease in white blood cell or platelet

count necessitating a decrease in dose or discontinuation of therapy.
IV. Perform a urinalysis and urine culture during therapy, then at 3 to 5 days and 1 month after discontinuation of antibiotics.
V. Follow-up urinalysis and urine culture is then performed every 3 to 6 months.

Urethral Prolapse

Definition and Causes

I. A red or purple mass protrudes from the tip of the penis.
II. The mass is only reported in male dogs and is most often seen in young, male English bulldogs.
III. The exact cause is unknown; however, prolonged sexual excitement, urolithiasis, urethral infections, and increased abdominal pressure (from coughing, stranguria, and tenesmus) have been implicated.

Clinical Signs

I. Excessive licking of the prepuce
II. Preputial bleeding
III. Straining to urinate

Diagnosis

I. Visually examine the extruded penis.
II. The prolapsed tissue is red to purple in color, swollen, involves 360 degrees of the urethral orifice, and extrudes 3 to 4 mm from the penis.

Differential Diagnosis

I. Squamous cell carcinoma or transitional cell carcinoma of the tip of the penis or urethra
   A. Usually asymmetrical and do not involve just the tip of penis
   B. Tend to occur in older animals
II. Transmissible venereal tumor
   A. Occurs in young dogs
   B. Cytology of mass reveals a round cell tumor

Treatment

I. Attempts can be made to reduce prolapsed tissue, followed by a purse-string suture; however, recurrence is likely.
II. Surgery is the treatment of choice.
   A. Tissue reduction technique (Bjorling, 2003)
      1. Insert a urinary catheter, then apply an encircling tourniquet caudal to the os penis to maintain the penis in an extruded position and to minimize hemorrhage.
      2. Incise through the prolapsed urethral mucosa at the point of reflection, continuing for 180 degrees.
      3. Suture the urethra circumferentially to the tunic of the penis with 4-0 or 5-0 nonabsorbable suture in an interrupted pattern.
      4. Continue the incision and suture the remaining 180 degrees of the urethra.
   B. Urethropexy technique (Kirsch et al., 2002)
      1. Manually extrude the penis.
      2. Introduce a groove director (Miltex Instrument Co, Lake Success, N.Y.) to the distal aspect of the os penis to reduce the prolapse.
      3. Pass a 2-0 or 3-0 absorbable suture through the full thickness of the penis, from the external surface (as far proximally on the penis as the needle curvature allows) to the intraluminal surface, directing the needle distally out the urethral orifice.
      4. In a reverse fashion, pass the needle from the urethral lumen to the external surface of the penis and exit 0.5 cm distal to the initial needle entry site.
      5. Tie the suture snuggly with four throws, starting with a surgeon's knot.
      6. A slight depression occurs in the surrounding tissue, such that the top of the knot is even with the surface of the mucosa.
      7. Repeat the procedure until two to four evenly spaced sutures are placed.
      8. Pass a urinary catheter to confirm urethral patency.
III. Systemic antibiotics are indicated when urinary infection is present.

Monitoring of Animal

I. Hemorrhage is the most common postoperative complication.
   A. Minor bleeding may be reported up to 2 weeks after surgery.
   B. Sedation and an Elizabethan collar may be necessary for 3 to 5 days after surgery to prevent self-inflicted trauma.
   C. Minimize excitement and limit access to other pets and bitches in heat.
II. After the urethropexy technique, sutures are not removed.
III. Consider castration to minimize recurrences.

URETHRAL UROLITHIASIS

Definition and Causes

I. Calculi located within the urethra typically cause complete or partial obstruction and traumatic urethritis.
II. See Chapter 50 for specific causes of calculi formation.

Pathophysiology

I. Generally small cystic calculi migrate to the neck of the bladder during voiding and pass into the urethra.
II. In male dogs, urethral calculi often lodge caudal to the os penis.
III. In female dogs, calculi may lodge at any location along the urethra.
IV. Urethral calculi cause urinary obstruction more commonly in male dogs than females.

Clinical Signs

I. Stranguria, hematuria, pollakiuria, with or without blood dripping from the prepuce or vulva
II. Complete urinary obstruction: abdominal distension and pain, straining with no urine passage, azotemia, hyperkalemia

III. Partial urinary obstruction: frequent attempts to void with passage of urine during urination, bladder moderately large in size
IV. Severity of signs: dependent on degree and duration of obstruction

Diagnosis

I. Compatible clinical signs and physical examination findings
II. Inability or difficulty in passing a urinary catheter
III. Survey radiography or positive-contrast retrograde urethrography
IV. Cystoscopic examination

Differential Diagnosis

I. Neoplasia
II. Urethral stricture
III. Urethritis
IV. Urethral trauma

Treatment

I. Attempt to relieve any complete urinary obstruction.
   A. Try passing a small-diameter urethral catheter alongside the calculus.
   B. Try to flush stones retrograde into the urinary bladder.
   C. Under sedation or anesthesia, pass the largest-bore, high-density polyethylene urinary catheter possible through the os penis to just distal to calculus.
   D. Flush the catheter with saline while compressing the tip of the penis with dry gauze.
   E. If this technique fails, then place a finger in the rectum, palpate the urethra, and occlude its lumen.
      1. Repeat the previous steps.
      2. When maximum pressure is exerted on the urethra by the saline, suddenly release the digital urethral occlusion, allowing the lodged calculi to move into the bladder.
   F. If unable to relieve the obstruction, then consider tube cystostomy or frequent cystocentesis until corrective surgery can be performed.
II. Remove calculi from the bladder via cystotomy.
III. Urethrotomy via an incision over the calculi may be performed to remove stones that cannot be retropulsed.
IV. Urethrostomy to establish a permanent opening may be indicated in cases of recurrent calculi (e.g., urate calculi in Dalmatians).
   A. Scrotal urethrostomy is the technique of choice.
   B. Castration is performed simultaneously, if necessary.
V. Holmium:yttrium-aluminum-garnet laser lithotripsy has been used to fragment urethral calculi, with few complications (Davidson et al., 2004).
VI. Treatment of UTI and dietary management of calculi are discussed in Chapter 50.

Monitoring of Animal

I. After cystostomy, small quantities of blood and blood clots may be passed for 2 to 3 days.
II. Animals with postrenal azotemia are kept on IV crystalloids until resolution of azotemia, which typically occurs in 24 to 48 hours.
III. After urethrotomy and urethrostomy, hemorrhage from the urethral stoma is the most common postsurgical complication.
   A. It generally occurs within 4 to 5 days and may last up to 2 weeks.
   B. An Elizabethan collar is applied to prevent self-inflicted trauma.
IV. Monitor for recurrence of pollakiuria, because this could indicate development of a urethral stricture.

NEOPLASIA

Definition

I. Primary neoplasia of the urethra in the dog is uncommon, but bladder and prostatic neoplasia may extend into the urethra.
II. Transitional cell carcinoma and squamous cell carcinoma are the most common tumors, but hemangiosarcoma and chondrosarcoma have also been reported.

Cause

I. The cause is unknown.
II. The reported incidence is higher in older, female dogs.

Pathophysiology

I. Urethral tumors are usually locally infiltrative and may metastasize to the sublumbar lymph nodes and lungs (Norris et al., 1992).
II. Urethral inflammation may arise secondary to erosion or ulceration of the mucosa by the invading neoplasm.

Clinical Signs

I. Stranguria, hematuria, pollakiuria
II. Vaginal discharge or dripping blood from prepuce
III. Partial or complete urinary obstruction

Diagnosis

I. Suggestive clinical signs
II. Physical examination findings
   A. Rectal palpation may reveal thickening or a mass effect in the urethra.
   B. An abnormal urethral papilla may be found on vaginal examination.
   C. It may not be possible to pass a urinary catheter beyond the lesion.
III. Laboratory results
   A. Urinalysis
      1. Microscopic hematuria is common.
      2. Rarely bacteriuria, pyuria, or neoplastic cells may be seen.
   B. Biochemical profile: ± azotemia and/or hyperkalemia with chronic obstruction
IV. Imaging studies

A. Survey radiography may reveal an enlarged bladder or sublumbar lymph nodes.
B. Ultrasonography may reveal a mass near the neck of the bladder, but the pelvic urethra is difficult to visualize with ultrasonography.
C. Positive-contrast cystography often reveals irregular filling defects within the urethra.

V. Urethral cytology
A. Often equivocal
B. ± Inflammation associated with secondary ulceration of neoplasm or urethritis

VI. Urethral biopsy
A. See previous discussion of Urethritis for techniques.
B. Cystoscopically obtained biopsies are often small and may be inadequate to confirm a diagnosis.
C. Biopsy may be difficult if tumor location is subepithelial.

Differential Diagnosis

I. Neoplasia of the bladder, prostate
II. Urethritis
III. Transmissible venereal tumor
IV. Urethral calculi
V. Nonpenetrating trauma

Treatment

I. If obstruction is present, then relieve the obstruction by inserting a urinary catheter attached to a collection system.
A. While hospitalized, the urinary collection system is changed SID to minimize ascending infection.
B. Treat any prerenal or postrenal azotemia.

II. Surgery may be attempted, using several approaches.
A. In dogs with tumors involving less than one third of the intrapelvic urethra, wide surgical excision via sagittal pubic osteotomy may be helpful (Davies and Read, 1990).
1. Postoperative complications include death, persistent uremia, and tumor recurrence.
2. Reported survival is 2 to 22 months.
B. Transurethral resection via rigid cystoscopy and electrocautery may successfully reduce tumor volume in dogs with urethral transitional cell carcinoma (Liptak et al., 2004).
1. Postoperative complications include hemorrhage and urethral perforation.
2. Transurethral resection syndrome (excessive absorption of lavage solution after perforation), bacteriuria, and seeding of the surrounding areas with tumor cells may also occur.
C. Urinary diversion may be done via ureterocolonic or trigonal-colonic anastomosis for long-term, palliative management of obstructions from urethral neoplasia (Smith et al., 1995).
1. Postsurgical complications include UTI, pyelonephritis, hypochloremic acidosis, low survival time (1.5 to 5 months) (Montgomery and Hanks, 1988; Smith et al., 1996).
2. Urinary bladder empties into the colon.
3. UTI is a frequent complication.
4. It does not reduce tumor burden.

III. Urinary diversion or urethral stenting are palliative procedures.
A. Permanent tube cystopexy through the body wall allows diversion of urine.
1. Owners must empty the tube several times a day.
2. UTI is a frequent complication.
B. Urethral stenting with expandable stents may be performed using interventional radiography (Weisse et al., 2006).

IV. Chemotherapy may be tried, but clinical studies of urethral tumors are lacking.

Monitoring of Animal

I. Monitor frequently for UTI via urinalysis and urine culture.
II. Animals with urinary diversion into the colon must be allowed to defecate four to five times per day.
A. Frequent evaluation of hydration status, electrolytes, and acid-base status are required.
B. Excretory urography or ultrasonography is performed at 3 and 6 months to evaluate the ureters and kidneys for signs of dilation, stricture, and infection.

TRAUMA

Definition and Causes

I. Urethral damage may result from blunt or penetrating injuries, or it may be secondary to perforation associated with catheterization.
II. Incidence is variable.
A. For dogs struck by cars, 2 per 600 had urethral injuries (Kolata and Johnson, 1975).
B. For dogs with pelvic trauma, urethral rupture ranged from 5% to 10% (Kleine and Thornton, 1971; Selcer, 1982).
C. Most dogs with urethral rupture have been males (Selcer, 1982).

Pathophysiology

I. Blunt trauma is more likely to cause contusions.
II. Lacerations are commonly associated with pubic or os penis fractures, penetrating wounds (knife, gunshot, animal bite), or catheterization.
III. Pubic or os penis fractures may cause urethral obstruction.

Clinical Signs

I. Partial or complete urethral obstruction
A. Pollakiuria is common with either no or little urine evacuation.
B. The bladder is inappropriately large for repeated attempts at urination.
C. With partial lacerations, hematuria may be the only clinical sign, and a urinary catheter may pass normally.

II. Urethral disruption leading to accumulation of urine within abdomen, pelvic canal, or subcutaneous tissues
III. Chronic subcutaneous leakage leading to formation of urethrocutaneous fistula

Diagnosis

I. Urethral trauma must be considered in animals with pelvic trauma or penetrating injuries.
II. Unexplained uremia after trauma is highly suggestive.
III. Plain radiography is rarely diagnostic.
IV. Positive-contrast urethrocystography usually identifies disruption of the urethra.
  A. Positive-contrast cystography (Essman, 2005)
    1. Before catheterization, fill the catheter with saline or 2% lidocaine to minimize air bubble artifact and prevent bladder spasm that can occur secondary to pain.
    2. Iodinated contrast media is used and sometimes diluted to a 20% solution before infusion (see Chapter 4).
  B. Retrograde urethrography (Burke and Feeney, 2003)
    1. An undiluted, water-soluble radiopaque contrast medium is used (see Chapter 4).
    2. The tip of a catheter is positioned just beyond the urethral papilla in female dogs and just caudal to the os penis in male dogs.
    3. Contrast is manually injected (forcibly), and a radiograph is obtained as the last portion of the contrast is injected.
    4. Distension of the urinary bladder may not be necessary.

Differential Diagnosis

I. Periurethral hematoma or abscess
II. Neoplasia
III. Trauma to other areas of the urinary tract

Treatment

I. Urethral contusion without rupture can often be managed medically.
  A. Urethral catheterization to relieve urinary obstruction
  B. Treatment of underlying cause (e.g., stabilization of pelvic fractures)
II. Incomplete laceration of the urethra may heal if urine is diverted by placement of a urethral catheter for 3 to 5 days (Cooley et al., 1999).
III. Complete urethral transection requires surgical intervention.
  A. Resection of damaged tissue is done, followed by anastomosis to prevent formation of strictures or a urethrocutaneous fistula.
  B. If primary suturing causes excessive tension, then closure of the urethra may be reinforced using a flap of muscle raised from the rectus abdominis or internal obturator.
  C. An indwelling urinary catheter is inserted for 3 to 5 days postoperatively.
IV. Intrapelvic urethral injuries may require pubic osteotomy to allow débridement and repair (Bjorling, 2003).
  A. Urethral repair is done with 4-0 or 5-0 monofilament absorbable suture in an interrupted pattern.
  B. Maintenance of a urethral catheter intraoperatively facilitates identification of the urethral lumen and may improve results of anastomosis (Layton et al., 1987).
V. Os penis injuries may require surgery (Kelly and Clark, 1995).
  A. Obstruction may result from callus and fibrous tissue formation.
  B. Avoidance of these sequelae may require stabilization with a finger bone plate.

Monitoring of Animal

I. Urine diversion is continued during the period of urethral healing.
  A. Indwelling catheters are connected to a closed collection system, which is changed once daily.
  B. Catheter patency and urine volume are monitored.
  C. Urine culture and sensitivity are performed after catheter removal.
II. To ensure healing, urethrography is repeated at the time of catheter removal, using caution to minimize breakdown of the healing area.
III. Activity is restricted in animals that have had a pubic osteotomy.
  A. Complete healing and osseous union may not occur for >4 months.
  B. Bony healing is monitored with serial radiography.
IV. Retrograde urethrography may be performed at 3 and 6 months to monitor for postoperative urethral stricture.

URETHRAL OBSTRUCTION

Definition and Causes

I. Urethral obstruction is a partial or complete inability to empty the urinary bladder because of impaired flow of urine through the urethra.
II. Structural causes include urethral neoplasia, calculi, mucus plugs, strictures, and urethritis.
III. Functional causes include urethral spasm, upper motor neuron spinal cord lesions, and feline idiopathic cystitis.
IV. It occurs more commonly in male dogs and cats than females.

Pathophysiology

I. With complete obstructions, contraction of the detrusor muscle is unable to overcome the obstruction, which leads to urine retention in the bladder.
II. With partial obstructions, small amounts of urine are passed.

Clinical Signs

I. Straining to urinate, with incomplete bladder emptying
II. Lethargy, anorexia, preputial licking, tenesmus, vocalization
III. Prolonged obstruction: bradycardia or tachycardia, acute renal failure, shock, acute death

Diagnosis

I. Large, firm, palpable, inexpressible bladder suggestive
II. Difficulty or inability to pass a catheter into the bladder

Differential Diagnosis

I. Pollakiuria associated with UTIs

II. Tenesmus from other causes
III. Micturition disorders (see Chapter 51)

Treatment

I. Maintain circulatory volume and correct acid-base and electrolyte abnormalities.
   A. A balanced crystalloid solution is administered IV to correct fluid deficits.
   B. Hyperkalemia is treated (see Acute Renal Failure in Chapter 48).
II. Relieve the urinary obstruction (see previous discussion of Urolithiasis).
   A. Perform hydropulsion for urethral calculi (see Chapter 50).
   B. For obstructions associated with feline idiopathic cystitis, insert a urinary catheter attached to a closed collection system for 24 to 72 hours.
   C. If a catheter cannot be passed, consider repeated cystocentesis until the animal can undergo anesthesia and surgery.
   D. Culture the urine retrieved from the obstructed bladder.
   E. Surgically correct any structural abnormalities after the animal is stabilized.
   F. For recurrences, consider a perineal urethrostomy in cats or a prescrotal urethrostomy in dogs.
III. After relief of the obstruction, institute diuresis.
   A. Continue IV or SC crystalloid solutions.
   B. Monitor urine output, because postobstructive diuresis is common.
   C. Meet or exceed urine output and needs for diuresis with appropriate amounts of the crystalloid solutions.
IV. Long-term management of urethral spasms may involve the following:
   A. Environmental enrichment for cats with idiopathic cystitis (see Chapter 50)
   B. Reduction of muscle spasms
      1. Phenoxybenzamine and prazosin
         a. Phenoxybenzamine 2.5 to 7.5 mg PO SID to BID
         b. Prazosin 0.25 mg PO SID to BID
         c. Little evidence of clinical efficacy
         d. Side effects: hypotension, weakness, nausea, vomiting
         e. Ideally initiated with urinary catheter in place because of their slow onset
      2. Diazepam and dantrolene
         a. Diazepam 0.1 to 0.25 mg/kg PO BID to TID
         b. Dantrolene 0.5 to 2.0 mg/kg PO TID
         c. Little evidence of clinical efficacy
         d. Side effects: hyperexcitability, acute hepatic failure in cats (diazepam), acute hepatopathy in dogs (dantrolene)
V. Institute preventative measures for other causes of urethral obstruction, such as urolithiasis and other forms of functional obstruction (see Chapter 51).

Monitoring of Animal

I. Monitor serum biochemistries SID until azotemia and hyperkalemia have resolved.
II. Monitor urine output until postobstructive diuresis has resolved.
III. Once the urinary catheter has been removed, closely monitor the animal's ability to urinate for at least 24 hours before discharge from the hospital.
IV. Animals receiving muscle relaxants are monitored for hypotension for 1 to 2 weeks after initiation of therapy.
V. Perform a biochemical profile within 1 to 2 weeks of initiating therapy in animals receiving diazepam or dantrolene.

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CHAPTER 53

Diseases of the Prostate

Kerry J. Heuter

DEGENERATIVE DISORDERS

Benign Hyperplasia and Cystic Hyperplasia

Definition

I. Benign prostatic hyperplasia (BPH) is a nonmalignant enlargement of the prostate from excessive cellular growth of the glandular and stromal elements.
   A. BPH is the most common prostatic disorder in the dog.
   B. All dogs with normal testes develop histologic evidence of BPH with aging, but most dogs are asymptomatic (Berry et al., 1986).
II. Cystic hyperplasia of the prostate is the formation of multiple fluid-filled cavities throughout the parenchyma.
III. The feline prostate does not develop age-related hyperplasia.

Causes

I. Hyperplasia occurs in two phases.
II. Benign glandular hyperplasia is characterized by an increase in the amount and size of secretory epithelium.
   A. Condition is first seen at 1 to 2 years of age.
   B. Condition is progressive for ≥10 years, and peaks at 5 to 6 years of age (Berry et al., 1986).
III. Benign complex hyperplasia is characterized by glandular hyperplasia intermingled with areas of atrophic secretory epithelium.
   A. A relative increase in the stroma occurs in the atrophic areas that is composed of collagen and muscle.
   B. Frequently, alveoli are dilated and filled with eosinophilic material.
   C. Cysts can be present anywhere in the gland but are most often found in the periurethral area.
   D. Chronic inflammation and squamous metaplasia of the epithelium may also be present.
   E. BPH begins at 2 to 3 years of age and continues to increase with age, reaching a prevalence of 70% at 8 to 9 years (Berry et al., 1986).

Pathophysiology

I. Development of hyperplasia is associated with an altered androgen:estrogen ratio and requires the presence of the testes.
   A. Proposed effects of absolute or relative excess of androgens
      1. Proliferation of prostatic epithelial cells occurs.
      2. 5α-Dihydrotestosterone (DHT) within the gland probably serves as main hormonal mediator for hyperplasia.
   B. Proposed effects of absolute or relative excess of estrogens
      1. Atrophy of glandular epithelial cells
      2. Proliferation of prostatic basal cells
      3. Squamous metaplasia of epithelial ducts
      4. Enhancement of androgen receptors
   C. Increased estrogen effects: allow development of hyperplasia even as androgen production decreases with age
II. Development of cysts is usually associated with fibromuscular proliferation or squamous metaplasia.
   A. Hyperplastic or metaplastic tissue causes obstruction of excretory ducts.
   B. Despite obstruction of the ducts, secretion continues by prostatic acini, which allows fluid to accumulate, creating cysts.
III. In dogs, BPH is a diffuse process that expands away from the urethra, making dysuria an uncommon clinical sign.
IV. Secondary effects of an enlarged prostate may cause the following:
   A. Partial urinary obstruction: rare in dogs (see previous point regarding dogs)
   B. Hemorrhagic urethral discharge and hematuria from increased vascularity of the prostate
   C. Partial obstruction of descending colon, causing constipation or tenesmus
   D. Occasional perineal hernias
V. Predisposition to prostatitis may arise from decreased flow of prostatic secretions, cyst formation, and/or alteration of the composition of prostatic fluid.

Clinical Signs

I. Most dogs are asymptomatic.
II. Symptomatic dogs are alert, active, and afebrile, with one or more of the following:
   A. Tenesmus associated with defecation
   B. Hematuria and/or urethral discharge (hemorrhagic to clear or yellow) independent of urination
   C. Rarely, dysuria

Diagnosis

I. Signalment: intact, mature male dog
II. Physical examination findings
  A. Rectal palpation reveals a nonpainful, symmetrically enlarged prostate with variable consistency (normal to mildly irregular).
  B. Perineal hernia is occasionally found.
III. Laboratory findings: urine or prostatic fluid normal or mildly hemorrhagic
IV. Radiographic findings
  A. Survey abdominal radiographs may show prostatomegaly with dorsal displacement of the colon and cranial displacement of the bladder.
  B. Positive-contrast retrograde urethrography may reveal a narrowed urethra or urethroprostatic reflux.
  C. Ultrasonography shows normal to moderate enlargement that is symmetrical.
    1. Smooth margins and normal to slightly increased echogenicity
    2. Small, well-defined cysts with smooth margins
V. Definitive diagnosis
  A. Diagnosis is obtained by biopsy.
  B. Presumptive diagnosis is often made with previously mentioned diagnostic tests.
  C. Positive response to treatment helps confirm the diagnosis.

Differential Diagnosis

I. BPH accompanies most other prostatic diseases in older, intact dogs.
II. It can be difficult to distinguish from chronic prostatitis or neoplasia.
  A. With chronic prostatitis, inflammation or infection is found in the urine or prostatic samples.
  B. Prostatic neoplasia does not respond to therapy for BPH.
III. Scottish terriers have prostate glands four times larger than those of other dog breeds of similar weight and age (Kutzler and Yeager, 2005).

Treatment

I. Castration is the recommended treatment.
II. Prostatic size decreases by 50%, and clinical signs are alleviated within 3 weeks after castration (Sirinarumitr et al., 2001).
III. Medical therapies are not as effective as castration in reducing prostatic size, but they offer an alternative for owners who decline surgery.
  A. Finasteride is a 5α-reductase inhibitor that prevents conversion of testosterone to 5α-DHT and causes a dose-dependent regression in prostate size.
    1. At a dose of 1 mg/kg/day PO, prostatic size was reduced by 70% within 10 weeks (Shibata et al., 2001).
    2. At a dose of 0.1 to 0.5 mg/kg/day PO for 16 weeks, serum DHT decreased by 58% and prostatic volume and secretory function decreased by 43%, without adversely affecting semen quality (Sirinarumitr et al., 2001).
    3. Treatment is lifelong; if stopped, then the effects are reversed in <8 weeks (Kutzler and Yeager, 2005).
    4. Drug is potentially teratogenic to male fetuses if pregnant females are exposed to the drug during the first one third of gestation.
  B. Several antiandrogenic drugs (e.g., chlormadinone acetate, osaterone acetate, flutamide, megestrol acetate) are effective at reducing prostate size but can adversely affect gonadal function and are not recommended in breeding animals.
  C. Liposterolic extract of the saw palmetto plant berries or the American dwarf palm tree *(Serenoa repens)* has had little effect in dogs (Barsanti et al., 2000).
  D. Estrogens have historically been used to treat BPH; however, because of the risk of myelosuppression and prostatic abscess formation, they are no longer recommended.

Monitoring of Animal

I. If the dog is asymptomatic and castration is declined, watch for the development of typical clinical signs and perform a rectal examination at every physical examination.
II. If the dog is symptomatic, palpate the prostate gland 3 weeks after castration to be sure that the gland is involuting as expected.
III. Failure of involution after surgery may indicate a more serious prostatic disease, such as neoplasia or prostatitis.
IV. If medical therapy is chosen, monitor for changes in prostatic size and for the development of adverse effects secondary to drug therapy.

Prostatic Cysts

Definition and Causes

I. Prostatic and paraprostatic cysts are single or multiple, epithelial-lined, fluid-filled (serosanguineous) structures.
II. Prostatic cysts can vary tremendously in number, size, and location.
  A. Small cysts may be present in a hyperplastic gland (see previous discussion under Cystic Hyperplasia).
  B. Prostatic retention cysts most likely develop secondary to obstruction of parenchymal ducts, resulting in accumulation of prostatic secretions.
    1. They can be very large but are intimately associated with the prostate.
    2. They may also connect to the urethra (Olson et al., 1987; White, 2000).
  C. In the past, researchers believed that paraprostatic cysts resulted from accumulation of fluid within remnants of the Müllerian duct (uterus masculinus).
    1. More recently, researchers theorize that paraprostatic cysts have the same origin as retention cysts (Olson et al., 1987; White, 2000).
    2. These cysts can be very large but are located outside the prostatic parenchyma, attached to the prostate via a stalk, and do not connect with the urethra.

Pathophysiology

I. Large cysts may impinge on the colon, urethra, or other abdominal organs.
II. Infection may occur secondary to prostatitis and urethral or iatrogenic contamination.
III. Mineralization of paraprostatic cysts has been reported (Head and Francis, 2002).

Clinical Signs

I. Cysts may produce no clinical signs until their size is sufficient to affect other structures, such as the urethra (dysuria) or colon (tenesmus or constipation).
II. Abdominal or perineal distention can develop secondary to a mass effect.
III. Infected cysts may cause hematuria, pyuria, and dysuria.

Diagnosis

I. Signalment
  A. Intact, mature male dog
  B. Rarely, male cats (Newell et al., 1992)
II. Physical examination findings
  A. Paraprostatic cysts may be palpable in the caudal abdomen or perineal area.
  B. With intraprostatic cysts, rectal palpation may reveal mild or marked enlargement of the prostate, with or without asymmetry.
  C. Fluctuant areas may or may not be palpable.
  D. Calcified cysts feel firm.
III. Laboratory test results
  A. Submit urine, prostatic wash fluid, or ejaculate for analysis and culture.
  B. Results may show hemorrhage and/or infection if communication between the cyst and the urethra exists.
IV. Prostatic fluid analysis
  A. Samples are often obtained via ultrasonography or surgery.
  B. Fluid is usually yellow to turbid and brown in color.
  C. It may reveal low numbers of white blood cells, variable numbers of red blood cells and epithelial cells, and is usually sterile.
  D. If infected, then the cyst is classified as an abscess.
V. Radiographic findings
  A. Survey abdominal radiographs may show asymmetrical prostatomegaly, two bladderlike structures, and possibly mineralization within the cyst.
  B. Positive-contrast retrograde urethrography may reveal a narrowed urethra and/or increased urethroprostatic reflux, and contrast may enter the cyst if communication with the urethra exists.
  C. Ultrasonography shows a fluid-filled cyst inside or outside of the parenchyma.
VI. Definitive diagnosis: exploratory laparotomy, excision, biopsy

Differential Diagnosis

I. Prostatic cysts are often associated with other prostatic diseases (BPH, prostatitis, neoplasia) that may coexist or contribute to cyst formation.
II. Without surgery, prostatic abscesses may be impossible to differentiate from an infected prostatic cyst.

Treatment

I. Recommended treatment is surgical drainage, with excision or omentalization (White, 2000).
II. Castration is also recommended to help prevent further cyst formation and other prostatic diseases.

Monitoring of Animal

I. Treat other coexisting prostatic diseases as indicated.
II. If infection is present, follow the recommendations under Prostatic Abscessation in the following section.

INFLAMMATORY DISEASES

Prostatitis and Prostatic Abscessation

Definition

I. Prostatitis is inflammation of the prostatic parenchyma in response to infection; it may be acute or chronic in nature.
II. Acute or chronic prostatitis may lead to encapsulation of infected material and cavitation within the prostate, thus forming a prostatic abscess.

Causes

I. Route of infection is usually ascending through the urethra.
II. Hematogenous spread or spread of infection from the kidneys, bladder, testes, or epididymis is also possible.
III. Causative organisms are usually those that are common in urinary infection, such as *Escherichia coli* (most common), *Staphylococcus* spp., *Klebsiella* spp., *Pseudomonas* spp., *Proteus* spp., *Streptococcus* spp., *Enterococcus* spp., and *Mycoplasma* spp. (Krawiec and Helfin, 1992; Klausner et al., 1995).
  A. *Brucella canis* may infect the canine prostate but is more commonly associated with testicular infection.
  B. Infection by anaerobic bacteria and fungi *(Blastomyces dermatitidis*, *Cryptococcus neoformans*, *Coccidioides immitis)* is rare.
IV. Prostate is predisposed to infections via several mechanisms.
  A. Urethral diseases: urolithiasis, neoplasia, strictures, congenital abnormalities
  B. Prostatic diseases: BPH, cyst formation, neoplasia, squamous metaplasia
  C. Urinary tract infections (UTIs)
  D. Impaired host immunity: drugs (corticosteroids, chemotherapy), disease (diabetes mellitus, hyperadrenocorticism)

Pathophysiology

I. Acute prostatitis
  A. Mild prostatic enlargement occurs unless coexisting prostatic disease exists.
  B. Acute prostatitis may result in systemic illness (septicemia) via hematogenous spread of infection or a secondary peritonitis.

II. Chronic prostatitis
  A. Mild prostatic enlargement occurs unless coexisting prostatic disease exists.
  B. It may develop secondary to an acute infection or progress gradually over time.
  C. The prostate may serve as a nidus of infection for the urinary tract.
  D. Chronic prostatitis is the second most common prostatic disorder in intact male dogs and may be the most common one associated with clinical signs (Krawiec and Helfin, 1992).
III. Prostatic abscessation
  A. Abscesses may form secondary to chronic infection and subsequent accumulation of pockets of purulent material.
  B. They may also form from acute infection of preexisting cysts.
  C. Abscesses may become quite large and rupture, leading to peritonitis.

Clinical Signs

I. Acute prostatitis
  A. Urinary tract signs: hematuria, pyuria, dysuria, urethral discharge (hemorrhagic or purulent), and/or urinary incontinence
  B. Constipation, tenesmus
  C. Pain: reluctance to rise, stiff gait, arched back, tensed abdomen
  D. Systemic signs: fever, anorexia, depression, tachycardia, vomiting
II. Chronic prostatitis
  A. Recurrent or chronic UTIs, urethral discharge, and/or hematuria
  B. Constipation, tenesmus
  C. Infertility
III. Prostatic abscess
  A. Signs are similar to those for either acute or chronic prostatitis, because abscessation is associated with prostatitis.
  B. With rupture of the abscess and subsequent peritonitis, the following may occur:
    1. Acute abdominal pain, fever, vomiting, lethargy
    2. Septic shock with tachycardia, icterus, injected or pale mucus membranes, collapse

Diagnosis

I. Acute prostatitis
  A. Signalment: intact, mature male dog
  B. Physical examination findings
    1. Rectal palpation commonly reveals prostatomegaly from coexisting disease (BPH, cysts, neoplasia).
    2. Pain and/or urethral discharge may be elicited on palpation.
  C. Laboratory results
    1. Neutrophilic leukocytosis often exists, with or without a left shift.
    2. Azotemia, electrolyte disturbances, or hemoconcentration may be seen if a systemic illness is present.
    3. Hematuria, pyuria, and bacteriuria are common.
    4. Urine culture results may be positive if concomitant UTI exists.
  D. Prostatic fluid analysis
    1. Samples are difficult to obtain (because of pain) and difficult to interpret when a concomitant UTI is present.
    2. If samples are obtained, then cytology shows evidence of inflammation and infection.
  E. Radiographic findings
    1. Survey abdominal radiographs may show prostatomegaly and/or loss of detail in the area of the prostate suggestive of local peritonitis.
    2. Positive-contrast urethrography may reveal urethroprostatic reflux.
    3. Ultrasonography may show a focal to diffuse increase in echogenicity of the prostate gland.
  F. Definitive diagnosis
    1. Requires biopsy and culture of prostatic tissue (not usually performed).
    2. Positive response to treatment helps confirm the diagnosis.
II. Chronic prostatitis
  A. Signalment: intact, mature male dog; rarely, male cats (Roura et al., 2002)
  B. Physical examination findings
    1. Rectal palpation commonly reveals prostatomegaly from coexisting disease (hyperplasia, cysts, or neoplasia).
    2. Prostate may be small and irregular, especially with significant fibrosis and loss of tissue.
  C. Laboratory findings
    1. Hematuria, pyuria, and bacteriuria are common.
    2. Urine cultures may be positive if a concomitant UTI exists.
  D. Prostatic fluid analysis
    1. Fluid collected by ejaculation is usually purulent, septic, and may also be hemorrhagic.
    2. Quantitative culture of urine and prostatic fluid yields significant numbers of the same organisms.
      a. Dogs with experimental chronic bacterial prostatitis had >1000 organisms/mL (Barsanti et al., 1983).
      b. Establishing a definitive number of bacteria to differentiate infection from contamination is difficult.
    3. Samples collected by ejaculation are preferred over prostatic wash samples.
      a. Prostatic wash samples are difficult to interpret because of the large number of bacteria present in the urinary tract.
      b. If prostatic wash samples are used, then the UTI must be controlled first.
    4. Ultrasound-assisted aspiration may also be used to obtain samples if cysts are present.
  E. Radiographic findings
    1. Survey abdominal radiographs may show prostatomegaly and/or intraprostatic mineralization.

2. Positive-contrast urethrography may reveal urethroprostatic reflux.
3. Ultrasonography may show multifocal mineralization.

F. Definitive diagnosis: prostatic tissue culture and histopathology

III. Prostatic abscess
A. Signalment: intact, mature male dog
B. Physical examination findings
1. Rectal palpation commonly reveals dramatic prostatomegaly, with marked asymmetry.
2. Pain and/or urethral discharge are often elicited on palpation.
C. Laboratory results
1. Neutrophilic leukocytosis with a left shift often exists.
2. Azotemia, electrolyte disturbances, or hemoconcentration may be seen if systemic illness is present.
3. Elevated liver enzymes, hyperbilirubinemia, and hypoglycemia may be seen with sepsis.
4. Hematuria, pyuria, and bacteriuria are common.
5. Urine culture is positive if a concomitant UTI exists.
D. Prostatic fluid analysis
1. Samples are often obtained via ultrasonography or surgery.
2. When obtained, the fluid is usually purulent and septic.
E. Radiographic findings
1. Survey abdominal radiographs show prostatomegaly.
2. Loss of detail in the area of the prostate or diffuse loss of detail is seen with peritonitis.
3. Intraprostatic mineralization may be present.
4. Positive-contrast urethrography may reveal periurethral asymmetry, narrowing of the prostatic urethra, and contrast medium entering the abscess if communication with the urethra is present.
5. Ultrasonography shows an asymmetrical prostate that is hyperechoic, with fluid-filled cavitations.
F. Definitive diagnosis
1. Diagnosis is made with ultrasound-guided aspiration and/or surgical exploration.
2. At surgery, samples are obtained for histopathology and culture (aerobic and anaerobic).

Differential Diagnosis

I. For acute prostatitis, consider the following:
A. Major differential considerations are prostatic neoplasia, prostatic abscess, and pyelonephritis.
B. All can induce a painful abdomen, signs of inflammation on laboratory tests, and systemic illness.

II. For chronic prostatitis, considerations are prostatic neoplasia and other causes of chronic UTI.

III. Prostatic abscessation, neoplasia, and paraprostatic cysts all cause marked prostatic enlargement.

Treatment

I. Acute prostatitis
A. Antibiotics (based on culture results) are given for at least 4 weeks.
1. Initially, all antibiotics reach the prostate because the blood-prostate barrier is not intact.
2. IV antibiotics may be ideal initially, but an oral antibiotic with prostatic penetration is preferred to finish the therapy (see Chronic Prostatitis, following).
B. Castration is not helpful immediately and may be dangerous in a systemically ill animal.
C. After stabilization, castration helps resolve the current infection and assists in preventing future infections.

II. Chronic prostatitis
A. Antibiotic that penetrates the blood-prostate barrier must be chosen if therapy is to be successful.
1. Enrofloxacin (5 to 10 mg/kg PO SID), chloramphenicol (25 to 50 mg/kg PO TID), clindamycin (5 to 11 mg/kg PO BID), erythromycin (10 to 22 mg/kg PO TID), trimethoprim-sulfonamide (15 to 30 mg/kg PO BID), and doxycycline (4.4 to 11 mg/kg PO BID) all penetrate the prostate (Greene et al., 2006).
2. Ciprofloxacin and norfloxacin do not concentrate in the prostate (Dorfman et al., 1995).
B. Antibiotics are continued for at least 6 to 8 weeks.
C. Castration may be beneficial in the resolution of chronic bacterial prostatitis.
1. In one study, castrated dogs cleared the infection in 4.2 weeks, compared with 9.5 weeks for intact dogs (Cowan et al., 1991).
2. Castration may also help prevent future infections and relapses.

III. Prostatic abscess
A. Surgery is the treatment of choice.
1. Current recommendation is intracapsular prostatic omentalization (White, 2000).
a. Most animals can be discharged from the hospital within 24 hours.
b. Complications include recurrence and urinary incontinence.
2. Castration is also recommended to help with involution of the prostate and to lessen the likelihood of recurrence.
3. Other surgeries (e.g., ventral drainage, prostatic marsupialization, and prostatectomy) are no longer recommended because of increased recurrence and complication rates, as well as prolonged recovery times.
B. Antibiotics, based on culture results, are given for at least 6 to 8 weeks.
1. Initially all antibiotics reach the prostate because the blood-prostate barrier is not intact.
2. IV antibiotics may be ideal to start, but an oral antibiotic with prostatic penetration is preferred to finish the therapy (see previous discussion under Chronic Prostatitis).
C. Nonsurgical methods of treatment have variable efficacy.
1. Antibiotic therapy in conjunction with castration has not been effective at resolving most prostatic abscesses (White, 2000).

2. Percutaneous, ultrasound-guided drainage followed by alcoholization of the cavity was effective at resolving a prostatic abscess in one dog (Kutzler and Yeager, 2005).

Monitoring of Animal

I. Acute prostatitis
   A. Physical examination and cytology and culture of urine and/or prostatic fluid are performed 7 days after finishing antibiotics.
   B. If any evidence of persistent infection is seen, antibiotics are continued for another 6 to 8 weeks (and the condition is treated as chronic prostatitis).
II. Chronic prostatitis
   A. Physical examination and cytology and culture of urine and/or prostatic fluid are performed at the following times:
      1. After 3 to 4 weeks of antibiotic therapy
      2. Seven days after finishing antibiotic therapy
      3. Monthly for 2 to 3 months after finishing antibiotic therapy
   B. Relapses are common within a few months after discontinuing antibiotics.
   C. If the initial therapy fails, then longer courses of antibiotics (12 weeks) must be given.
III. Prostatic abscess
   A. Repeated examinations are as outlined for chronic prostatitis.
   B. In addition, ultrasonography is performed at the previously mentioned times until resolution of the abscess is confirmed.
   C. Reabscessation and recurrent UTIs are common.

NEOPLASIA

Definition

I. Primary prostatic neoplasia is a tumor arising from any of the cellular elements of the prostate gland.
   A. Prostatic neoplasia is the most common prostatic disease diagnosed in dogs castrated before development of clinical signs (Krawiec and Heflin, 1992).
   B. Adenocarcinoma is the most common tumor type.
   C. Transitional cell carcinoma and undifferentiated carcinomas also occur.
   D. Other primary tumors, such as leiomyosarcomas, are rare (Hayden, 1999).
II. Prostate may also be the site of metastasis of other tumors.

Causes

I. Effects of hormones and castration are still being investigated, but some conclusions are as follows:
   A. Castration does not protect against the development of prostatic carcinoma (Obradovich et al., 1987).
   B. Castration does not initiate development of prostatic carcinoma, but it does favor tumor progression (Teske et al., 2002).
II. High-grade prostatic intraepithelial neoplasia is considered to be a precursor of malignancy in dogs and humans (Cooley and Waters, 2001).
   A. Atypical lesion diagnosed on histopathology
   B. Prostatic carcinoma often accompanied by intraepithelial neoplasia

Pathophysiology

I. Local invasion of prostatic neoplasia may cause the following:
   A. Enlarged, irregular prostate gland
   B. Growth into the urethra causing dysuria or obstruction
   C. Growth into the trigone of bladder, with obstruction of ureters
   D. Outward extension that impinges on the colon and causes tenesmus and constipation
   E. Growth through blood vessels causing hematuria
   F. Obstruction of normal ducts causing cyst formation and predisposing to infection
II. Metastasis is commonly found in the regional lymph nodes and lungs.
III. Skeletal metastasis is common and frequently occurs in the lumbar vertebrae and pelvis.

Clinical Signs

I. No clinical signs may occur initially.
II. Most clinical signs are related to local effects.
   A. Hematuria, dysuria, incontinence, urethral discharge (hemorrhagic or purulent)
   B. Constipation, tenesmus
   C. Mimics other prostatic diseases
III. Signs may also be related to metastasis.
   A. Abnormal gait, myelopathic signs with skeletal metastases
   B. Dyspnea, hemoptysis, cough with pulmonary metastases
   C. Fever, anorexia, weight loss with systemic illness

Diagnosis

I. Signalment: mature, male dog (intact or castrated); rarely, male cats
II. Physical examination findings
   A. Rectal palpation usually reveals an enlarged and asymmetrical prostate, with increased firmness and obliteration of the median raphe.
   B. The prostate may be painful and/or fixed to the pelvic floor.
   C. Sublumbar lymph nodes may be palpably enlarged.
III. Laboratory results
   A. Neutrophilia, with or without a left shift, and/or a mild nonregenerative anemia may be present (Bell et al., 1991).
   B. Azotemia may occur from systemic illness and/or obstruction of urine flow.
   C. Many dogs have elevations of serum alkaline phosphatase, and only some of these have skeletal metastases (Bell et al., 1991).

D. Samples of urine, prostatic wash, or ejaculate may be hemorrhagic, show signs of inflammation, and occasionally reveal malignant cells.
E. No serum biochemical marker has been found in dogs.

IV. Radiographic findings
A. Survey abdominal radiographs may show asymmetrical prostatomegaly, intraprostatic calcification, sublumbar lymphadenopathy, and/or lytic or proliferative changes in the lumbar vertebrae, pelvis, or long bones.
B. Survey thoracic radiographs may reveal evidence of metastases.
1. Metastases appear as generalized, increased nodular-interstitial densities or single to multiple discrete nodules.
2. In one study, 38% of dogs with normal thoracic radiographs had pulmonary metastases at necropsy (Bell et al., 1991).
C. Positive-contrast retrograde urethrography may reveal a narrowed or irregular urethra and/or urethroprostatic reflux, with or without local invasion of the bladder.
D. Ultrasonography may show focal to multifocal increased echogenicity of the prostate and/or an irregular prostatic contour.
1. Focal or multifocal mineralization may also be present.
2. Other lesions may be seen from concurrent diseases (BPH, prostatitis, cyst formation).

V. Definitive diagnosis
A. Requires cytological or histopathologic examination.
B. Aspirates and/or biopsies may be obtained transabdominally, perirectally, or surgically.
C. Enlarged lymph nodes are also sampled.
D. In some cases, neoplasia and nonneoplastic disease coexist within the prostate, so neoplasia cannot be excluded if another process is found.

Differential Diagnosis

I. Prostatic neoplasia must be distinguished from BPH, prostatitis, and a prostatic abscess.
II. Because these diseases may coexist with neoplasia, a definitive diagnosis can be difficult.
III. Scottish terriers have prostate glands four times larger than those of other breeds of similar weight and age, which can be mistaken for prostatic masses (Kutzler and Yeager, 2005).

Treatment

I. Prostatectomy may be effective for local control or palliation of clinical signs.
A. Surgery is technically difficult and complications are common.
B. Laser-assisted transurethral partial resection of the prostate (TURP) may provide short-term palliation, with a median survival time of 103 days in one report (L'Eplattenier, 2006).

II. Balloon-expanding or self-expanding metallic stents may provide palliative relief of urethral obstruction from prostatic neoplasia (Weisse et al., 2006).
III. Prostatic neoplasia is considered poorly responsive to chemotherapy or radiation therapy.
IV. Intraoperative radiotherapy is the current treatment of choice for local control of prostatic adenocarcinoma.
A. Median survival of 10 dogs treated for prostatic carcinoma with radiation therapy to surgically exposed tumors was 114 days (Turrel, 1987).
B. Median survival for seven dogs with only local disease was 180 days, as compared with the median survival of 80 days in the three dogs with metastatic disease (Turrel, 1987).
C. External beam radiation therapy may be more readily available than intraoperative radiation therapy.
D. Palliative doses may have lower risk of long-term radiation side effects (urethritis, cystitis, colitis), but no reports of efficacy are available (Anderson et al., 2002).

V. Piroxicam, a cyclooxygenase inhibitor, administered at 0.3 mg/kg PO SID has been used successfully to reduce the size of several canine carcinomas (Knapp et al., 1994; Schmidt et al., 2001), and in vitro experiments suggest the drug is effective for prostatic adenocarcinomas (van der Boon, 2002).
VI. No current treatments are effective against extraprostatic metastases (Cooley and Waters, 2001).
VII. Castration has no beneficial effects on the tumor itself, but is recommended to help with concurrent diseases that contribute to the clinical signs.

Monitoring of Animal

I. Prognosis for dogs with prostatic adenocarcinoma is guarded.
II. Early cancers are seldom detected, and metastases are usually present at the time of diagnosis.
III. During treatment, the size of the prostate is monitored and urine is routinely evaluated for any secondary infections.
IV. The animal's quality of life is monitored and euthanasia must be considered at the appropriate time.

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CHAPTER 54

Introduction

Ronald M. Bright

GENERAL INFORMATION

Definition

I. Reproductive problems encompass a wide variety of disorders.
II. They may result in limited or nonexistent reproductive capacity.
III. Sometimes the purposeful surgical removal of an affected organ renders the animal sterile.
  A. Reasons for surgery: inflammatory, infectious, behavioral, metabolic, hormonal, or neoplastic diseases
  B. Rationale for ovariohysterectomy: sterilization, treatment of pyometra or metritis, adjunctive therapy for mammary neoplasia, management of diabetes mellitus
  C. Rationale for castration: prostatitis, prostatic abscessation
  D. Prevention of (or treatment for) tumors that are influenced by reproductive hormones
    1. Dogs: perianal adenomas, tumors of the testes
    2. Dogs and cats: mammary neoplasia
IV. Some reproductive problems are congenital diseases.
  A. Testicular hypoplasia, cryptorchidism (see Chapter 56)
  B. Vaginal hymen membrane remnants or hypoplasia, double vagina, blind-ending vaginal pouch (see Chapter 58)
  C. Persistent penile frenulum, paraphimosis, phimosis, preputial abnormalities (see Chapter 59)
V. Various reproductive disorders may respond to medical management.
  A. Dystocia
  B. Pyometra
  C. Infertility
  D. Neoplasia
  E. Inflammatory conditions

Diagnosis

I. History, clinical signs
II. Physical examination
  A. Rectal palpation
  B. Vaginal examination
  C. Abdominal palpation
  D. Thorough mammary evaluation
III. Clinicopathologic data: complete blood count, biochemistry profile
IV. Cytology of vaginal smears, prostatic washes, fine-needle aspirates of tumors
V. Diagnostic imaging
  A. Radiography
    1. Staging neoplastic disease: abdominal, thoracic, osseous
    2. Contrast cystourethrogram
    3. Contrast vaginography
  B. Ultrasonography
  C. Computed tomography, magnetic resonance imaging
  D. Bone scans
VI. Endoscopy
VII. Hormonal assays

NEWER CLINICAL APPROACHES

I. Male genitalia (see Chapter 59)
  A. Inguinal retained testes are more common than abdominal testes.
  B. Preventing recurrence of paraphimosis may be achieved with a phallopexy.
II. Feline reproductive disorders (see Chapter 62)
  A. Intravaginal and transcervical insemination is successful, but surgical insemination appears to be superior with respect to rates of pregnancy.

B. Housing the tom and queen together only at the time of breeding may enhance the tom's ability to successfully impregnate the queen.
C. Inability of the tom to complete copulation may result in the need for artificial insemination.

III. Uterine disorders (see Chapter 57)
A. Progesterone receptor blockers not yet available in the United States may be safe and effective treatments for pyometra.
B. Research has shown that the efficacy of prostaglandin $F_2\alpha$ in treating pyometra is related to the status of the cervix (open versus closed).

IV. Mammary gland diseases (see Chapter 60)
A. Metoclopramide appears to have some influence on promoting lactin secretion, so it may be helpful for agalactia.
B. Agalactia and galactostasis are now considered separate entities, and therapeutic decisions must be based on the correct diagnosis.
C. Influence of the time of spaying in dogs with mammary neoplasia is further defined with respect to survival.
D. Mammary duct ectasia is described as a separate entity.

RECENT ADVANCES

I. Mammary neoplasia
A. Possible use of piroxicam and meloxicam as antineoplastic agents (Knottenbelt et al., 2006)
B. Review of mammary tumors in the female dog (Hellmen, 2005)
C. Incidence of mammary tumors and survival of female dogs in a large population in Sweden (Egenvall et al., 2005)
D. Genetic links for mammary cancer in beagles (Lloyd et al., 2005)
E. Role of steroid hormones and prolactin in canine mammary cancer (Queiroga et al., 2005)
F. Relationship between dysplastic and neoplastic mammary lesions and pseudopregnancy in the bitch (Veronesi et al., 2003)
G. Histological grading and prognosis for dogs with mammary carcinomas (Karayannopoulou et al., 2005)

II. Reproductive problems
A. Relationship of urinary incontinence to early spaying in bitches (Stocklin-Gautschi et al., 2001)
B. Comparison of laparoscopic ovariohysterectomy and standard ovariohysterectomy in dogs (Davidson et al., 2004)
C. Neodymium:yttrium-aluminum-garnet surgical laser versus bipolar electrocoagulation for laparoscopic ovariectomy in dogs (Van Nimwegen et al., 2005)
D. Cryopreservation of canine ovaries (Ishijimai et al., 2006)

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CHAPTER 55

Diseases of the Ovary

Lisa M. Howe

CYSTIC OVARIAN DISEASE

Definition and Cause

I. Ovarian cysts are fluid-filled cavities within the ovaries of dogs and cats.
II. Exact cause of most cysts is unknown.

Pathophysiology

I. Follicular cysts represent failure of fluid to be absorbed from an incompletely developed follicle.
II. Cysts may be small (diameter <1 cm) or large (diameter >10 cm).
III. Functional cysts may produce estrogen and progesterone.

Clinical Signs

I. Most cats and dogs show no clinical signs or reproductive abnormalities.
II. Clinical signs of ovarian cysts are related to excess sex hormone secretion by the cyst or decreased function of the remaining ovarian tissue.
III. Persistent estrus is commonly observed.
  A. In the bitch, the duration of estrus is typically 5 to 9 days and is considered abnormal if it lasts longer than 3 weeks.
  B. Continuous secretion of estrogen by follicular cysts or by functional ovarian tumors may be the cause.
  C. Prolonged behavior consistent with estrus or a persistent hemorrhagic vaginal discharge may be noted.
  D. Prolonged proestrus behavior without sexual receptivity can also occur.
IV. Persistent anestrus may also be seen.
  A. Increased interestrous interval or persistent anestrus is a common clinical sign with follicular and luteinized cysts.
  B. With nonfunctional follicular cysts, persistent anestrus is probably the result of a decrease in the surrounding functional ovarian tissue from a mass effect as the cyst enlarges.
  C. Prolonged progesterone secretion from luteinized cysts results in persistent anestrus.
V. Persistent nonseasonal estrus can occur in older queens with cystic follicular hyperplasia.
VI. Occasionally, very large ovarian cysts result in a palpable abdominal mass.
VII. Dogs and cats with functional follicular cysts are at risk for cystic endometrial hyperplasia and pyometra complex because of estrogen-induced endometrial changes.

Diagnosis

I. Most ovarian cysts do not result in clinical signs, and diagnosis occurs incidentally at ovariohysterectomy (OHE).
II. Vaginal cytology is performed to confirm persistent estrus.
III. Plasma estrogen concentrations may confirm excess serum estradiol secretion.
  A. Normal levels in the bitch are <15 pg/mL for anestrus and 15 to 100 pg/mL for proestrus; however, normal concentrations may vary greatly in different laboratories (Susaneck and Cain, 1997).
  B. With follicular cysts, estrogen concentrations are often similar to those occurring during proestrus.
  C. Normal estrogen concentrations do not rule out functional ovarian cysts.
  D. In cats, follicular cysts also result in elevated (>20 pg/mL) estrogen concentrations.
IV. Abdominal radiography may be helpful in identifying very large cysts.
V. Abdominal ultrasonography helps identify cystic ovarian structures, but cannot definitively identify normal from abnormal cystic structures.
VI. Surgical exploration with histopathology provides a definitive diagnosis.

Differential Diagnosis

I. Ovarian neoplasia or neoplasia of kidneys or adrenals
II. Polycystic kidneys
III. Ovarian neoplasia
IV. Midabdominal masses of other organs
V. Overlapping periods of follicular activity in queens that result in persistent estrus

Treatment

I. Many follicular cysts resolve spontaneously in a few months without treatment.
II. OHE is the treatment of choice for nonbreeding animals and is curative.
III. Medical management has limited success.
  A. In breeding bitches, pharmacologic agents may be used to induce luteinization of cysts.

1. Gonadotropin-releasing hormone (GnRH) 50 to 100 μg IM SID for one to three treatments
2. Human chorionic gonadotropin (HCG) 22 IU/kg IM (may be repeated once 48 hours later) (Davidson and Feldman, 2004)

B. Positive response to medical management is termination of estrus behavior or a decrease of estrogen and an increase of progesterone serum concentrations.
C. Within 2 to 3 weeks the animal completely ceases sexual activity.

IV. Because follicular cysts may spontaneously undergo atresia, not all bitches require treatment.

Monitoring of Animal

I. Bitches treated with GnRH or HCG are at risk for pyometra.
II. They must be monitored closely for 60 to 90 days after treatment (luteal phase).
III. Monitoring of morphology with ultrasonography shows regression of hypoechoic structures.

OVARIAN REMNANT SYNDROME

Definition

I. Ovarian remnant syndrome is the presence of functional ovarian tissue in the abdomen after OHE in dogs and cats.
II. Signs of proestrus, estrus, and (rarely) false pregnancy may occur from persistent production of estrogen and progesterone.

Causes and Pathophysiology

I. Ovarian remnant syndrome occurs after routine OHE.
II. Incomplete removal of all ovarian tissue results from inappropriate surgical techniques.

Clinical Signs

I. Ovarian remnant syndrome causes signs of proestrus and estrus.
II. Syndrome may occur days to years after OHE.
III. Signs of false pregnancy with lactation rarely occur and are more commonly seen in the dog than in the cat.

Diagnosis

I. Vaginal cytology during proestrus or estrus is the easiest (and least expensive) method to diagnose ovarian remnant syndrome.
   A. Elevated serum estrogen concentrations result in cornification of vaginal epithelial cells.
   B. Exogenously administered estrogen, such as diethylstilbestrol, can also cause vaginal cytology changes consistent with ovarian remnant syndrome; therefore clinicians should question owners about exogenous sources of estrogen.
II. Hormonal assays may be helpful in making the diagnosis.
   A. Resting serum estradiol concentrations may be measured, but timing and interpretation are critical when using single samples.
      1. In the bitch the sample is collected during proestrus because estrogen levels peak toward the end of proestrus and then rapidly decline.
      2. Serum estradiol concentration >20 pg/mL is consistent with follicular activity (Wallace, 1992).
      3. In the queen the sample is collected during estrus behavior, although some queens will continue to exhibit signs of estrus for several days after the serum estradiol levels have decreased.
      4. Resting estradiol assays are unreliable because the assays are affected by serum lipids, the rise in estradiol may be transient, and the low concentrations of estradiols that occur in dogs and cats may be below the sensitivities of certain assays (Wallace, 1992).
   B. Serum progesterone assays are more useful (especially in bitches) than estradiol assays.
      1. In bitches, the sample is collected in early diestrus or 1 to 3 weeks after completion of estrus.
      2. Serum progesterone values >2 ng/mL are consistent with the presence of an ovarian remnant (Johnston et al., 2001).
      3. In cats the test is not useful as a diagnostic tool because the cat is an induced ovulator, and no detectable rise in serum progesterone may occur.
   C. Hormone challenge tests can be used.
      1. Challenge testing is the best way to use the serum progesterone assay to confirm the presence of ovarian tissue in the cat.
      2. Administration of a gonadotropin that mimics the luteinizing hormone surge causes the follicles to ovulate, luteinize, and secrete progesterone.
      3. HCG is given during behavioral and cytologic estrus at 44 IU/kg IM in dogs and 250 IU IM in cats.
      4. GnRH is an alternative to HCG.
         a. It is administered during behavioral and cytologic estrus.
         b. Dose in dogs is 2.2 μg/kg IM and the dose in cats is 25 μg IM.
      5. With HCG or GnRH stimulation tests, poststimulation progesterone concentration >2 ng/mL confirms the presence of functional ovarian tissue.
   D. In many instances, the diagnosis is made during exploratory laparotomy.

Differential Diagnosis

I. Owner confusion about reproductive status of animal (intact versus neutered)
II. Vaginitis, vaginal neoplasia
III. Causes of hematuria
IV. Uterine stump pyometra
V. Trauma
VI. Coagulopathy

Treatment

I. Surgical exploration with excision of the remnant tissue is the treatment of choice.
II. Delay surgery until the animal is in estrus (for easier identification of the remnant).

III. Submit all excised tissue for histologic evaluation.
IV. Clinical signs resolve within days of removal of the ovarian remnant.

Monitoring of Animal

I. The animal is carefully monitored for any recurrent signs of proestrus or estrus.
II. Absence of such signs confirms resolution of the problem.

NEOPLASIA

Definition

I. Tumors may occur in the ovaries of dogs and cats, but they are rare.
II. They include granulosa cell tumors, thecal cell tumors, adenocarcinomas, adenomas, teratomas, dysgerminomas, leiomyomas, fibromas, and metastatic carcinomas and sarcomas.

Causes and Pathophysiology

I. Most ovarian tumors are of unknown cause.
II. Experimental administration of diethylstilbestrol in young dogs has produced malignant adenocarcinomas of the ovaries.
III. Sex-cord stromal tumors are composed of granulosa or thecal cells and are the functional counterpart to Sertoli's cell tumors in males.
  A. Granulosa cell tumors
    1. They occur frequently in the bitch and are the most common ovarian tumor in the queen.
    2. English bulldogs are at increased risk for development.
    3. They are often large, unilateral tumors that may be palpable.
    4. They are malignant in the cat but are often benign in the dog, with metastasis occurring in only 10% to 25% of cases (Johnston et al., 2001).
  B. Thecomas and luteomas
    1. Rarely occur
    2. May be found in combination with granulosa cell tumors
IV. Three important epithelial tumor types exist.
  A. Papillary adenoma
    1. Benign tumor that often occurs bilaterally
    2. One of the most common ovarian tumors in the bitch
  B. Cystadenoma
    1. Less common benign tumor
    2. Consists of multiple cysts
  C. Adenocarcinoma
    1. Malignant tumor that may occur bilaterally
    2. Most common malignant tumor of the ovary of the bitch
    3. May metastasize through the ovarian bursa into the abdominal cavity, as well as to regional lymph nodes and distant sites
    4. Peritoneal effusion possible from abdominal cavity metastasis
V. Two germ cell–origin tumors are of importance.
  A. Teratomas
    1. Large, palpable unilateral tumors that may result in abdominal enlargement
    2. Often benign and well-differentiated, containing multiple tissue types (e.g., hair, bone, cartilage, epithelium, or nervous tissue)
  B. Dysgerminomas
    1. Rare, large, unilateral tumors of primordial germ cells of the ovary
    2. Metastasis unusual (10% to 20% of cases) (Johnston et al., 2001)
VI. Miscellaneous ovarian tumors include leiomyomas, fibromas, and metastatic tumors from other locations.

Clinical Signs

I. Possibly no signs with many benign ovarian tumors (unless very large)
II. Granulosa and thecal cell tumors
  A. They may produce abdominal enlargement and a palpable abdominal mass.
  B. Clinical signs of endocrine disease occur with tumor production of estrogen and progesterone.
  C. Irregular or persistent signs of estrus, vulvar enlargement, nipple enlargement, and alopecia may also occur.
  D. High levels of estrogen may result in bone marrow hypoplasia and bleeding diatheses.
  E. Cystic endometrial hyperplasia and pyometra complex are possible.
III. Ovarian adenocarcinoma
  A. Vaginal bleeding unrelated to estrous cycles may occur.
  B. Tumor rupture may result in seeding of the abdomen with tumor cells.
    1. Tumor cells may implant on the diaphragm, omentum, mesentery, lymph nodes, or other abdominal organs.
    2. Ascites and abdominal enlargement often result.
IV. Teratomas and dysgerminomas
  A. They are often asymptomatic unless they become very large.
  B. With large tumors, clinical signs may include abdominal enlargement, lethargy, depression, anorexia, intestinal obstruction, and bloody vaginal discharge.

Diagnosis

I. Midabdominal mass may be found with abdominal palpation.
II. Abdominal radiography may identify or confirm an abdominal mass.
III. Abdominal ultrasonography is useful in determining the origin of the mass.
IV. Fluid analysis of ascitic fluid may be performed.
V. Exploratory laparotomy with histopathology is often necessary for a definitive diagnosis.

Differential Diagnosis

I. Ovarian cysts
II. Renal tumors or cysts

III. Other tumors of abdominal organs
IV. Other causes of neoplastic effusions or ascites

Treatment

I. OHE is the treatment of choice.
II. Treatment may be curative for certain tumor types if metastasis has not occurred.

Monitoring of Animal

I. Monitoring for evidence of metastasis is indicated with malignant ovarian tumors.
II. Physical examination and thoracic and abdominal radiography (or abdominal ultrasonography) are performed every 3 months to monitor for recurrence or metastasis.

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CHAPTER 56

Diseases of the Testes and Epididymides

Harry W. Boothe

CONGENITAL/DEVELOPMENTAL DISORDERS

Anorchism and Monorchism

Definition and Clinical Signs

I. Anorchism is the congenital absence of both testes.
II. Monorchism is the absence of one testicle and usually involves the left testis (Johnston and Archibald, 1984).

Diagnosis

I. Diagnosis is made by careful palpation of the scrotum and inguinal region, followed by exploratory celiotomy.
II. Search the abdomen thoroughly to establish the lack of one or both testes, epididymides, and ductus deferentes.

Differential Diagnosis

I. Cryptorchidism
II. Testicular hypoplasia

Treatment

No treatment is available.

Testicular Hypoplasia

Definition and Causes

I. Testicular hypoplasia results from abnormal development of the seminiferous tubular germinal epithelium (Soderberg, 2000).
II. It may be unilateral or bilateral.
III. Some dogs with testicular hypoplasia exhibit signs of feminization.

Clinical Signs

I. Hypoplastic testes are usually freely movable within the scrotum and may be difficult to palpate, particularly in the obese animal.
II. Hypoplastic testes are usually normal or soft in consistency.
III. When accompanied by excessive connective tissue, however, the hypoplastic testis is firmer than normal (Ladds, 1993).

Diagnosis

The diagnosis is based on the previously mentioned clinical signs and physical examination findings.

Differential Diagnosis

I. Anorchism, monorchism
II. Cryptorchidism

Treatment

Treatment is orchidectomy.

Cryptorchidism

Definition

Cryptorchidism is a failure of one or both testes to descend into the scrotum at the usual time.

Causes and Clinical Signs

I. Testicular descent usually occurs at birth, although it may occur normally at any time up to 6 months of age (Dunn et al., 1968).
II. Cryptorchidism may be unilateral or bilateral, and the position of the ectopic testis may be prescrotal, inguinal, or abdominal.
   A. Unilateral cryptorchidism is most common, with the right testis being more commonly affected in dogs (Dunn et al., 1968; Yates et al., 2003).
   B. Inguinal ectopic testes are more common than abdominal ectopic testes (Yates et al., 2003).
   C. Dogs have a reported prevalence of 0.8% to 10% (Reif and Brodey, 1969).
   D. Cats have a reported prevalence of 0.4% to 2% (Millis et al., 1992).
III. The ectopic testis has endocrine function, but not exocrine function.
   A. Secondary sexual characteristics develop, even in the bilateral cryptorchid.
   B. Unilateral cryptorchidism results in disturbed scrotal testicular function (Kawakami et al., 1988).

Diagnosis

I. Ectopic testes, particularly intraabdominal testes, are more susceptible to torsion and neoplasia than descended testes (Pearson and Kelley, 1975; Cox et al., 1978).
   A. Presumably, the ectopic position allows greater movement of the testis than is possible in the scrotum (Pearson and Kelly, 1975).

B. Cryptorchid dogs have a 13.6 times greater risk of testicular tumors than normal dogs (Hayes and Pendergrass, 1976).
C. Approximately 50% of Sertoli's cell tumors and 33% of seminomas occur in cryptorchid testes, compared with 10% and 12%, respectively, in breed-matched noncryptorchid control dogs (Cox et al., 1978).
D. Neoplasms of ectopic testes are also observed at a younger age than neoplasms of descended testes.

II. Diagnosis, particularly in a young pup or kitten, may be difficult.
A. Scrotal testes are difficult to palpate because of their small size, especially in the obese pup.
B. Testes may freely move between the scrotum and inguinal region.
C. Extraabdominal ectopic testes can often be palpated; however, only enlarged intraabdominal ectopic testes are palpable.

III. Commonly affected breeds are the boxer, Chihuahua, German shepherd dog, miniature schnauzer, Pomeranian, poodle, Shetland sheepdog, Siberian husky, Yorkshire terrier, and Persian cat (Yates et al., 2003).
IV. Small breeds have a 2.7 times greater risk of cryptorchidism than other breeds (Pendergrass and Hayes, 1975).
V. The higher risk of neoplasia in cryptorchid testes justifies bilateral orchidectomy (Burke and Reynolds, 1993).

Differential Diagnosis

I. Anorchism, monorchism
II. Testicular hypoplasia
III. Palpably small but descended testis

Treatment and Monitoring

I. Technique for removal of the cryptorchid testis varies with its location.
A. Remove the extraabdominal ectopic testis by the usual technique, except make the skin incision directly over the testis.
B. Approach abdominal testes in the dog from a paraprepatial skin and ventral median abdominal incision.
C. Make a caudal ventral midline incision in the cat (Millis et al., 1992).
D. Locate the ectopic testis by tracing the ductus deferens from its prostatic termination to the testis.

II. Prognosis after cryptorchid castration is generally good, although inadvertent prostatectomy has been identified as a complication (Schulz et al., 1996).

INFLAMMATORY DISORDERS

Orchitis and Epididymitis

Definition

I. Orchitis is inflammation or infection of the testis.
II. Infection of the testis is frequently accompanied by epididymitis.

Causes and Pathophysiology

I. Testicular infection occurs most commonly by reflux along the ductus deferens from the urinary tract or prostate, although infection via the hematogenous route or local extension (penetrating scrotal wounds) is also possible (Johnston and Archibald, 1984; Ladds, 1993).
II. Frequently found bacterial organisms include *Escherichia coli*, *Staphylococcus* spp., *Streptococcus* spp., and *Mycoplasma* spp. (Flanders et al., 2000).
III. Orchitis may occur with *Brucella canis* infections (George et al., 1979).
IV. Epididymitis can result from an ascending infection of the genital tract, canine distemper virus, or a hematogenous infection (particularly *B. canis*).
V. Canine distemper virus produces cytoplasmic and intranuclear inclusions in the epididymal epithelial cells (Ladds, 1993).

Clinical Signs

I. Clinical signs of acute orchitis and epididymitis include testicular pain, epididymal enlargement, and scrotal edema.
A. Acute orchitis is usually suppurative and may progress to abscess formation.
B. Systemic signs of infection, such as leukocytosis, pyrexia, anorexia, and listlessness, may be present.
C. Inflammation of the parietal vaginal tunic may result in fistula formation through the scrotal skin (Ladds, 1993).

II. Evidence of chronic orchitis includes a small, firm, irregular testis with an enlarged epididymis and palpable adhesions between scrotal contents and tunics (Ladds, 1993).
III. Because of accompanying inflammation and an autoimmune reaction, testicular infection rapidly results in reduced fertility or infertility (Feldman, 1989; Flanders et al., 2000).

Diagnosis

I. Diagnosis is made by physical examination, cytological and bacteriological examination of the semen, and possibly serological examination.
II. Identification of the causative organism often requires microbiological testing of semen, urine, fluid within the vaginal tunics, and possibly blood.
A. Diagnosis of canine brucellosis involves both serological and bacteriological testing (see Chapter 113).
B. Canine distemper-induced epididymitis is diagnosed by histological evaluation.

Differential Diagnosis

I. Testicular neoplasia
II. Testicular trauma and secondary immune-mediated orchitis
III. Urethritis, prostatitis
IV. Testicular torsion

Treatment

I. Treatment of orchitis depends on the extent of infection and the intended breeding use of the animal.

II. Surgically remove abscessed or chronically inflamed testes to prevent episodes of acute inflammation (Burke and Reynolds, 1993).
III. Use antimicrobial drugs, local hypothermia, and possibly antiinflammatory drugs to treat less severe orchitis and epididymitis (Feldman, 1989).
  A. Drain the cavity of the vaginal tunics and allow it to heal by second intention (Johnston and Archibald, 1984).
  B. Use antimicrobial agents to control infection based on culture and susceptibility testing.
IV. Eliminate any primary foci of infection elsewhere in the urogenital tract.
V. Locally treat sinus tracts in the parietal tunic and scrotum by excising, draining, and flushing them with appropriate antimicrobial agents.
VI. No uniformly successful treatment exists for canine brucellosis (see Chapter 113).

Monitoring of Animal

I. Testicular atrophy and fibrosis and epididymal stenosis are possible sequelae.
II. Repeated physical, ultrasonographic, and possibly semen examinations are indicated to determine outcome.
III. Prognosis for maintaining fertility after orchitis and epididymitis is guarded, because orchitis is usually quite resistant to medical treatment.

Testicular Torsion

Definition

I. Testicular torsion or torsion of the spermatic cord varies from a loose 360-degree torsion to several tight revolutions (Pearson and Kelly, 1975).
II. Torsion is more commonly seen with retained, neoplastic abdominal testes than with scrotal testes, presumably because of their greater mobility.
III. Torsion may also occur in scrotal testes.

Causes

I. A retained neoplastic testicle may be prone to torsion from its increased mass and weight.
II. For torsion of a scrotal testicle to occur, the scrotal ligament must be anatomically absent, abnormal, or have traumatically ruptured.

Clinical Signs

I. With retained testes, signs of acute abdominal pain, vomiting, abdominal distention, pyrexia, and lethargy are commonly observed (see Chapter 39).
II. Scrotal testicular enlargement occurs with torsion of the spermatic cord.
  A. Testicular enlargement may precede torsion, especially with neoplasia.
  B. Venous occlusion, edema, and inflammation cause testicular enlargement.

Diagnosis

I. Presumptive diagnosis is based on clinical signs and the presence of at least one ectopic testis.
II. Ultrasonography may reveal a uniform decreased echogenicity and absence of blood flow in the affected testis.
III. Definitive diagnosis is by exploratory surgery.

Treatment and Monitoring

I. Bilateral orchiectomy is used to treat the animal.
II. Animals with acute abdominal signs are stabilized with IV fluid therapy and supportive care before surgery.
III. See Chapter 39 for further treatment and monitoring advice for acute abdomen syndrome.

Spermatocele

Definition and Causes

I. Spermatoceles are localized areas of sperm in stasis within the epididymis.
II. Sperm granulomas result from a granulomatous inflammatory reaction to spermatoceles after leakage of sperm.
III. Possible causes include trauma, infection, and congenital anomalies (Johnston et al., 2001).

Clinical Signs and Diagnosis

I. Palpable nodule in testis
II. Decreased production of sperm
III. Varying degrees of infertility
IV. Definitive diagnosis: biopsy and histopathology

Differential Diagnosis

I. Epididymitis
II. Chronic or subclinical orchitis
III. Neoplasia

Treatment and Monitoring

I. No effective treatment has been described.
II. Castration is recommended, especially to prevent antisperm antibodies (immune-mediated orchitis) from developing.

NEOPLASIA

Definition

I. Testicular tumors are the second most frequently reported tumor in the male dog.
II. They include seminomas, interstitial cell tumors, and Sertoli's cell tumors, with each occurring in about equal frequency (Hayes and Pendergrass, 1976; Reif et al., 1979).
III. Tumors in scrotal testes are most often benign.
IV. Seminomas and Sertoli's cell tumors involving ectopic testes are more likely to be malignant.
V. Interstitial cell tumors are usually tumors of the scrotal testes.
VI. Sertoli's cell tumors are the most common testicular neoplasm in retained testes.

Clinical Signs

I. Testicular tumors occur commonly in older dogs, with age at diagnosis ranging from 9 to 11 years (Johnston et al., 2001).
II. Clinical signs may include increased testicular firmness or nodular enlargement, pain, or signs of feminization (Barrett and Theilen, 1977).
  A. Enlarged and firm testes are more likely with seminomas and Sertoli's cell tumors.
  B. Signs of feminization include a bilateral, symmetrical alopecia of the trunk and flanks, hyperpigmentation of the inguinal skin, gynecomastia, attraction of male dogs, and bone marrow depression in severe cases (see Chapter 87).
  C. Sertoli's cell tumors are most likely to produce signs of feminization.
III. Testicular tumors can occur individually or in combination within a testis.

Diagnosis

I. Signs of feminization in an intact male dog are suggestive of Sertoli's cell tumor.
II. Testosterone-producing tumors (e.g., interstitial cell tumor) can contribute to benign prostatic hyperplasia.
III. Definitive diagnosis of testicular neoplasia is by biopsy of the involved testis.
  A. Excisional wedge biopsy away from the epididymis is performed.
    1. Hemorrhage is controlled with digital pressure and closure of the tunica albuginea.
    2. Adhesions are reduced by offsetting incisions in the parietal vaginal tunic and the tunica albuginea (Feldman and Nelson, 1996).
  B. Percutaneous needle biopsy techniques are less informative (Burke, 1983).

Differential Diagnosis

I. Torsion of the spermatic cord
II. Testicular and spermatic cord trauma
III. Orchitis and epididymitis
IV. Spermatocele
V. Scrotal hernia or neoplasia

Treatment

I. Bilateral orchidectomy is the recommended treatment for testicular neoplasia.
II. In dogs, orchidectomy is performed by either open or closed methods.
  A. In the open method, the parietal vaginal tunic is incised over the spermatic cord at the point where ligatures are to be placed.
    1. Doubly ligate the spermatic cord using transfixation ligations.
    2. Ligate the parietal vaginal tunic and cremaster muscle distal to the spermatic cord ligation.
    3. Alternatively, incise the parietal vaginal tunic before exteriorizing the testis.
  B. In the closed method, the intact spermatic cord and vaginal tunics are doubly ligated using transfixation ligations.
III. Castration in cats is performed through longitudinal scrotal incisions.

Monitoring of Animal

I. Feminizing signs usually resolve within 21 days of removal of a Sertoli's cell tumor.
II. Chemotherapy (single agent or combination) or radiotherapy has been used for metastatic seminomas and Sertoli's cell tumors (McDonald et al., 1988; Dhaliwal et al., 1999).
III. Hyperestrogenism in dogs with Sertoli's cell tumor can be monitored by exfoliative cytology of the preputial mucosa (Johnston et al., 2001).

TESTICULAR TRAUMA

Definition and Causes

I. Testicular injury may occur via blunt or penetrating trauma.
II. Testicular trauma is uncommon in dogs and cats.

Clinical Signs

I. Clinical signs usually include local pain, testicular swelling, and possibly pelvic limb lameness.
II. Scrotal swelling and bruising are seen with more severe testicular lesions.
III. Massive scrotal hematoma formation from local hemorrhage and rupture of the tunica albuginea may occur with severe blunt trauma.
IV. Penetrating wounds frequently cause hemorrhage and may lead to local infection.
V. Any trauma to the testis, epididymis, or spermatic cord is potentially dangerous.
  A. Hemorrhage frequently accompanies trauma to these tissues.
  B. The expansile nature of the scrotum permits development of large hematomas (Burke and Reynolds, 1993).
VI. Damage to testicular tissue causes sperm leakage into the interstitial tissue and eventual spermatic granuloma formation owing to the antigenic properties of sperm.
  A. Immune-mediated orchitis may develop.
  B. Reduced spermatogenesis throughout both testes may result.
VII. Reduced fertility from trauma-induced testicular hyperthermia can also occur.
VIII. Traumatized testes are predisposed to infectious orchiepididymitis because of accompanying edema and congestion (Larsen, 1977).
IX. Self-inflicted scrotal trauma often aggravates the original injury.

Diagnosis

I. Carefully palpate the testis to evaluate the integrity of the tunica albuginea and epididymis.

II. Ultrasonography may help determine the extent of damage.
   A. Rupture of the tunica albuginea is often difficult to detect because of scrotal and testicular swelling.
   B. Local hypothermia, loss of sensation, and bluish scrotal discoloration are grave signs indicating irreversible damage from ischemia.

Treatment

I. Medical treatment is indicated for minor testicular trauma.
   A. Local hypothermia, antimicrobials, corticosteroids, analgesics, and possibly supportive bandaging are used.
   B. Aseptically aspirate any fluid accumulations.
II. Surgically explore the testis by longitudinally incising the cranial scrotum.
   A. Remove fluid and systematically search the scrotum and testes.
   B. Ligate bleeding vessels with fine synthetic absorbable sutures.
   C. Incise the parietal vaginal tunic to repair wounds of the tunica albuginea.
   D. Suture tears in the tunica albuginea with fine synthetic absorbable sutures after excising protruding testicular tissue, and thoroughly lavage with physiologic saline solution.
   E. Separately close the parietal vaginal tunic and scrotum with fine sutures.
III. Severe testicular trauma often requires unilateral or bilateral orchidectomy, with possible scrotal ablation.
   A. Delay orchidectomy until the extent of the injury can be assessed.
   B. Indications for orchidectomy after trauma include persistent pain, swelling, or local hyperthermia (Burke and Reynolds, 1993).
   C. With scrotal ablation, make curvilinear incisions near the scrotal base, leaving adequate skin for closure (Harvey, 1973).
   D. Control bleeding by cautery or ligation, and remove both testes.
   E. After transecting the scrotal septum, close the skin in the usual manner.

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CHAPTER 57

Diseases of the Uterus

Lisa M. Howe

INFLAMMATORY DISORDERS

Cystic Endometrial Hyperplasia/ Pyometra Complex

Definition

I. Cystic endometrial hyperplasia (CEH) complex is a common condition of older, intact, female dogs.
II. CEH is the result of an abnormal and exaggerated response of the endometrium to chronic exposure to progesterone.
III. CEH predisposes to pyometra.

Causes and Pathophysiology

I. Progesterone promotes endometrial glandular secretion, suppresses myometrial activity, and inhibits leukocyte responses, which promote the accumulation of secretions and stimulates endometrial hyperplasia.
II. Pyometra is a hormonally mediated condition of diestrus.
  A. It is typically preceded by progesterone-induced CEH in dogs older than 6 years.
  B. Pyometra is caused by an ascending bacterial infection within the uterus.
  C. It is also observed in bitches <6 years of age, but that group is less likely to have CEH.
  D. Estrogen compounds administered for mismating may produce acute endometritis or pyometra in young dogs 1 to 10 weeks after treatment (Johnston et al., 2001)
  E. In cats, CEH and pyometra can arise secondary to influence of progesterone or estrogen.

Diagnosis

I. Suggestive historical features
  A. Middle-aged or older bitch in diestrus
  B. Young bitch recently treated with estrogens for mismating
  C. Previous treatment with megestrol acetate or other progestin
  D. Pseudopregnant queen
II. Compatible physical examination findings
  A. Purulent vulvar discharge
  B. Evidence of systemic illness
  C. Palpable uterine enlargement (avoid overzealous palpation to prevent rupture)
III. Hematologic abnormalities
  A. Neutrophilia (usually >25,000 cells/μL), with a left shift
  B. Degenerative left shift with toxic neutrophils
  C. Normal or decreased white blood cell counts
  D. Mild normocytic normochromic, nonregenerative anemia (hematocrit 25% to 35%)
IV. Biochemical profile results
  A. Hyperproteinemia with hyperglobulinemia, hypoalbuminemia
  B. Increased blood urea nitrogen
  C. Occasionally abnormal liver enzymes
V. Urinalysis
  A. Variable specific gravity, pyuria, hematuria, and/or proteinuria may be noted.
  B. Cystocentesis is not recommended, because rupture of a friable uterus may occur.
VI. Radiographic findings
  A. A fluid-dense tubular structure, larger than small intestinal loops, may be seen in the ventrocaudal abdomen.
  B. With an open-cervix pyometra, the uterus may not be visibly enlarged.
VII. Abdominal ultrasonography
  A. Allows determination of uterine size, wall thickness, and the presence of intraluminal fluid.
  B. Stump pyometras can be visualized dorsal to bladder.

Differential Diagnosis

I. Pregnancy
II. Mucometra or hydrometra
III. Metritis
IV. Vaginitis
V. Uterine neoplasia
VI. Other conditions causing systemic illness or septicemia and toxemia

Treatment

I. Ovariohysterectomy (OHE) is the preferred treatment for pyometra.
II. Medical management is tried only for open-cervix pyometra with few signs of systemic illness.
III. In the valuable breeding animal, medical management may be considered; however, the owner must be educated as to the dangers of delaying surgical treatment.
IV. Surgical treatment and perioperative care is important in managing these cases successfully.

A. Before, during, and after surgery, treat with adequate fluid therapy and broad-spectrum antimicrobials.
B. Other appropriate therapy is provided to stabilize the animal before surgery (e.g., treatment for shock, azotemia), but do not unduly delay surgery in the severely ill animal.

V. Prostaglandin $F_2\alpha$ ($PGF_2\alpha$) therapy is used in select cases.
A. $PGF_2\alpha$ therapy may be attempted if the owner wishes to salvage the dog for breeding purposes.
B. $PGF_2\alpha$ use is limited to animals <6 to 8 years of age that are not critically ill, have an open cervix, and do not have concurrent illnesses (Kustritz, 2004).
C. The use of $PGF_2\alpha$ may not result in improvement for 48 hours to 2 weeks.
D. If the cervix is closed or the uterus is friable, then $PGF_2\alpha$ use may result in uterine rupture or expulsion of uterine contents into the abdomen.
E. Only naturally occurring $PGF_2\alpha$ *(Lutalyse)* is used, because synthetic $PGF_2\alpha$ products are more potent and their use could result in shock and death (Kustritz, 2004).
1. In the dog, *Lutalyse* is given at 0.25 mg/kg SC SID for 5 to 7 days.
a. To help the bitch acclimate to the drug, a lower dose is given initially (0.1 mg/kg on day 1 and 0.2 mg/kg on day 2).
b. Give injections in the morning so that the bitch may be observed throughout the day.
2. In the queen a dose of 0.1 mg/kg SC SID is effective.
3. $PGF_2\alpha$ therapy is generally needed for <7 days.
4. Appropriate ancillary medical therapy is also given.

VI. Progesterone receptor blockers (mifepristone, aglepristone) are reported to be safe and effective treatments for pyometra (Kustritz, 2004); however, they are not currently available in the United States.

VII. Many animals with pyometra have a concurrent urinary tract infection that requires treatment.

Monitoring of Animal

I. Animals receiving $PGF_2\alpha$ must be closely monitored throughout the treatment period.
A. Perform abdominal ultrasonography before treatment and then every 2 to 3 days thereafter until uterine size approaches normal.
B. In addition, evaluate the animal for evidence of peritonitis.

II. Evidence that $PGF_2\alpha$ is producing the desired clinical effect includes resolution of clinical signs, decrease in uterine size, change of purulent discharge to serous discharge, and return of leukogram values to normal.

III. Side effects of $PGF_2\alpha$ commonly occur and include restlessness, pacing, vomiting, hypersalivation, panting, defecation, tachycardia, fever, and abdominal cramping.
A. Cats often show intense grooming and vocalization.
B. Side effects usually begin within 5 to 60 minutes of administration and last 20 to 30 minutes.

IV. Efficacy of $PGF_2\alpha$ therapy varies with the status of the cervix (Kustritz, 2004).
A. In selected animals with open-cervix pyometra, the efficacy is good; some treated animals may eventually whelp healthy litters.
B. Reported recurrence of pyometra in bitches is 10% to 77% within 27 months of therapy (Kustritz, 2004).
C. In closed-cervix pyometra, the efficacy of $PGF_2\alpha$ is diminished, with only 34% of dogs responding (Feldman, 2000).

V. After $PGF_2\alpha$ treatment, bitches are bred during the next estrus cycle.

Metritis

See Chapter 61.

Subinvolution of Placental Sites

See Chapter 61.

UTERINE PROLAPSE

Definition

I. Uterine prolapse is an extrusion of a portion of the uterus through the cervix into the vagina that usually develops when the cervix is dilated during or after parturition (or abortion).

II. The condition is rare but occurs more commonly in the queen than in the bitch.

Causes

I. Excessive straining during parturition

II. Forced fetal extraction or excessive traction on retained fetal membranes

III. Metritis

IV. Retained placenta

V. After normal parturition from idiopathic causes, particularly in the cat

Clinical Signs

I. Mucosal mass is found protruding from the vulva.
A. Everted tissue is doughnut shaped and often discolored from venous congestion, attached debris, or trauma.
B. Tissue may be ischemic or necrotic, and self-mutilation may occur.

II. If the prolapse does not extend through the vulva, then a mass is not visible; however, the following clinical signs may be noted:
A. Abdominal pain, restlessness
B. Vaginal discharge, licking
C. Straining, dysuria
D. Perineal bulging
E. Abnormal postures

III. Signs of hemorrhagic shock may occur if the ovarian or uterine vessels are ruptured.

Diagnosis

I. Partial uterine prolapse that does not protrude through the vulva is diagnosed using digital examination of the vagina or by vaginoscopy.

II. If the mucosal mass protrudes through the vulva, then it must be examined closely to determine if the mass is uterine or vaginal in origin.

Differential Diagnosis

I. Vaginal prolapse, hyperplasia, or edema
II. Vaginal tumor
III. Vaginal hyperplasia
IV. Uterine neoplasia
V. Uterine torsion

Treatment

I. Stabilize the animal before definitive treatment of the prolapse with therapy for shock, dehydration, and blood loss.
II. OHE is often necessary because manual reduction is not very successful.
III. Manual reduction may be attempted if the prolapsed uterus is not devitalized, and reduction may necessitate an episiotomy.
   A. Administer systemic antimicrobial agents to treat metritis if the uterus is replaced.
   B. If external manual reduction is unsuccessful and the animal's reproductive capacity is important, then internal reduction may be performed.
   C. General or epidural anesthesia is required before attempting uterine reduction.
      1. Prolapsed tissue is cleaned with an antiseptic solution and any necessary debridement performed.
         a. Lavage with warm saline or hypertonic dextrose solution, and gently massage to help decrease uterine edema.
         b. Lubricate the mass thoroughly with a water-soluble lubricant gel and manually replace it.
      2. After reduction, oxytocin (5 to 10 U SC) may help induce uterine involution.
IV. External amputation is performed only if the uterus cannot be reduced or if it has become devitalized or necrotic.
V. OHE is performed after any uterine amputation.

Monitoring of Animal

I. After manual reduction or surgery, monitor the animal closely for hemorrhage, shock, dehydration, dysuria or anuria (urethral obstruction), recurrence, or infection.
II. Within 24 hours, the animal's cervix should be closed enough to prevent recurrence.
III. Continue antimicrobials if the uterus is traumatized and OHE was not performed.

UTERINE TORSION

Definition

I. Uterine torsion is a twisting of all or part of the uterus perpendicular to its long axis.
II. Uterine torsion is rare in small animals but generally occurs near the end of gestation (although the condition is reported to occur without pregnancy) and may result in dystocia.

Causes

I. Torsions occur during pregnancy or near the end of gestation, because a heavy, gravid uterus is more susceptible to rotational forces than is a nongravid uterus.
II. Other pathologic conditions of the uterus that may predispose to uterine torsion include uterine tumors, pyometra, mucometra, and hydrometra.

Clinical Signs

I. Clinical signs include abdominal pain, abdominal distention, bloody or mucoid vulvar discharge, anorexia, depression, lethargy, vomiting, and shock.
II. History of prolonged unproductive labor is common, although normal delivery of some offspring may occur 24 to 48 hours earlier if torsion involves only one horn.
III. Abdominal palpation often reveals a caudal abdominal mass, and the abdomen may be distended with fluid if uterine rupture has occurred.
IV. Potentially fatal hemorrhagic shock can occur if the uterine artery ruptures.

Diagnosis

I. Abdominal radiographs are consistent with either a gravid or fluid-filled uterus.
II. If fetal death has occurred, then radiographic signs include intrauterine and fetal gas formation, decomposition, and collapse of the cranial bones.
III. Abdominal ultrasonography confirms pregnancy and determines fetal viability.
IV. Exploratory surgery permits a definitive diagnosis of uterine torsion.

Differential Diagnosis

I. Dystocia
II. Pyometra, mucometra, hydrometra
III. Uterine neoplasia
IV. Neoplasia of other caudal abdominal organs

Treatment

I. Before surgery, aggressive supportive therapy is initiated.
II. OHE is the treatment of choice because uterine tissue is often devitalized or necrotic.
III. The friable uterus is surgically isolated from the rest of the abdomen and minimally manipulated during removal.
IV. Avoid attempts to derotate the uterus before removal, if possible.

Monitoring of Animal

I. Postoperatively, monitor for hemorrhage, shock, and infection.
II. Continued use of antimicrobials is indicated for the following conditions:
   A. Uterus was devitalized, necrotic, or ruptured.
   B. Fetal death occurred.
   C. Systemic signs of infection are present.

NEOPLASIA

Definition and Causes

I. Benign uterine tumors include the leiomyoma (most common uterine tumor in the dog), fibroleiomyoma, fibroma, fibroadenoma, and endometrial polyps.
II. Malignant uterine tumors include the adenocarcinoma (most common uterine tumor in cats), undifferentiated carcinoma, endometrial carcinoma, lymphosarcoma, and metastatic transmissible venereal tumor.
III. The cause of most uterine tumors is unknown.

Clinical Signs

I. Uterine tumors are uncommon in female dogs and cats.
II. They usually occur in bitches >10 years of age.
III. Uterine tumors may not cause any clinical signs and may be discovered as an incidental finding during abdominal surgery or necropsy.
IV. Large uterine tumors may cause abdominal enlargement or distention; they may also cause compression of the urinary or gastrointestinal tracts, resulting in dysuria or tenesmus.
V. Carcinomas often result in mucoid, purulent, or hemorrhagic vaginal discharge; if located near the cervix, they may cause uterine obstruction, with secondary pyometra or mucometra.
VI. Infertility may result from a large intrauterine tumor.
VII. If an animal with a uterine tumor does become pregnant, then the tumor may cause dystocia during parturition.

Diagnosis

I. Suspicious findings include a palpable or radiographically detectable caudal abdominal mass in an intact queen or bitch.
II. Ultrasonography is valuable in localizing the mass to the uterus and in differentiating it from pregnancy or pyometra.
III. Exploratory laparotomy and histopathology are often needed for a definitive diagnosis.

Differential Diagnosis

I. Other causes of uterine enlargement
II. Other causes of vulvar discharge
III. Neoplasia of other caudal abdominal organs

Treatment

I. OHE is the treatment of choice for uterine neoplasia and is potentially curative unless metastasis has occurred.
II. Biopsy of the sublumbar lymph nodes assists in determining prognosis and is particularly important with adenocarcinomas.

Monitoring of Animal

I. After diagnosis of a malignancy, abdominal and thoracic radiographys are taken every 3 to 6 months to monitor for evidence of metastasis.
II. Leiomyosarcoma metastasizes late and most commonly metastasizes to the lung.
III. Uterine adenocarcinoma commonly spreads to the sublumbar and iliac lymph nodes.

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CHAPTER 58

Diseases of the Vagina

Caroline Prymak | Ronald M. Bright

CONGENITAL DISORDERS

Definition and Cause

I. Several types of vaginal defects have been identified (Wykes and Soderberg, 1983).
   A. Hymen membrane remnants
   B. Segmental hypoplasia and aplasia
   C. Double vagina
   D. Blind-ending vaginal pouch (secondary vaginal pouch) (Mayenco-Aguirre et al., 2002)
   E. Hydrocolpos secondary to congenital vaginal obstruction (Viehoff and Sjollema, 2003)
II. The causes and heritability patterns are unknown.

Pathophysiology

I. Abnormal embryonic development is responsible for most congenital abnormalities.
II. Normal embryonic development of the vagina is as follows (McEntee, 1990):
   A. The vagina arises from fusion of the distal paired paramesonephric ducts (Müllerian ducts).
   B. The vestibule develops from part of the urogenital sinus.
   C. The hymen forms from fusion of the distal paired paramesonephric ducts with the urogenital sinus and normally disappears after birth, creating a patent vestibulovaginal junction.
III. Abnormal embryonic development may result in the following abnormalities (Wykes, 1986):
   A. Incomplete breakdown of the hymen membrane
      1. Annular remnants may cause circumferential narrowing at the vestibulovaginal junction.
      2. Vertical bands transect and often obstruct the vestibulovaginal lumen.
   B. Development of segmental hypoplasia or aplasia of the vagina or vestibulovaginal junction
   C. Incomplete fusion of all or part of the medial walls of the paramesonephric ducts, creating a double vagina or blind-ending vaginal pouch

Clinical Signs

I. Vestibulovaginal hymen remnants, double or blind-ending vagina, segmental vaginal hypoplasia, and aplasia may all have similar clinical signs.
II. The following signs can occur alone or in combination:
   A. Vaginitis from retention of vaginal fluids
   B. Pyometra from retention of uterine secretions
   C. Difficulty in breeding or inability to breed
   D. Dystocia
   E. Chronic urinary tract infections
   F. Urinary incontinence

Diagnosis

I. Compatible signalment, history, and clinical signs
II. Digital vaginal examination
   A. Vaginal bands or septa are usually palpated just cranial to the urethral tubercle at the vestibulovaginal junction, and a small opening may be palpated on either side of the partition.
   B. Segmental hypoplasia or annular hymen remnants may prevent digital penetration of the vagina.
III. Vaginoscopy
   A. Endoscopy is the preferred technique for examination of the cranial vagina, and insufflation with air is often necessary to prevent the mucosal folds from obscuring visualization of abnormalities.
   B. The caudal vagina is sometimes examined using simple instrumentation, such as a vaginal speculum or otoscope.
IV. Positive-contrast radiography
   A. Contrast radiography may be useful in identifying and differentiating vaginal hypoplasia, vaginal aplasia, persistent vaginal bands, double vagina, and a blind-ending vaginal pouch.
   B. It may also be useful in crudely assessing the ability of the vaginal tract to distend.
V. Vaginal cultures
   A. Congenital vaginal abnormalities may predispose to secondary infection.
   B. Guarded swabs taken from the cranial vagina are cultured for aerobic and anaerobic bacteria, as well as *Mycoplasma* spp. and *Ureaplasma* spp.

Differential Diagnosis

I. Closed pyometra: differentiated from pyometra secondary to segmental aplasia or hypoplasia using contrast radiography
II. Physiologic narrowing of the vestibulovaginal junction
   A. Anesthesia may relax a contracted vestibularis muscle.

B. Vestibulovaginal narrowing detected in anestrus may resolve with estrus.

III. Vaginitis from other causes
A. Immaturity of the vaginal tract secondary to estrogen deficiency
B. Primary infectious cystitis or metritis
C. Trauma
D. Neoplasia
E. Infectious diseases
F. Immunologic conditions

Treatment

I. Incidental findings in asymptomatic animals may not require treatment, especially if the following are true:
A. The bitch is not intended for breeding.
B. Future problems are not anticipated based on lack of clinical signs at the time of diagnosis.

II. Surgical treatment is recommended in certain cases.
A. Breeding and/or parturition will be affected.
B. Future problems such as pyometra are anticipated.
C. Clinical signs are present.

III. Type of surgical treatment depends on the specific lesion.
A. Annular hymen remnants and hypoplasia at the vestibulovaginal junction (Kyles et al., 1996)
1. Generally poor response to manual dilatation
2. T-shaped vaginoplasty to enlarge the luminal diameter
3. Partial vaginectomy and anastomosis
4. Complete vaginectomy
B. Small, thin vaginal bands
1. Surgical resection via episiotomy
2. Endoscopic resection
C. Large, thick vaginal septum or band
1. Episiotomy and band resection
2. Mucosal closure at the origin and insertion of the band to prevent scarring
D. Caudal and midvaginal segmental hypoplasia in breeding bitches
1. Segmental vaginal resection and anastomosis (Wykes and Olson, 1985)
2. Elective cesarean section at conclusion of pregnancy
E. Extensive hypoplasia or failure of the previous treatments
1. Ovariohysterectomy
2. Vaginectomy

Monitoring of Animal

I. Bitches may have multiple congenital anomalies, and a successful outcome requires treatment of all of them.
A. Annular-vertical hymen membrane remnants may occur in combination with vaginal hypoplasia.
B. Short vertical bands may give the impression of a concurrent annular band.

II. Repeatedly evaluate the diameter of the vaginal lumen after each surgical procedure.

INFLAMMATORY DISORDERS

Vaginal Edema

Definition

I. Marked edema of the vagina that mainly affects the ventral, distal surface (Johnston, 1989)
II. Synonyms: vaginal hyperplasia, vaginal prolapse, vaginal fold prolapse

Causes

I. The condition arises from the effects of estrogen on the vaginal wall.
II. Clinical signs occur during proestrus and estrus.
III. The condition is not considered to be hereditary.
IV. Certain breeds may be predisposed, including the boxer, English bulldog, mastiff, German shepherd dog, Saint Bernard, Labrador retriever, Chesapeake Bay retriever, Airedale terrier, and weimaraner.

Pathophysiology

I. Edematous tissue is most pronounced on the ventral wall of the caudal vagina, just cranial to the urethral tubercle.
II. Classification systems are based on the degree of vaginal swelling.
A. Type I: mild eversion of the vaginal wall
1. Vaginal mucosa is not visible at the vulva.
2. The perineum may bulge slightly.
B. Type II: protrusion of a fold of vaginal mucosa through the vulva
C. Type III: a doughnut-shaped prolapse of the entire circumference of the distal vagina and urethral orifice through the vulva

Clinical Signs

I. Usually affects young bitches
II. Protruding mass from the vulva
III. Difficulty in mating
IV. Perineal swelling
V. Excessive licking of the perineal region
VI. Dysuria, stranguria, pollakiuria

Diagnosis

I. History of previous episode of vaginal edema
II. Clinical signs as described previously
III. Compatible stage in the estrus cycle: proestrus, estrus
IV. Visible mass on vaginoscopy in the typical location
V. Palpation of a pedunculated or doughnut-shaped vaginal mass

Differential Diagnosis

I. Vaginal tumors
II. Uterine prolapse

Treatment and Monitoring

I. Supportive therapy
A. Keep the exposed mucosa clean and lubricated with saline-soaked gauze.

B. Prevent self-inflicted trauma by using an Elizabethan collar.
C. Place temporary retention sutures across the vulva to prevent vaginal prolapse and tissue trauma.
D. Ensure that urination is possible; place a temporary urinary catheter if urinary retention occurs.
E. Edematous tissue normally resolves spontaneously at the end of estrus.

II. Hormonal therapy
A. Induction of ovulation during the follicular phase of the estrus cycle can be tried.
B. Gonadotropin-releasing hormone at 2.2 μg/kg IM shortens the time of estradiol release if given before ovulation.

III. Surgical therapy
A. Surgery is performed in late estrus or diestrus to reduce surgical bleeding.
B. Ovariohysterectomy is both a primary therapy and prevents future recurrence.
C. Resection of edematous vaginal tissues may be indicated in certain cases (Pettit, 1998).
1. Resolution of the edematous tissue is prevented by secondary fibrosis.
2. Exposed tissue is devitalized or traumatized.
3. The physical effects of the edematous tissue cause abnormal urination despite conservative therapy.

Vaginitis

Definition

I. Vaginitis is inflammation of the vagina.
II. Secondary infection from overgrowth of resident organisms is common.

Causes and Pathophysiology

I. May occur at any age in intact or spayed females
II. Predisposing factors
A. Anatomical abnormalities of the vagina
1. Persistent hymen remnants
2. Vaginal hypoplasia or segmental aplasia
3. Double vagina or blind-ending vaginal pouch
B. Clitoral hypertrophy
1. Androgenic stimulation
2. Chronic inflammation
C. Vaginal trauma
1. Mating
2. Parturition
3. Iatrogenesis
4. Foreign bodies
D. Vaginal neoplasia
E. Vaginal wall immaturity (Johnson, 1991)
1. Juvenile vaginitis occurs in prepubertal puppies.
2. Cytological examination generally shows a nonseptic inflammatory response.
F. Urine pooling
1. Urinary tract abnormalities
2. Example: ectopic ureters entering the vagina
G. Urinary tract infections
1. Possible concurrent anatomic abnormalities
2. Especially chronic and recurrent infections

III. Primary bacterial infections
A. In most cases, bacterial cultures are qualitatively and quantitatively similar to normal vaginal flora and may reveal the following agents:
1. *Escherichia coli*
2. *Staphylococcus* spp.
3. *Streptococcus* spp.
4. *Proteus* spp.
5. *Pasteurella* spp.
6. *Corynebacterium* spp.
7. *Brucella canis*
B. Infection usually occurs secondary to other predisposing factors (Olson and Mather, 1986).

IV. *Mycoplasma* spp. and *Ureaplasma* spp.: both normal commensals and pathogens
V. Viral infections
A. Herpesvirus infection
B. Latent infections reactivated in times of stress

Clinical Signs

I. May occur at any age in intact or spayed females
II. Perineal irritation
A. Vulval licking
B. Rubbing the perineal area
III. Vulval discharge
IV. Discomfort during or after urination
V. Males interested in spayed, juvenile, or anestrus females
VI. Reluctance to mate

Diagnosis

I. Compatible clinical signs
II. Vaginoscopy
A. Vaginal wall inflammation
1. Ulceration
2. Hyperemia
3. Nodular lymphoid hyperplasia
B. Possible presence of congenital abnormalities, trauma, neoplasia, urine pooling

III. Laboratory evaluation
A. Vaginal cytology
1. Neutrophilia: healthy to degenerate cells
2. Bacteria: general increase in numbers or specific bacterial overgrowth
3. Macrophages and lymphocytes: suggestive of chronic inflammation
4. Intracytoplasmic inclusions: *Mycoplasma* spp., *Ureaplasma* spp., *Chlamydia* spp.
B. Urinalysis and culture
1. Rule out urinary tract infection as a predisposing factor.
2. Obtain urine by cystocentesis to prevent secondary contamination.

IV. Vaginal bacteriology
A. Results are often difficult to interpret because of contamination and overgrowth of normal flora.

B. Secondary infections commonly occur.
C. Special sampling techniques are indicated.
1. Guarded swab
2. Sample from the cranial vagina
3. Sample during anestrus
D. Special media are required for *Mycoplasma* spp. and *Ureaplasma* spp.
E. Perform titers or polymerase chain reaction assays for *Brucella canis* and herpesvirus infections.

V. Vaginal biopsy
A. Assess for inflammatory changes.
B. Rule out neoplasia.

VI. Diagnostic imaging
A. Survey abdominal radiography and ultrasonography are rarely diagnostic.
B. Positive-contrast vaginography is indicated to rule out neoplasia and anatomic abnormalities.
C. Excretory urography may rule out ectopic ureters.

Differential Diagnosis

I. Open-cervix pyometra
A. History of recent estrus
B. Systemic illness
C. Uterine abnormalities on abdominal radiography and ultrasonography
D. Systemic leukocytosis

II. Metritis
A. History of recent whelping
B. Uterine wall thickening on ultrasonography

III. Uterine stump granuloma
A. Abdominal radiography
B. Ultrasonography

Treatment

I. Correction of predisposing factors

II. Juvenile (prepubertal) vaginitis
A. The condition may resolve after the first estrus.
B. Estrogens allow maturation of the genital tract, with encouragement of the natural defense systems.
C. Ovariohysterectomy is postponed until after the first estrus and after the vaginitis has resolved.
D. Systemic antibiotics, douches, and vaginal suppositories are rarely beneficial.

III. Bacterial infections
A. Treat bacteria only if they are the primary cause.
B. Systemic antibiotics are chosen based on the results of culture and sensitivity testing.

IV. Viral infections
A. No therapy is currently recommended.
B. Avoid stress.
C. Isolate affected animal from pregnant bitches and neonatal puppies.

Monitoring of Animal

I. If signs persist, then reconsider the original diagnosis and repeat diagnostic tests (as outlined previously).

II. Avoid breeding animals with active vaginitis.

NEOPLASIA

Definition and Causes

I. Common benign tumors include the leiomyoma and fibroma (Ogilvie and Moore, 1996).

II. Malignant vaginal tumors include the leiomyoma sarcoma, fibroma sarcoma, squamous cell carcinoma, rhabdomyosarcoma, and transmissible venereal tumor (TVT).

III. Vaginal tumors are more common in intact bitches, suggesting a possible hormonal influence.

IV. Vaginal tumors usually occur in older animals, with a mean age of 11 years (range 5 to 16 years), except for TVT, which is more common in young, sexually active animals (Thacher and Bradley, 1983; Ogilvie and Moore, 1996).

V. No obvious breed predisposition exists.

Pathophysiology

I. Vaginal tumors may develop anywhere in the wall of the vagina.

II. Benign vaginal tumors are more common than malignant tumors (Thacher and Bradley, 1983).

III. Pedunculated vaginal tumors tend to be benign.

IV. Multiple vaginal tumors may develop in the wall of the vagina.

V. Malignant vaginal tumors can vary in their metastatic potential.

VI. TVT is often transmitted during coitus, and metastasis occurs in <5% of cases (usually in immunosuppressed animals).

Clinical Signs

I. Perineal swelling

II. Tumor prolapsed from the vulva

III. Vulvar bleeding

IV. Dysuria and pollakiuria

V. Fecal tenesmus and constipation

VI. Difficulty in mating

VII. Solitary or multiple soft, friable masses: characteristic of TVT

Diagnosis

I. Suspicious signalment, history, and clinical signs

II. Evidence of mass on vaginal and rectal examination

III. Identification of a mass with vaginoscopy

IV. Diagnostic imaging
A. Positive-contrast vaginography to further evaluate origin and size of mass
B. Magnetic resonance imaging (MRI) or computed tomography (CT) to assess degree of infiltration

V. Definitive diagnosis: biopsy via tissue sampling

VI. Tumor staging
A. The metastatic potential of a vaginal tumor depends on the tumor type and its biologic behavior.
B. For most malignant tumors, metastasis first occurs to the subiliac lymph nodes.
C. Distant metastatic spread may occur later in the disease process.

D. Imaging techniques are used to detect gross metastatic disease.
   1. Abdominal ultrasonography
   2. Abdominal and thoracic radiography
   3. MRI and CT

Differential Diagnosis

I. Vaginitis
II. Vaginal trauma
III. Tumors arising from the lower urinary tract, cervix, or uterus
IV. Perivaginal tumors
V. Vaginal edema
VI. Uterine prolapse

Treatment

I. Surgery
   A. Surgery is the treatment of choice for nonmetastatic vaginal tumors except TVT.
   B. Solitary benign tumors in the caudal vagina are removed by episiotomy and local resection.
   C. Multiple benign tumors, malignant tumors, and tumors extending into the cranial vagina are best removed by vaginectomy (Bilbrey et al., 1989).
   D. Nonpedunculated, vaginal tumors may require vaginectomy combined with an urethroplasty (Salomon et al., 2004).
   E. Ovariohysterectomy eliminates any hormonal influence and is necessary when a complete vaginectomy is performed.
II. Chemotherapy
   A. Chemotherapy is the treatment of choice for TVT.
      1. Vincristine is administered at 0.6 mg/m^2 IV weekly.
      2. The cure rate is reported to be nearly 100% (Boscos, 1988).
      3. The response time is usually within 2 to 6 weeks.
   B. The benefits of chemotherapy alone or combined with surgical resection of malignant tumors are not well documented.
III. Radiation therapy
   A. Radiation therapy is very effective in the treatment of solitary TVT.
   B. A single radiation dose of 10 Gy is reported to result in a 100% cure rate (Thrall, 1982).

Monitoring of Animal

I. For malignant tumors, follow-up examinations are performed at 1, 3, and 6 months posttreatment.
   A. Assess for local recurrence.
   B. Assess for distant metastasis.
II. After excision of benign tumors, monitor animal for 1 to 3 months to ensure excision was complete and effective.

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CHAPTER 59

Diseases of the External Male Genitalia

Harry W. Boothe

CONGENITAL/DEVELOPMENTAL DISORDERS

Hypospadias

Definition

I. Hypospadias is a fusion failure of the urogenital folds, with incomplete formation of the penile urethra.
II. Glandular, penile, scrotal, and perineal hypospadias have been reported (Ader and Hobson, 1978).
III. Rather than at the tip of the penis, the urethral orifice is located on the ventral aspect of the penis or the perineal area.

Causes and Pathophysiology

I. Hypospadias is the most common developmental anomaly of the male external genitalia.
II. The condition is encountered most frequently in Boston terriers (Johnston and Archibald, 1984).
III. Hypospadias is usually associated with preputial fusion failure and underdevelopment of the penis.

Clinical Signs

I. Clinical signs may be absent if the prepuce is normal and the external urethral orifice is near the end of the penis.
II. Occasionally the skin and hair around the urethral orifice are urine soaked and irritated.

Diagnosis

I. Diagnosis of hypospadias is made by close inspection of the penis.
II. The external urethral orifice is found anywhere on the ventral aspect of the penis.

Treatment and Monitoring

I. Surgical correction is not usually attempted in the dog because the urethra cranial to the abnormal orifice is deficient (Johnston and Archibald, 1984).
II. Excision of preputial and penile remnants, bilateral orchidectomy, and maintenance of the urethral orifice in the perineal region may be indicated in severe cases (Hobson, 1998).

Persistent Penile Frenulum

Definition and Cause

I. Persistent penile frenulum is a persistent connection between the penis and prepuce after puberty.
II. Cause is unknown.

Pathophysiology

I. In the immature dog, the frenulum (a fine band of connective tissue) joins the penis and prepuce ventrally.
II. The frenulum normally ruptures by puberty under androgenic influences (Bharadwaj and Calhoun, 1961).

Clinical Signs

I. Persistence of the penile frenulum occurs in the cocker spaniel, miniature poodle, Pekingese, and in mixed-breed dogs (Begg, 1963; Hutchison, 1973).
II. Pain may be evident during sexual excitement or when the penis is extruded.
III. The animal may also continually lick the area.
IV. A ventral deviation of the glans is usually noted when extrusion is attempted.
V. Balanoposthitis may also be seen.

Diagnosis

I. Suggestive clinical signs
II. Close examination of penis

Treatment

Surgically sever the minimally vascular connective tissue.

Paraphimosis

Definition and Causes

I. Paraphimosis occurs when the penis protrudes from the preputial sheath and cannot be returned to its normal position.
II. Paraphimosis has both congenital and acquired causes.
   A. Congenital causes include a narrowed preputial orifice and an abnormally shortened prepuce.
   B. Acquired causes include trauma, infection, and priapism (Hobson, 1993).

III. Paraphimosis is usually seen after coitus, trauma, or masturbation, particularly in young male dogs (Johnston and Archibald, 1984).

Clinical Signs

I. Clinical signs depend on the duration of paraphimosis.
II. Exteriorized glans penis becomes congested and discolored because of the constricting ring of retracted prepuce.
III. Dog frequently licks at the exposed penis, exacerbating the inflammation.
IV. Severe penile damage can result from prolonged paraphimosis.
V. Necrosis of the exposed penis and urethral obstruction can occur quickly.

Diagnosis

I. Diagnosis of paraphimosis is made by close inspection of the penis and prepuce.
II. Inability to replace the penis into the preputial sheath is indicative of paraphimosis.

Differential Diagnosis

I. Penile trauma
II. Priapism

Treatment and Monitoring

I. Treatment is directed at replacement of the penis into the prepuce.
II. Lubricants, hyperosmolar solutions, and local heat or cold may be adequate to reduce the size of the penis and permit replacement.
III. With the animal sedated, push the penis caudally as the prepuce is drawn cranially.
IV. If replacement cannot be accomplished within a few hours, suture an indwelling urethral catheter in place.
V. Temporary or permanent surgical enlargement of the preputial orifice may be necessary.
VI. Creation of a permanent adhesion between the dorsal penile surface and the adjacent preputial mucosa has been described (Somerville and Anderson, 2001).
VII. Long-standing cases accompanied by necrosis require partial penile amputation.
VIII. Paraphimosis complicated by a deficient prepuce usually requires partial penile amputation to be effective.
IX. Monitor the animal for recurrence, particularly with congenital causes (Hobson, 1993).

Phimosis

Definition and Causes

I. Phimosis is the inability to protrude the penis beyond the preputial orifice.
II. Two general causes exist.
   A. Congenital
   B. Acquired: scarring after preputial trauma, neoplasia

Clinical Signs

I. Clinical signs depend on the cause (congenital or acquired) and size of the preputial orifice.
II. Congenital phimosis is usually accompanied by a distended prepuce and inability to urinate normally.
III. Urine is often passed only in drops or as a thin stream (Johnston and Archibald, 1984).
IV. Preputial retention of urine results in balanoposthitis, and the infected area may ulcerate (Proescholdt et al., 1977).
V. Acquired phimosis is accompanied by preputial inflammation and edema.
VI. Associated licking of the area is common.
VII. Neoplasia or a healing wound may also be present.
VIII. Retention of urine within the prepuce can occur in severe cases.

Diagnosis

Diagnosis is made by close inspection of the prepuce.

Treatment

I. Surgically enlarge the preputial orifice and correct the primary condition.
II. Create a triangular incision over the dorsal preputial surface near the preputial orifice.
III. Remove adequate tissue, while ensuring that the penis remains covered by the prepuce.
IV. Excise or treat neoplasms appropriately, avoiding stenosis of the preputial orifice.
V. Ligate or cauterize bleeding vessels and suture the preputial mucosa to the skin with simple interrupted, fine, nonabsorbable sutures.

Monitoring of Animal

I. Recheck young animals at regular intervals until growth is complete, because another surgery may be necessary to further enlarge the preputial orifice after the dog is fully grown.
II. If phimosis is caused by neoplasia, monitor for recurrence of the tumor.
III. Monitor the size of the preputial orifice, because postoperative fibrosis can be significant.
IV. Monitor for paraphimosis, which can occur if too much tissue is removed, particularly from the ventral prepuce.

Preputial Abnormalities

Definition and Causes

I. The prepuce may be hypoplastic or absent, or it may fail to fuse normally.
II. Failure of closure of the genital folds over the penis results in a deficient prepuce.
III. Failure of preputial fusion usually accompanies hypospadias and underdevelopment or absence of the penis (Croshaw and Brodey, 1960).
IV. Deficiency in the length of the prepuce is seen occasionally in the dog.

Clinical Signs

I. Clinical signs arise from exposure of the distal penis.
II. The dog frequently licks at the penis, causing inflammation.

III. The end of the penis is exposed, subjecting it to trauma and drying.
IV. Trauma results in hemorrhage.

Treatment

I. Failure of preputial fusion is usually treated by removal of the open prepuce, partial penile amputation, orchidectomy, and scrotal or perineal urethrostomy (Hobson, 1993).
II. A deficiency in the length of the prepuce is corrected by advancing the prepuce cranially along the abdominal wall or by partial penile amputation (Leighton, 1976).
III. Simple cranial advancement of the prepuce is often unsuccessful if much of the distal penis is exposed.
IV. Partial penile amputation and cranial advancement of the prepuce may be necessary to treat a severely deficient prepuce.

Monitoring of Animal

I. Monitor for adequate penile coverage by the prepuce after recovery from anesthesia.
II. Monitor for urethral stricture after partial penile amputation, especially if healing is complicated.

INFLAMMATORY DISORDERS

Balanoposthitis

Definition

I. Balanoposthitis is inflammation of the penile or preputial mucosa.
II. Infection of the penis and prepuce is fairly common, constituting approximately 20% of canine penile and preputial lesions (Ndiritu, 1979).

Causes

I. Penile injury
II. Phimosis
III. Preputial foreign body
IV. Neoplasia
V. Atopic dermatitis (Root Kustritz, 2001)

Clinical Signs

I. A copious yellow or blood-tinged preputial discharge suggests balanoposthitis or prostatic disease.
II. The affected dog frequently licks at the prepuce.

Diagnosis

I. Examination reveals an inflamed, thickened penile and preputial mucosa.
II. Enlarged lymphoid nodules are seen, particularly near the fornix of the preputial cavity.
III. Adhesions may develop between the prepuce and penis in severe cases.

Differential Diagnosis

I. Prostatic disease
II. Penile or preputial neoplasia

Treatment

I. Treatment is directed at eliminating the primary cause.
II. Anesthetize the animal to allow complete examination and treatment.
III. Thoroughly irrigate the penis and preputial cavity with warm saline solution.
IV. Superficially curette the lymphoid nodules with a gauze sponge.
V. Sever adhesions between the penis and prepuce.
VI. Instill dilute povidone-iodine or chlorhexidine solution into the preputial cavity.
VII. Instill an antimicrobial ointment into the preputial cavity for a few days after curettage.

Monitoring of Animal

I. Monitor the dog for recurrence of balanoposthitis.
II. Look for recurrence of a copious preputial discharge.

Priapism

Definition and Causes

I. Priapism is persistent erection that is not associated with sexual excitement.
II. Priapism is usually secondary to spinal cord injury, although it may accompany constipation or genitourinary infection (Johnston and Archibald, 1984).

Diagnosis

I. Priapism is distinguished from paraphimosis by the fact that the penis can be manually replaced into the prepuce with priapism.
II. This distinguishing feature is lost with additional penile congestion and swelling from drying and licking.

Differential Diagnosis

I. Paraphimosis
II. Penile strangulation

Treatment

I. Treatment is directed at eliminating the primary cause.
II. The exposed penis is kept clean and moist by applying a soothing ointment.
III. Use of an Elizabethan collar prevents licking.

NEOPLASIA

Definition and Causes

I. Tumors involving the penis of dogs include transmissible venereal tumor (TVT), papilloma, and squamous cell carcinoma (O'Keefe, 1995).
II. Prepuce and scrotum are affected by the same tumors as the skin (Barron, 1949; Weipers and Jarrett, 1954; O'Keefe, 1995).
   A. Mast cell tumors are frequently reported.
   B. TVTs, melanomas, and perianal gland tumors also occur (Ladds, 1993).

Clinical Signs

I. Licking and a serosanguineous preputial discharge are seen commonly with penile TVT (Brown et al., 1980).
II. Signs are often minimal, unless the tumor ulcerates or involves the preputial orifice.
III. Phimosis and balanoposthitis can result.

Diagnosis

I. Diagnosis is frequently made by cytologic evaluation of fine-needle aspirates or impression smears from the mass.
II. Biopsy (incisional or excisional) confirms the diagnosis.

Differential Diagnosis

I. Urethral prolapse
II. Balanoposthitis

Treatment

I. TVTs respond to many modes of treatment, including radiation therapy, chemotherapy, and surgery (Richardson, 1981).
   A. Simple surgical excision may be tried, but recurrence is common.
   B. Radiotherapy may be used alone or in combination with surgery.
      1. Total dose of 1000 to 2000 rad is commonly used (Theilen and Madewell, 1979).
      2. Most tumors recede entirely and do not recur with this therapy.
   C. Vincristine is the chemotherapeutic agent of choice.
      1. Dosage is 0.5 to 0.7 mg/m^2 IV once weekly.
      2. Most tumors begin to shrink within 2 weeks and require four to six treatments.
II. Other tumors involving the distal penis may require partial penile amputation, while more extensive or proximal tumors may necessitate ablation of the external genitalia.
   A. Surgically remove the tumor and close the prepuce in two layers.
   B. Take care to assure that the penis remains covered by the prepuce.
   C. In addition, consider a partial penile amputation if a large portion of the prepuce has been excised.
III. Wide excision of a scrotal neoplasm may necessitate orchidectomy and scrotal ablation.

Monitoring of Animal

I. Observe the external genitalia and regional lymph nodes for tumor recurrence.
II. Monitor for distant metastasis with malignant tumors via repeated physical examinations, abdominal and thoracic radiographs, and abdominal ultrasonography.

PENILE, PREPUTIAL, AND SCROTAL TRAUMA

Definition

I. Penile wounds include lacerations, crush injuries, fractures of the os penis, and urethral trauma.
II. Trauma to the prepuce can result from a laceration, an abrasion, or a foreign body.
III. Scrotal injuries include abrasions and lacerations.

Causes and Pathophysiology

I. Because of their exposed location, the penis, prepuce, and scrotum are relatively accessible to injury.
II. Penile and preputial wounds may occur during mating, fights, and fence jumping, as well as from automobile accidents and gunshot wounds (Hall and Swenberg, 1977; Ndiritu, 1979).
   A. Repeated hemorrhage is associated with penile erection, which in turn is caused by irritation from injury.
   B. Penile lacerations and gunshot wounds may involve the urethra.
   C. Severe penile trauma may produce a fracture of the os penis.
   D. Fractures usually are transverse and cause limited soft-tissue damage, although they may be comminuted (Johnston and Archibald, 1984).
   E. Malicious application of a rubber band around the penis or constriction of a ring of preputial hairs can cause strangulation of the penis.
III. Wounds that penetrate into the preputial cavity or are near the preputial orifice are most likely to require surgical management.
IV. Migration of a foreign body through the preputial mucosa at the fornix results in swelling and abscessation of the tissues surrounding the penis.

Clinical Signs

I. Hemorrhage, frequently intermittent but often profuse, is most commonly seen with penile wounds.
II. The dog usually exhibits pain and may frequently lick the prepuce.
III. Rupture of the penile urethra is usually accompanied by fluctuant subcutaneous swelling associated with urine extravasation.
   A. Dysuria and hematuria are commonly observed with fracture of the os penis.
   B. Crepitus is apparent, and urethral obstruction may be present.
IV. With penile strangulation, the penile mucosa becomes swollen with an encircling necrotic area, or the entire penis distal to the constriction may be necrotic (Johnston and Archibald, 1984).
V. Local preputial swelling, edema, and irritation are typical of superficial lacerations.
VI. Purulent, blood-tinged preputial discharge may accompany frequent licking of the prepuce when a preputial foreign body is present.
   A. The animal with a preputial foreign body is usually in pain, listless, mildly pyretic, and walks stiffly.
   B. A draining tract may be present ventral or lateral to the prepuce.
VII. The scrotum is frequently sensitive to palpation and may be bruised after soft tissue trauma.

Diagnosis

I. Closely inspect the extruded penis, prepuce, preputial cavity, and scrotum for injury.
II. Determine the amount of damage to the os penis using radiography.
III. Radiography, including contrast urethrography, may be indicated to determine the extent of urethral damage.

Differential Diagnosis

I. Paraphimosis
II. Urethral prolapse

Treatment

I. Clean minor wounds and treat them with a topical antimicrobial ointment.
II. Minor wounds are usually allowed to heal by second intention.
III. To avoid self-inflicted trauma, prevent licking of the wound through use of an Elizabethan collar.
IV. Remove any foreign body from the preputial cavity.
    A. Open draining tracts and explore for foreign bodies.
    B. After removal of the foreign body, flush the tract and preputial cavity with an antiseptic solution.
V. If significant hemorrhage occurs, debride and suture the wound.
    A. Control arterial bleeding by ligation; control cavernous bleeding by suturing the tunica albuginea with fine absorbable material.
    B. Close the penile mucosa with fine absorbable material.
    C. Suture full-thickness preputial wounds by closing the preputial mucosa and skin separately, after thorough cleansing and possible wound debridement.
VI. Treat wounds of the penile urethra by catheterization, provided that the urethra has not been transected.
    A. Suture a transected urethra with fine absorbable material and catheterize the urethra.
    B. Maintain a closed catheter system for 5 to 7 days for minor penile urethral tears.
    C. Maintain a closed catheter system for 10 days after urethral anastomosis.
VII. Minimally displaced simple fractures of the os penis do not require immobilization (Johnston and Archibald, 1984).
    A. Some fractures can be adequately immobilized with a urethral catheter.
    B. Position the end of the catheter beyond the fracture site and maintain a closed collection system for 7 days.
    C. If a catheter cannot be passed because of urethral damage, or if the fracture is unstable following urethral catheterization, open reduction and fixation with a finger plate may be performed (Stead, 1972).
    D. Fractures accompanied by severe penile trauma may necessitate partial penile amputation.
VIII. Severe penile wounds may require partial penile amputation and a scrotal urethrostomy.
IX. Use parenteral and local antimicrobials postoperatively.
X. Prevent penile erection by sedating the animal.
XI. Avoid antiseptics on the scrotum because they may be irritating.
XII. Perform orchidectomy and scrotal ablation for severely contaminated scrotal wounds.

Monitoring of Animal

I. Monitor urination carefully, particularly if urethral trauma has occurred.
II. Urethral stricture is possible, especially following transection and anastomosis.
III. Monitor for urethral obstruction associated with callus formation from healing of an os penis fracture, and perform a prescrotal urethrostomy as needed.
IV. Monitor healing of draining tracts.

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CHAPTER 60

Diseases of the Mammary Glands

Robert N. White

CONDITIONS OF LACTATING MAMMARY GLANDS

Galactostasis (Congestion)

Definition and Causes

I. Galactostasis is either cessation of milk secretion or an abnormal collection of milk in the mammary glands.
II. The condition may be associated with sterile or septic mastitis.

Pathophysiology and Clinical Signs

I. Galactostasis is a condition of uncertain etiology and is seen just before or shortly after parturition, after weaning, or during pseudopregnancy.
II. The condition may also develop in a dam after abrupt weaning of the litter.
III. Engorgement of the glands with residual milk induces localized inflammation and discomfort of the mammae, leading to a further failure of milk let-down.
IV. The cranial glands may be more commonly affected in lactating queens (Colby and Stein, 1983).
V. The condition is not generally associated with signs of systemic illness, although in cases of septic mastitis, severe systemic disease can occur.

Diagnosis

I. Galactostasis is a likely sequela to mastitis.
II. The condition is more commonly seen in bitches on a high plane of nutrition.
III. Galactostasis is most likely to develop during the early period of lactation, when the nursing young are inexperienced at suckling.
IV. The teat anatomy of affected glands (commonly, inverted nipples) may play a role in the development and progression of the condition.
V. Cytological examination of the milk taken from affected glands may be unremarkable, although an elevated white blood cell (WBC) count (>3000/μL) can be found (Wheeler et al., 1984).
VI. Other cytological findings, such as nondegenerate neutrophils and macrophages, are considered nonspecific, although the presence of phagocytosed fat droplets can indicate the stasis of milk within an affected gland.

Differential Diagnosis

Galactostasis must be differentiated from agalactia because the treatment and outcome for these conditions are different.

Treatment

I. Treatment depends on the underlying cause of the galactostasis.
II. When the condition is seen in early lactation and is possibly associated with inexperienced neonate sucking behavior, do the following:
   A. Confirm the neonates' ability to suckle.
   B. Confirm the dam's acceptance of the offspring and her ability to nurse.
   C. Attempt to evert any inverted nipples.
   D. Fast the dam for 24 hours, followed by a more limited feeding regimen.
   E. Consider manual milking of affected glands.
III. When the condition is related to mastitis, consider the following measures:
   A. Treat the mastitis as described (see Mastitis).
   B. Apart from the notable exceptions discussed under Mastitis, the neonates may be encouraged to suckle.
IV. When the condition is associated with abrupt weaning or pseudopregnancy, institute the following:
   A. In these instances the suckling of offspring is unlikely to relieve congestion; therefore the goal is to reduce further production of milk.
   B. Do not encourage manual milking of glands, because this causes additional milk production and let-down.
   C. Lower the dam's plane of nutrition and institute a limited feeding regimen for several days.
   D. Remove any further stimulus for milk production (e.g., the local presence of the recently weaned offspring).
   E. Cool compresses are applied to the affected gland(s) to reduce local inflammation and provide some comfort to the dam.
   F. Diuretics and glucocorticoids are, in most cases, of no benefit.

Monitoring of Animal

I. Most cases respond to treatment within a few days.
II. The sooner the condition is recognized and treatment initiated, the quicker the response to therapy.

III. Cases that are not recognized and treated promptly have the greatest likelihood of developing complications, such as mastitis.

Mammary Duct Ectasia

Definition and Causes

I. Mammary duct ectasia is a common cause of nonneoplastic enlargement of the mammae in the bitch.
II. The condition is characterized by dilatation of the ducts, inspissation of secretions, and a marked periductal and interstitial chronic granulomatous inflammatory reaction.

Pathophysiology and Clinical Signs

I. Mammary duct ectasia comprised 48% of nonneoplastic mammary gland disease in the dog (Miller et al., 2001).
II. The underlying cause of the ectasia remains unclear.
III. Mature, sexually intact and spayed bitches over a wide age range are affected.
IV. Ectasia is nodular, cystic, or multiglandular, and affects the caudal glands most frequently.
V. It may develop independently of ovarian or exogenous progestogens and has an inconsistent association with pregnancy or lactation.
VI. It causes gross enlargement and engorgement of mamma or mammae.

Diagnosis and Differential Diagnosis

I. Diagnosis of mammary duct ectasia is made histologically after incisional or excisional biopsy of affected glandular tissue.
II. Mammary duct ectasia can be commonly mistaken for mammary neoplasia.

Treatment and Monitoring

I. Mastectomy of affected glands is considered the treatment of choice for mammary duct ectasia.
II. Mastectomy is usually curative, although all excised lesions must be submitted for histopathology to rule out neoplasia.
III. Unsubstantiated evidence indicates that in some individuals the condition might recur after excision of affected mammae.

Galactorrhea

Definition

I. Galactorrhea is an excessive or spontaneous flow of milk that persists irrespective of nursing.
II. This lactation is not associated with pregnancy or parturition and is considered inappropriate.

Causes and Pathophysiology

I. Inappropriate lactation is mostly dependent on increasing prolactin and decreasing progesterone serum concentrations.
II. It occurs most commonly in association with pseudopregnancy (England, 1998).
III. Ovariohysterectomy or ovariectomy during diestrus mimics luteal regression, and this sometimes induces galactorrhea.
IV. The withdrawal of exogenous progestogen administration can cause inappropriate lactation in both the dog and cat (Johnston and Hayden, 1980).

Clinical Signs

Galactorrhea is evidenced by inappropriate mammary development and lactation that are unrelated to pregnancy and parturition.

Diagnosis

I. Presence of pseudopregnancy 6 to 12 weeks after the end of estrus
II. History of removal of the ovaries during the luteal phase
III. History of recent cessation of exogenous progestogen treatment

Treatment

I. Spontaneous resolution
   A. Galactorrhea associated with pseudopregnancy often resolves spontaneously and requires no treatment.
   B. Eliminating the stimulus for continued lactation, such as suckling neonates, helps galactorrhea subside.
II. Conservative treatment
   A. Application of an Elizabethan collar prevents bitches from stimulating further milk production and let-down through licking of the teats.
   B. Sedative agents (not phenothiazines because they are dopamine agonists and produce a rise in serum prolactin concentrations) may calm an agitated bitch and minimize licking of the teats (Figure 60-1).
   C. Administration of diuretics (e.g., furosemide) may lead to some improvement.
   D. Decreasing food and water for 24 to 48 hours to lessen milk production is recommended.
III. Administration of steroid preparations
   A. Progestogen
      1. Induces suppression of pituitary release of prolactin (see Figure 60-1)
      2. Available agents
         a. Megestrol acetate *(Ovaban, Ovarid)* 2 mg/kg PO SID for 5 days
         b. Proligestone (*Delvosteron,* not available in United States) 20 to 30 mg/kg SC
         c. Delmadinone acetate (*Tardak,* not available in United States) 1.0 to 1.5 mg/kg SC
         d. Medroxyprogesterone acetate (MPA [*Depo-Provera*]) 5 to 11 mg/kg SC, IM (maximum three times per year)
      3. Adverse effects
         a. Mammary gland enlargement
         b. Coat and temperament changes
         c. Delayed return to estrus after administration
   B. Estrogens and androgens
      1. Mechanism of action the same as that of progesterone (see Figure 60-1)
      2. Available androgenic agents

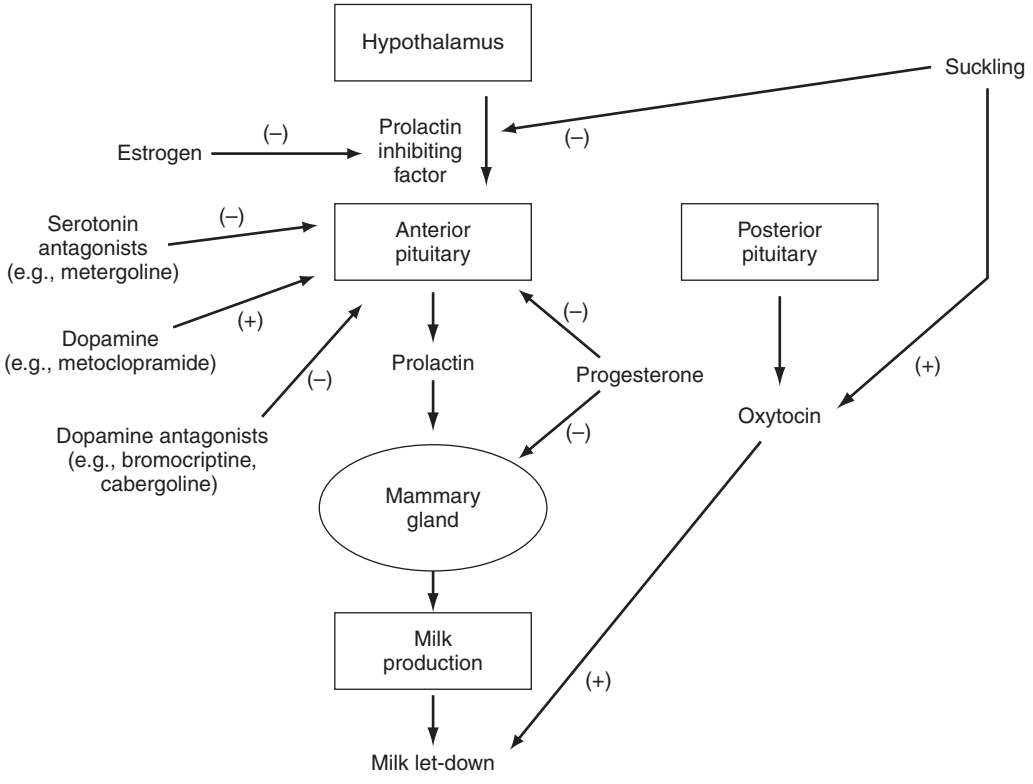

FIGURE 60-1 Pharmacophysiology of milk production and let-down.

a. Mibolerone *(Cheque Drops)* 16 µg/kg PO SID for 5 days
b. Methyltestosterone
(1) Plus estradiol (*Sesoral*, not available in the United States) at 0.7 mg/kg of methyltestosterone PO SID for 5 to 10 days
(2) Methyltestosterone *(Estratest)* 1 to 2 mg/kg PO for 5 to 7 days (maximum 25 mg/kg)

3. Adverse effects of estrogens: bone marrow suppression
4. Adverse effects of androgens: clitoral enlargement, aggression
5. Androgens not recommended in cats

IV. Administration of prolactin antagonists
A. Mechanism of action: dopamine antagonism that inhibits prolactin secretion (see Figure 60-1)
B. Available agents
1. Bromocriptine mesylate 20 µg/kg PO SID for up to 10 days
2. Cabergoline *(Galastop, Dostinex)* 5 µg/kg PO SID for 5 to 10 days
C. Adverse effects
1. Vomition common with bromocriptine
2. Reduction in plasma progesterone concentration leading to fetal resorption or abortion in pregnant animals
3. Reduction of the interval to the next fertile estrus

V. Ovariohysterectomy
A. Ovariectomy (or ovariohysterectomy) has no value for the treatment of clinical pseudopregnancy; removal of the ovaries causes a further reduction in plasma progesterone and potentiates the rise in prolactin.
B. Ovariohysterectomy prevents the occurrence of pseudopregnancy, but the procedure must be performed during deep anestrus (at least 3 months after the end of estrus).
C. In bitches that have repeated clinical pseudopregnancy, the best time to perform surgery is during the subsequent estrus.

Monitoring of Animal

I. Pseudopregnancy often recurs after subsequent heats; therefore unless affected bitches are to be used for breeding, spaying during anestrus is advised.
II. Treatment for bitches that have been spayed and appear to have "permanent" galactorrhea is reproductive steroids or bromocriptine.

Agalactia

Definition

I. Agalactia is defined as an absence or failure of the secretion of milk.
II. It occurs as a result of either failure of milk let-down or a failure in milk production.

Causes and Pathophysiology

I. It may occur when a congenital failure of mammary gland development occurs.
A. This is a very rare cause of agalactia in small animals.

B. The underlying cause is poorly understood, and the condition is not well documented.

II. Failure in milk let-down develops in association with psychological abnormalities or inappropriate hormonal interactions.
   A. Young, possibly primiparous or highly nervous dams may fail to settle and allow the litter to suckle.
   B. In the highly stressed animal, the release of oxytocin from the pituitary may be blocked by the production of excessive amounts of adrenaline.

III. Other debilitating conditions such as metritis, mastitis, and systemic infections can also lead to agalactia.

IV. Poor nutrition is an uncommon cause of decreased milk production.

Diagnosis

I. Diagnosis is based on clinical examination revealing an absence of milk in the teat canal.

II. The mammary glands often appear normal on physical examination.

Differential Diagnosis

Agalactia must be differentiated from galactostasis because the treatment and prognosis for these conditions are different.

Treatment

I. Congenital abnormalities in mammary gland development are unlikely to be treatable.

II. In very nervous dams, judiciously try sedatives such as acepromazine.
   A. The recommended dosage in dogs is 0.125 to 0.5 mg/kg PO BID to TID.
   B. Acepromazine can also increase milk production directly because the drug is a dopamine agonist (see Figure 60-1).

III. Metoclopramide, acting as a dopamine antagonist, can be used to promote prolactin secretion.
   A. The recommended dose in dogs is 0.2 to 0.5 mg/kg IM, SC, PO BID to TID.
   B. Metoclopramide may infrequently cause mental changes ranging from hyperactivity to depression.

IV. Suckling by the litter is encouraged, and in cases with persistent failure of milk letdown, the use of oxytocin is considered.
   A. The recommended dose of oxytocin in dogs is 2 to 20 IU SC, IM and in cats is 1 to 10 IU SC, IM.
   B. Treatment continues daily until milk production is established.
   C. The use of oxytocin to stimulate milk letdown is only effective in bitches with adequate milk production.

V. Severe debilitation from poor nutrition or systemic disease is managed according to the disease process present.

Monitoring of Animal

I. The prognosis for stimulating milk let-down in dams with true agalactia is poor.
   A. The offspring require hand rearing.
   B. Ideally, affected dams are not bred again.

II. Nervous dams can usually be persuaded to allow the litter to suckle, and adequate milk production can be achieved, with or without the use of oxytocin.
   A. The young may require supplemental feeding for a few days.
   B. Most affected dams do not suffer from agalactia after the birth of subsequent litters.

CONDITIONS OF NONLACTATING MAMMARY GLANDS

Mammary Fibroadenomatous Hyperplasia

Definition

I. Mammary fibroadenomatous hyperplasia is characterized by a marked increase in the size of one or multiple mammary glands (Hayden and Johnson, 1986).

II. It usually develops in young estrous-cycling cats and pregnant cats, but may also be seen in aged or neutered individuals of either sex after prolonged treatment with exogenous progestogens (Hayden et al., 1989).

III. It occurs rarely in dogs of either sex receiving exogenous progestogens.

IV. Other names for the same condition include *fibroadenomatosis, fibroadenoma, mammary fibroepithelial hyperplasia, benign mammary gland hyperplasia,* and *feline mammary hypertrophy*.

Causes

I. The exact mechanism is poorly understood.

II. High levels of serum progesterone exert a growth-stimulating effect on mammary gland epithelium (Hayden et al., 1981).

III. Significant quantities of growth hormone are produced directly by the feline mammary gland in response to increased levels of serum progesterone.
   A. Associated with the luteal phase of the estrous cycle in the young queen and with early stages of pregnancy
   B. Occurs after prolonged administration of progestogen compounds (e.g., megestrol acetate, methylprogesterone)

Pathophysiology

I. The increase in size of the mammary tissue is generally well circumscribed and within one or more of the gland complexes.

II. The condition is characterized by a proliferation of mammary duct epithelia and periglandular myoepithelial cells, marked edema, and increased amounts of connective tissue surrounding the glands (Nimmo and Plummer, 1981).

III. Two distinct histologic forms have been described and are considered to have similar biologic behavior and response to treatment.
   A. Diffuse fibroepithelial hyperplasia
      1. Characterized by proliferation of fibroglandular elements within the affected tissues
      2. Typical of lesions seen in young, postestral queens (Johnston and Hayden, 1980)

B. Intraductular papillary hyperplasia
   1. Characterized by proliferation of the ductular epithelium
   2. Typical of lesions induced by exogenous progestogen therapy (Hayden et al., 1989)

Clinical Signs

I. A few or all mammary glands are symmetrically enlarged.
II. Multiple lesions can occur in mammary glands, making it possible to have more swellings than there are glands.
III. Affected glands vary considerably in size (from 2 to 10 cm in diameter); in some instances the overlying skin may be tense and erythematous, with multiple cutaneous ulcerations.
IV. Milk secretion is uncommon.
V. Enlarged glands are usually nonpainful and soft on palpation.
VI. When gland enlargement is profound, glands may become inflamed and palpation may be resented.

Diagnosis and Differential Diagnosis

I. Diagnosis is based on signalment, age of the animal, sexual status, reproductive history (including treatment with progestogens), and clinical findings.
II. Differentiating the condition from mammary carcinoma and mastitis is important.
   A. These conditions can be readily distinguished by histologic examination of biopsy tissue.
   B. Aspiration cytology is often inconclusive; therefore obtaining a core biopsy specimen is desirable.
   C. Generally, excisional biopsy is not required.

Treatment and Monitoring

I. Treatment is usually aimed at the elimination of the source of progestin.
II. In animals not receiving exogenous progesterone, the condition can regress spontaneously.
III. Ovariectomy is considered the treatment of choice in young cycling females and usually leads to regression of the mammary tissue within 3 to 4 weeks, although in some cases regression may take up to 5 to 6 months.
IV. The administration of antiprogestins may be tried (Wehrend et al., 2001).
   A. Aglépristone (*Alizine,* not available in the United States) 10 mg/kg SC SID for 4 to 5 days can be used.
   B. Complete involution of the hyperplastic mammary glands may take 3 to 4 weeks.
   C. No side effects are reported.
   D. When treating intact female cats, pregnancy must be ruled out before treatment because of the abortive effects of antiprogestins (Gorlinger et al., 2002).
V. Stop the exogenous administration of progestogens.
   A. In such cases, regression of lesions may take up to 5 to 6 months.
   B. Testosterone and cabergoline may hasten the regression of hyperplastic tissues.
VI. Surgical excision is controversial.
   A. Excision is reserved for cases that fail to respond to conventional therapy.
   B. Excision may be indicated in severe cases when the glands show evidence of trauma or infection.

Mastitis

Definition

I. Inflammation of the mammary glands (mastitis) is a disease almost entirely limited to lactating glands and is restricted to the postpartum or pseudopregnant bitch or queen.
II. The condition is uncommon in small animals.

Causes and Pathophysiology

I. Most cases have an infectious component.
   A. Ascending bacterial infection via the streak canal (teat orifice) is most likely, although infection via the blood stream is a possibility.
      1. The streak canal is an anatomic barrier that normally prevents bacteria from entering the gland.
      2. Alterations during lactation allow ascending bacteria easier access.
      3. Chemical, cellular, and immune responses provide further defenses within the gland, but these mechanisms may be overwhelmed during the period of lactation.
   B. Causal organisms include coliforms (especially *Escherichia coli*), streptococci, and staphylococci (Johnston and Hayden, 1980).
II. It can be associated with prolonged galactostasis or keeping animals in poor sanitary conditions.
III. It rarely results from trauma (possibly from suckling pups or kittens).

Clinical Signs

I. Acute mastitis
   A. One or more glands are affected; the caudal glands are the most commonly involved.
   B. Affected mammae are painful, erythematous, and swollen.
   C. Anorexia, malaise, and pyrexia are often present.
   D. Dams may be brought to the clinic because of neonatal morbidity or mortality.
   E. Abnormal secretions may be expressed from the affected glands.
      1. The presence of discolored milk, or hemorrhagic or purulent secretions, is highly suggestive.
      2. Mastitis may occur in animals with apparently normal milk production and also in those with agalactia (especially of the affected mammae).
   F. In certain cases the glands may become gangrenous or abscessed.
      1. Affected glands are discolored, bruised, and cool to the touch.
      2. In more advanced cases, deep ulceration develops.
      3. Signs of systemic sepsis may be present.

II. Chronic mastitis
  A. Chronic bacterial mastitis may occur as an incidental finding in older, nonlactating queens (Colby and Stein, 1983).
  B. Inflammatory changes are usually minimal, although affected glands may appear thickened, with palpable nodules.
  C. Importantly, the gross changes observed are very similar to those of mammary neoplasia.
III. Associated conditions
  A. Consider a diagnosis of mastitis for any dam whose nursing neonates become sick or die unexpectedly.
    1. Dams with mastitis probably provide inadequate passive immunity, nutrition, and hydration to their offspring.
    2. Ingestion of infected milk is an unproven cause of neonatal septicemia.
    3. Neonates with bacterial diseases may cause an ascending mastitis in the dam during suckling (Wheeler et al., 1984).
  B. Many of the clinical signs associated with galactostasis are similar to those observed in animals with mastitis.

Diagnosis

I. Suggestive physical findings
II. Hematology
  A. In general, hemograms reveal a neutrophilic leukocytosis.
  B. In the peracute case the hemogram is often normal.
III. Cytological assessment and culture of milk samples from affected glands
  A. Degenerative neutrophils are the predominant cell type.
  B. Free and phagocytosed bacteria within degenerative neutrophils and macrophages may be present.
  C. Significant elevations in WBC counts (>3000/μL) are considered abnormal.
  D. Note that elevated WBC counts are occasionally observed in samples taken from apparently normal dams (perhaps indicating subclinical disease).
  E. Bacterial culture and sensitivity and evaluation of the pH of infected milk (see following section) aid in antimicrobial selection.

Treatment

I. Treatment is instituted as soon as possible after diagnosis.
II. Administer an antibiotic based on the results of culture and sensitivity testing.
III. If culture results are not available, then do not delay treatment using a broad-spectrum antibiotic.
IV. In acutely inflamed mammary glands, most antibiotics achieve therapeutic levels because a breakdown of the milk-plasma barrier occurs.
V. In the more chronic or relapsing cases, the presence of the milk-plasma barrier makes assessment of culture and sensitivity tests, as well as milk pH evaluations, critical for the effective management of the condition.
  A. If milk is more acidic than normal plasma pH, then antibiotics that are weak bases (e.g., potentiated sulfonamides, lincomycin) are indicated.
  B. If milk is more alkaline than normal plasma pH, then antibiotics that are weak acids (e.g., ampicillin, cephalexin) are used.
  C. Be careful when considering the use of agents that may have an adverse effect on the nursing neonates; for example, tetracyclines are not to be used because they potentially cause staining of the tooth enamel in nursing pups and kittens.
VI. Aminoglycosides are not recommended because of their poor penetration of the blood-mammary gland barrier.
VII. Keep the affected glands empty of abnormal secretions; methods by which this is achieved are controversial.
  A. Manual milking by the owner can be performed, but is often difficult and ineffective.
  B. The neonates may be allowed to continue nursing from the affected dam.
    1. Affected milk is likely to have a poor nutritional content.
    2. The nursing neonates ingest any medications that are administered to the dam that cross the milk-plasma barrier (see previous discussion).
    3. Do not allow neonates to suckle from severely infected glands or from those with abcessation or gangrene.
      a. If only one or two glands are involved, then bandages may be applied around the bitch to cover the affected glands, thereby preventing interference from the young.
      b. Neonates that cannot be nursed by the dam require hand rearing.
      c. Offer specific advice regarding hand-rearing techniques to the owners of such animals.
VIII. Gangrenous or abscessed mammae require more aggressive therapy.
  A. Anaerobic organisms may be involved, so choose antibiotics accordingly.
  B. Prevent offspring from suckling from affected glands.
  C. Milk secretions are stripped manually from affected glands at least twice daily.
  D. In severe cases surgical drainage may be required.
  E. The use of warm compresses may provide some relief for the dam.
  F. Chronic, persistently infected glands ultimately require mastectomy.
IX. Individuals with signs of systemic disease associated with the mastitis (septicemia) often require intensive management including IV fluid therapy and IV antibiotics.

Monitoring of Animal

I. Prognosis for animals suffering from peracute mastitis with concurrent systemic sepsis is guarded.
II. Prognosis for the majority of cases with acute or chronic mastitis is good, provided that therapy is instituted without delay.

NEOPLASIA

Definition

I. Mammary tumors are neoplasms of epithelial and/or myoepithelial cells of the mammae.
II. Mammary tumors are the second most common tumors in all dogs and the most common tumor in the bitch (Rutteman et al., 2001).
  A. Occur most commonly in older animals (mean age 10 years)
  B. Usually occur in animals that are intact or have been spayed after numerous estrous cycles
  C. All breeds affected
III. In the cat, mammary tumors occur less frequently but are still the third most common type of all tumors (Rutteman et al., 2001).
  A. Older cats are most often affected (mean age 10 to 12 years).
  B. Intact animals are usually affected.
  C. Siamese cats may be more at risk than other breeds (Hayes et al., 1981).

Causes

I. The production of estrogen and progesterone is linked to the development of mammary tumors in both dogs and cats.
II. The relative risk of developing a mammary tumor is related to the number of estrus cycles a bitch has experienced.
  A. Relative risk with ovariohysterectomy after first season is 0.05%.
  B. Relative risk after first estrus is 8%.
  C. Risk after second estrus is 26% (Schneider et al., 1969).
III. In the intact cat a sevenfold increase exists in the risk of developing mammary tumors compared with cats neutered at puberty (Dorn et al., 1968).
IV. Both estrogen and/or progesterone receptors are present in 40% to 70% of canine mammary tumors (Sartin et al., 1992).
  A. Administration of some progestogens increases the risk of benign tumor development in dogs (Schneider et al., 1969).
  B. In the bitch, more malignant, undifferentiated tumors tend to be receptor negative.
V. Low concentrations of progesterone receptors are reported in feline mammary tumors, and approximately 10% of tumors contain estrogen receptors (Hamilton et al., 1976).
VI. Use of progesterone-type drugs in the cat may increase the development of benign or malignant mammary masses.

Pathophysiology

I. Benign tumors
  A. Do not invade locally or metastasize
  B. Tendency for bitches to develop multiple benign tumors
  C. Tendency for new benign tumors to develop in the same or other glands after excision of an existing nodule
II. Malignant tumors
  A. They may behave relatively benignly or very aggressively.
  B. Rapid metastasis occurs with tumors showing local invasion.
    1. Local lymph nodes: superficial inguinal for caudal glands, axillary or cranial sternal for cranial glands
    2. Lungs
    3. Abdominal organs and bones
  C. Feline mammary carcinomas are especially aggressive and have often metastasized by time of presentation.

Clinical Signs

I. The caudal two pairs of mammary glands are most often affected in the dog.
II. Cranial glands are most commonly affected in the cat.
III. Tumors are often easily palpable as discrete nodules or masses within mammary glands.
  A. May be single or multiple
  B. May be attached to overlying skin or underlying muscle
  C. ± Skin ulceration
IV. Small benign masses may be an incidental finding.
V. Some aggressive inflammatory carcinomas are accompanied by diffuse mammary swelling, edema, and ulceration.
VI. Respiratory distress is rarely noted in dogs with pulmonary metastasis, but is common in cats from pleural carcinomatosis and extensive pulmonary involvement.
VII. Paraneoplastic syndromes are responsible for some systemic signs.
  A. Some dogs with advanced tumors may have hemorrhagic diatheses or disseminated intravascular coagulation.
  B. Subclinical hemostatic abnormalities are more likely (Stockhaus et al., 1999).

Diagnosis

I. Signalment and history often suggest neoplasia.
II. Hematological and biochemistry tests are generally normal.
III. Radiographic assessment of the lungs for metastasis is undertaken when malignant disease is either confirmed or thought likely.
  A. Abdominal films may show sublumbar lymph node enlargement.
  B. Skeletal survey films may indicate bony metastasis.
IV. Ultrasonography may be used to image the primary lesion but is most often used to screen local lymph nodes and the abdomen for evidence of metastasis.
V. Scintigraphy may be used to detect bony metastasis.
VI. Biopsy is required for a definitive diagnosis.
  A. Fine-needle aspiration is not always easy to interpret by cytologic examination but may give an indication of whether the lesion is neoplastic or nonneoplastic.
  B. Fine-needle aspiration is most useful for assessment of metastasis to the local lymph nodes.
  C. Mammary lesions may be wedge or core biopsied to provide a sufficient sample size for histopathologic investigation.

D. Small nodules are best biopsied via complete excision, as part of the treatment.
E. Incisional biopsy usually is not necessary for mammary tumors, because the type of surgical treatment for most cases does not depend on their histologic type.
F. Incisional biopsy helps, however, to distinguish neoplasms from nonneoplastic conditions that may not require surgery.

VII. The frequency of various canine mammary tumors is almost evenly distributed (Box 60-1).
A. In the bitch several different tumor types may occur in the same gland or affect different glands in the same animal.
B. In the bitch the most important feature of carcinomas that predicts their behavior and likely outcome is whether they appear well defined or if they are infiltrative and invasive.
C. In cats nearly all mammary tumors are malignant; over 80% are carcinomas, and the rest are mainly fibroadenomas.

VIII. Tumor-node-metastasis (TNM) staging systems are used for mammary carcinomas in both the dog and cat (Box 60-2).
A. Multiple tumors are evaluated independently.
B. The staging process includes the results of clinical and radiographic evaluations, and it may also include findings obtained at the time of surgery.

Differential Diagnosis

I. Mastitis
II. Mammary hyperplasia
III. Galactostasis
IV. Other benign and malignant tumors, such as lipomas or mast cell tumors
V. Mammary duct ectasia in the dog

Box 60-1

Frequency of Morphologic Types of Canine Mammary Tumors

Tumor Type	Relative Frequency (%)
Benign Mammary Tumors (total)	**51.0**
Benign mixed tumors/fibroadenomas/ complex adenomas	45.5
Simple adenomas	5.0
Benign mesenchymal tumors	0.5
Malignant Mammary Tumors (total)	**49.0**
Total carcinomas	44.9
Solid carcinomas	16.9
Tubular adenocarcinomas	15.4
Papillary adenocarcinomas	8.6
Anaplastic carcinomas	4.0
Sarcomas	3.1
Carcinoma/malignant mixed tumors	1.0

From Bostock DE: Canine and feline mammary neoplasms. Br Vet J 142:506, 1986; with permission.

Treatment

I. The treatment for most mammary tumors is surgical excision.
A. A number of surgical options exist.
1. Nodulectomy and lumpectomy are used as a biopsy procedure for small, unifocal lesions <0.5 cm in diameter.
2. Mammectomy, or removal of the affected gland, may be sufficient for fixed or mobile tumors centrally positioned within the gland.
3. Local mastectomy is removal of the affected gland along with any glands that drain lymph or blood from it.
4. Total or radical mastectomy is removal of the entire mammary chain.
5. In the dog, no study has shown that the type of surgery performed influences the outcome dramatically, and many surgeons favor simple mastectomy over radical mastectomy, ignoring lymphatic drainage patterns.

Box 60-2

TNM Staging of Canine and Feline Mammary Tumors*

T	Primary Tumor†
T0	No evidence of tumor
T1	Tumor <3 cm maximum diameter (<1 cm in cat)
T1a	Not fixed
T1b	Fixed to skin
T1c	Fixed to muscle
T2	Tumor 3-5 cm maximum diameter (1-3 cm in cat)
T2a	Not fixed
T2b	Fixed to skin
T2c	Fixed to muscle
T3	Tumor >5 cm maximum diameter (>3 cm in cat)
T3a	Not fixed
T3b	Fixed to skin
T3c	Fixed to muscle
T4	Tumor any size, inflammatory carcinoma
N	**Regional Lymph Nodes**
N0	No evidence of involvement
N1	Ipsilateral involvement
N1a	Not fixed
N1b	Fixed
N2	Bilateral involvement
N2a	Not fixed
N2b	Fixed
M	**Distant Metastasis**
M0	No evidence of metastasis
M1	Distant metastasis including distant lymph nodes

From Owen LN: TNM Classification of Tumours in Domestic Animals. World Health Organization, Geneva, 1980; with permission.
TNM, Tumor-node-metastasis.
*Tumor sizes for the cat are given in parentheses where appropriate.
†Evaluate multiple tumors independently.

6. Feline mammary tumors are usually very aggressive, so in most cases radical mastectomy is indicated.

B. Larger and multiple tumors require either local or radical mastectomy.
   1. Inguinal lymph nodes are removed as part of the most caudal gland.
   2. Axillary lymph nodes are only excised if they are enlarged or have been shown to contain neoplastic cells.
   3. Performing complete bilateral mastectomy during the same procedure is not recommended because closure may prove very difficult and postoperative dehiscence is a likely consequence.

C. Although researchers thought that concurrent ovariohysterectomy at the time of mammary tumor excision in the bitch had no effect on the development of new benign tumors, the progression of malignant tumors, the time to metastasis, or overall survival (Morris et al., 1998), more recent work suggests that bitches spayed <2 years before their mammary surgery survive longer (45%) compared with dogs that were either intact or spayed >2 years before their mastectomy surgery (Sorenmo et al., 2000).

D. In cats, ovariohysterectomy is considered part of the treatment, because ovarian and uterine disease occasionally coexists with mammary tumors in this species.

II. Radiotherapy has not been effective in the treatment of canine and feline mammary tumors (Rutteman et al., 2001).

III. Chemotherapy has been attempted for mammary carcinomas, but no protocol has been very effective in improving disease-free interval or survival beyond that obtained by surgery alone.

A. Doxorubicin has antitumor effects in vitro, but its effects in the clinical situation are variable (Ogilvie et al., 1989).

B. The advanced nature of most feline mammary tumors results in a poor response to chemotherapy; however, doxorubicin (25 mg/m^2 IV slowly), alone or in combination with cyclophosphamide (50 to 100 mg/m^2 PO on certain days after doxorubicin administration), may help to delay metastasis after surgery (Mauldin et al., 1988).

Monitoring of Animal

I. The prognosis for most benign canine mammary tumors that are surgically excised is good.

II. The prognosis for well-differentiated carcinomas is reasonable, with survival times >2 years for some histological types (Bostock, 1975).

III. The prognosis for invasive carcinomas is grave, because most metastasize rapidly despite surgical removal (Morris and Dobson, 2001).

A. Solid carcinomas: survival time of 36 weeks

B. Anaplastic carcinomas: survival time of 11 weeks

C. Sarcomas: survival time of approximately 6 months

IV. Recent studies suggest that in dogs, tumor stage, tumor size, and ovariohysterectomy status are significant prognostic factors associated with survival 2 years after malignant tumor resection (Chang et al., 2005).

A. Tumors ≥5 cm in diameter that were present for >6 months before resection had a higher risk of lymph node metastasis.

B. Dogs in which ovariohysterectomy had been performed had a better prognosis, especially in individuals with complex carcinomas.

V. In cats, the prognosis for mammary tumors is much more guarded, because most are highly malignant and local recurrence and metastasis are common.

VI. Recent studies suggest that cats spayed before 1 year of age have significantly decreased risk of mammary carcinomas (Overley et al., 2005).

A. Cats spayed before 6 months of age have a 91% reduction in risk, whereas those spayed before 1 year have an 86% reduction in risk.

B. Parity does not show any effect on mammary carcinoma development.

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CHAPTER 61

Disorders of Canine Reproduction

Margaret V. Root Kustritz

DISORDERS OF INFERTILITY

Infertility in the Bitch

Definition

I. Infertility in the bitch is defined as lack of pregnancy after ovulation of normal ova into a patent, healthy reproductive tract and insemination with normal semen near the time of ovulation.
II. Normal estrous cycling is a prerequisite of normal fertility in the bitch.
  A. Primary anestrus is the lack of obvious estrous cycling by 24 months of age.
  B. Secondary anestrus is the lack of estrous cycling within 12 months of a previous estrous cycle.
  C. Normal interestrous interval (number of days between onset of proestrus and the subsequent proestrus) averages 5 to 8 months in dogs but may range from 4.5 months (German shepherd dogs, rottweilers) to 12 months (basenjis, wild dog crosses).

Causes and Clinical Signs

I. Primary or secondary anestrus may arise from malnutrition, stress, lack of exposure to cycling bitches, systemic disease, previous ovariohysterectomy, silent heat (normal ovarian activity without external signs), or chromosomal abnormalities (Johnston, 1991).
II. Improper breeding management (mistimed or inadequate number of breedings), the most common cause of apparent infertility in bitches that are cycling normally, is reported in 40% to 50% of infertility cases (Johnston et al., 1994).
  A. The average bitch ovulates about 12 days after first signs of vulvar swelling and exudation of serosanguineous vaginal discharge; however, ovulation may occur as early as 3 to 4 days or as late as 25 to 26 days after proestrus onset.
  B. Breeding by day of the cycle alone yields pregnancy rates as low as 78% (England, 1992).
  C. Secretion of estrogen from the mature preovulatory follicle stimulates division of vaginal epithelial cells.
    1. Cytological specimens contain an increasing percentage of cornified cells as dogs progress through proestrus.
    2. Estrus, or standing heat, is defined cytologically as complete cornification, with >50% of the cells appearing anuclear.
    3. Six days after ovulation, cornified cells are sloughed, and the onset of diestrus is signaled by an abrupt return to noncornified vaginal cytology (Holst and Phemister, 1974).
  D. Ovulation timing is best performed by measurement of serum progesterone.
    1. Serum progesterone concentration is 2 ng/mL 2 days before ovulation and 4 to 10 ng/mL on ovulation day (Box 61-1) (Johnston and Root, 1995).
    2. Luteinizing hormone (LH) can be measured using a commercially available semiquantitative assay (Status-LH; Synbiotics, San Diego, Calif.).
    3. Serum LH concentration >1 ng/mL occurs (on average) 2 days before ovulation.
III. Subclinical uterine infection is a reported cause of infertility in bitches.
  A. Infection may cause conception failure by creating a hostile environment for the ova and spermatozoa, or

Box 61-1

Use of Serum Progesterone Concentration to Determine Ovulation Day in the Bitch

Serum Progesterone Concentration (ng/mL)	Event, Recommendation
<1.0	Well before ovulation—recheck in several days
1.0-1.9	±3 days before ovulation—recommend recheck
2.0-2.9	2 days before ovulation
3.0-3.9	1 day before ovulation
4.0-10.0	Ovulation day NOTE: Optimal breeding day is 2 days after ovulation
>10.0 with cornified vaginal cytology	1-5 days after ovulation—breed immediately
>10.0 with noncornified vaginal cytology	Diestrus—too late to breed this season

by causing early embryonic death (see Pregnancy Loss later in this chapter).
   1. Because the canine uterus is inaccessible to most practitioners without performing laparotomy and hysterotomy, culture samples taken from the cranial vagina during estrus have traditionally been used to infer the presence of uterine infection (Bjurstrom and Linde-Forsberg, 1992; Bjurstrom, 1993).
   2. Requesting quantitative culture results, with the assumption that heavy growth of a single organism is indicative of reproductive tract infection, may enhance accuracy.
   3. Some breeders require negative vaginal cultures of breeding bitches before introduction to the male, but this is an illogical practice and is discouraged.

B. Canine brucellosis is a specific uterine infection associated with infertility (see Pregnancy Loss later in this chapter).

IV. Hypothyroidism has been associated with infertility in the bitch.
   A. It may cause primary anestrus, prolonged or irregular interestrous intervals, prolonged proestrus, decreased intensity or duration of estrous cycles, galactorrhea, and increased incidence of spontaneous abortion.
   B. Many dogs with reproductive dysfunction secondary to hypothyroidism exhibit no extrareproductive clinical signs (Reimers, 1983; Johnson et al., 1997).

V. Hypoluteoidism is a proposed cause of infertility and pregnancy loss in dogs.

Diagnosis

I. The recommended diagnostic tests depend on the presence or absence of normal estrous cycling in the bitch (Box 61-2).

II. Cases refractory to standard diagnostic tests may benefit from the following tests:
   A. Uterine biopsy via laparotomy and hysterotomy to look for cystic endometrial hyperplasia, an age-related change in the uterine lining that may interfere with implantation and placentation and predispose the bitch to uterine infection
   B. Direct uterine culture via laparotomy and hysterotomy (often performed at the time of uterine biopsy)
   C. Abdominal ultrasonography to assess the uterus
      1. The normal, nonpregnant canine uterus is not visible as a distinct entity on ultrasonography.
      2. If the uterus is visible, and especially if the uterine lining can be visualized as a fluffy gray layer, then cystic endometrial hyperplasia is present.

Treatment

I. Attempt to convert primary and secondary causes of anestrus.
   A. Ensure the bitch is on a proper plane of nutrition and is not stressed by the environment in which she is housed or by overwork.
   B. Perform a complete blood count, serum chemistry profile, and urinalysis to assess for treatable systemic diseases.
   C. Measure canine thyroid-stimulating hormone and free thyroxine in serum to assess for hypothyroidism.
   D. Perform vaginal cytological examination weekly and/or progesterone assays monthly to identify silent heat.
   E. Submit whole blood or tissue for a karyotype to determine if the bitch has a normal chromosome complement.
   F. Attempt estrus induction.
      1. Diethylstilbestrol 5 mg PO SID for 6 to 9 days or until proestrus is induced
      2. Cabergoline 5 μg/kg PO SID for 7 to 10 days or until proestrus is induced
      3. Efficacy of estrus induction protocols: variable in dogs

II. Minimize improper breeding practices by optimizing the time of breeding.
   A. Optimal breeding time is 2 days after ovulation.
   B. If dogs are to be bred by natural service, then they are mated every other day while the bitch allows the male to mount.
   C. If the number of breedings by natural service is limited in number, or if artificial insemination with fresh or

Box 61-2

Diagnostic Scheme for Infertility in Bitches

Is Normal Estrous Cycling Occurring?

No	Yes
1. Evaluate husbandry and nutrition.	**1.** Assess fertility of male dog.
2. House with cycling bitches.	**2.** Obtain serum chemistry profile, complete blood count, urinalysis to assess general health.
3. Obtain serum chemistry profile, complete blood count, urinalysis to assess general health.	**3.** Perform serologic testing for canine brucellosis (see Table 61-1).
4. Evaluate thyroid hormones: concurrent measurement of free thyroxine by dialysis and canine thyroid-stimulating hormone for assessment of hypothyroidism (Panciera, 1994; Peterson et al., 1997).	**4.** Optimize breeding management with measurement of serum progesterone.
5. Perform serial vaginal cytology to monitor for silent heat.	**5.** Perform quantitative anterior vaginal culture during proestrus. Treat with appropriate antibiotic therapy throughout proestrus and estrus if necessary.
6. Consider karyotyping.	
7. Perform serologic testing for canine brucellosis (see Table 61-1).	

Modified from Johnston SD, Olson PN, Root MV: Clinical approach to infertility in the bitch. Semin Vet Med Surg (Small Anim) 9:2, 1994.

chilled semen is intended, then vaginal insemination is performed 2 and 4 days after ovulation.
D. If frozen-thawed semen is to be used, then intrauterine insemination is undertaken 3 or 4 days after ovulation.

III. Institute appropriate antibiotic therapy for subclinical uterine infection.
A. Retrieve a culture specimen from the anterior vagina of the estrous bitch early in proestrus; moderate to heavy growth of a single organism is significant.
B. Treat with an appropriate antibiotic based on sensitivity testing until the bitch enters diestrus, as evidenced by lack of vulvar discharge and standing behavior, or abrupt onset of noncornified vaginal cytology.
C. Empiric antibiotic treatment without culture is not recommended.

IV. Canine brucellosis is not curable in dogs; no recommended treatment exists for infertility caused by *Brucella canis*.
A. Euthanize *Brucella*-positive bitches housed in a kennel situation.
B. Individually housed bitches may be treated by performing ovariohysterectomy and administering tetracycline 30 mg/kg PO BID for 28 days and streptomycin 20 mg/kg IM SID for 14 days.
1. Oral enrofloxacin may be used to treat canine brucellosis, but no specific dose regimen has been described.
2. Antibiotic therapy induces remission, but does not eradicate the organism.
C. Canine brucellosis is a zoonotic disease; therefore caution owners of *Brucella*-positive bitches of possible human transmission, especially if pediatric, geriatric, or immunosuppressed persons live in the household.

V. Start thyroid supplementation.
A. Supplement with L-thyroxine 0.01 to 0.02 mg/kg PO BID.
B. Recheck serum concentration of thyroxine 4 to 6 weeks after treatment is instituted.
C. Hypothyroidism may be hereditary in dogs, so advise owners that bitches with hypothyroidism are not good candidates for breeding.

VI. Bitches with apparently normal reproductive tracts, normal estrous cycling, no evidence of intrauterine infection, negative brucellosis serology, and normal thyroid hormone status may benefit from intrauterine insemination.
A. Intrauterine insemination is performed surgically or with endoscopy.
B. Surgical intrauterine insemination requires general anesthesia and laparotomy.
1. Exteriorize the uterine body and horns, and inject semen through the uterine wall with a 22-gauge needle or catheter and syringe.
2. Hold off the injection spot briefly, and close the abdomen routinely.
C. Endoscopic intrauterine insemination requires neither general anesthesia nor sedation.
1. Pass a long, narrow-diameter, rigid endoscope the length of the vagina to visualize the cervix.
2. Pass a polypropylene urinary catheter through the cervix and into the uterus, and inject the semen through the catheter.

Monitoring of Animal

I. Prognosis for return to fertility varies with the cause.
A. Proper breeding management, with collection of serial vaginal cytology specimens and measurement of serum progesterone concentrations, is corrective of apparent infertility in 40% to 50% of cases.
B. Diagnosis and treatment of subclinical uterine infection with appropriate antibiotic therapy is the next most common corrective therapy for infertility.
C. Brucellosis is an irreversible cause of infertility in bitches.
D. Hypothyroidism may be a reversible cause of infertility with proper supplementation with thyroxine; however, bitches with hypothyroidism are not good candidates for breeding.
E. Abnormal chromosome complement is an irreversible cause of infertility in bitches.

II. The owner may benefit from a discussion regarding potential heritability of the cause of the animal's infertility, as well as the wisdom of removing subfertile animals from the breeding program.

Infertility in the Male Dog

Definition

I. Infertility in the male dog is defined as complete inability to effect pregnancy in normal females bred multiple times near the time of ovulation (Ellington, 1994).

II. Subfertility is defined as the siring of litters infrequently or the siring of litters containing few pups for that particular breed.

Causes and Clinical Signs

I. Lack of normal breeding behavior and poor libido
A. Inability to copulate
1. Failure of normal copulation in dogs may have behavioral or physical causes.
2. Behavioral causes include introduction to a nonreceptive female, attempting to breed to a dominant female that will not allow the male to mount, and inexperience or apprehension (Root Kustritz, 2005).
3. Intact male dogs that have been disciplined throughout their lives whenever exhibiting mounting and thrusting behavior are unlikely to show normal breeding behavior at the desired time.
4. Physical causes for failure of normal copulation include prostate disease and any painful condition of the spine or hind limbs that prohibits the male from mounting, thrusting, and maintaining the copulatory lock.
B. Inability to ejaculate
1. Lack of ejaculation may have behavioral or physical causes.

2. Behavioral causes for an ejaculation include lack of sexual maturity, inexperience, and apprehension.
3. Conversely, some very experienced stud dogs will not ejaculate in the absence of an estrous teaser bitch.
4. Subordinate males may refuse to mount a bitch they perceive to be dominant.
5. Physical causes for lack of ejaculation include prostate disease, any painful condition of the spine or hind limbs, or retrograde ejaculation (ejaculation of semen into the urinary bladder instead of antegrade, through the penile urethra).

II. Poor semen quality (Table 61-1)

III. Prostate disease
   A. Benign prostatic hypertrophy, prostatitis, and prostatic neoplasia may be associated with pain during prostatic contraction.
   B. Prostatic contraction occurs whenever the male is excited and throughout ejaculation (Olson et al., 1987).

Diagnosis

I. Collect historical data.
   A. Determine whether normal copulation is occurring.
      1. Causes of abnormal copulation include pain in the spine or pelvic limbs and prostate disease.
      2. Behavioral incompatibilities between the bitch and male dog may also preclude normal copulation.
   B. Determine whether normal ejaculation is occurring.
      1. Causes of abnormal ejaculation include pain in the spine or pelvic limbs, prostate disease, and apprehension on the part of the male.
      2. Retrograde ejaculation of semen into the urinary bladder may appear as lack of ejaculation.
         a. Diagnosis requires collection of a urine sample by cystocentesis after semen collection.
         b. Compare the numbers of spermatozoa in the antegrade ejaculate and in the urine sediment.

II. Perform a complete physical examination.
   A. Evaluate the dog for any evidence of systemic disease and clinical signs of hypothyroidism, such as weight gain and bilaterally symmetrical alopecia (Box 61-3).
   B. Prostate disease is diagnosed by rectal palpation of the prostate, culture of seminal fluid, and imaging of the prostate, either by retrograde urethrography or ultrasonography (see Chapter 53).

III. Collect and evaluate semen.
   A. Note color and turbidity of sample.
      1. Normal semen is milky white.
      2. Red or brown discoloration indicates contamination with fresh or old blood, and yellow discoloration indicates contamination with urine.
      3. A clear sample is indicative of azoospermia.
   B. Evaluate percentage of progressive motility of spermatozoa.
      1. Examine an unstained, undiluted drop of semen under the ×10 objective of a light microscope.
      2. Make a subjective assessment of percentage of spermatozoa moving forward.
      3. The normal percentage of progressively motile spermatozoa is >70%.
   C. Calculate the total number of spermatozoa in the ejaculate. The hemacytometric method described is more accurate than computer-assisted systems (Kuster, 2005).
      1. Measure concentration of spermatozoa by dispensing semen with the capillary pipette into the diluent container provided with the white blood cell Unopette kit. Dispense the diluted semen into a hemacytometer chamber.
      2. The number of spermatozoa in one of the nine large squares of the hemacytometer grid visible under the ×10 objective of the light microscope is the concentration in millions (millions of spermatozoa per milliliter).
      3. The total number of spermatozoa is the more valuable number, because concentration varies with the amount of prostatic fluid collected in the ejaculate.
         a. The total number is calculated by multiplying concentration (millions of spermatozoa per milliliter) by volume collected (milliliters per ejaculate).
         b. The normal total number of spermatozoa is 300 million to 2 billion.

Box 61-3

Diagnostic Scheme for Infertility in Male Dogs

Are Normal Copulation and Ejaculation Occurring?

Yes	No
1. Measure serum thyroid hormones: concurrent measurement of free thyroxine by dialysis and canine thyroid-stimulating hormone for assessment of hypothyroidism (Panciera, 1994; Peterson et al., 1997).	**1.** Investigate the prostate by rectal palpation, quantitative culture of seminal fluid, and ultrasonography and radiographic imaging, with possible fine-needle aspirate or biopsy.
2. Perform serological testing for canine brucellosis (see Table 60-3).	**2.** Investigate sites of pain in the spine or hind limbs by complete physical examination and radiography.
3. Collect and evaluate semen (see Table 60-3).	**3.** Assess for behavioral problems described in text.
4. Investigate the prostate by rectal palpation, quantitative culture of seminal fluid, and ultrasonography and radiographic imaging, with possible fine-needle aspirate or biopsy.	**4.** Assess for retrograde ejaculation by collection of a urine sample by cystocentesis after breeding or semen collection.

Data from Meyers-Wallen (1991), Olson (1991), and Olson et al. (1992).

TABLE 61-1

Types of Semen Abnormalities Described in the Dog

DEFINITION	CAUSES	DIAGNOSIS
Azoospermia: ejaculation of seminal fluid containing no spermatozoa	Pretesticular causes include hypothyroidism, fever (as may be seen with illness), drug therapy Testicular causes include intersex states, bilateral cryptorchidism, direct testicular injury, indirect testicular injury following increased intrascrotal temperature as may occur with testicular neoplasia or inguinal hernia, orchitis Post-testicular causes include outflow obstruction of the epididymes	Physical examination findings: abnormally small, soft, or firm testes may have been damaged and may not regain function Measurement of alkaline phosphatase in seminal fluid: concentration of >5000 IU/L indicates complete ejaculation with no outflow obstruction (Frenette et al., 1986) Measurement of thyroid hormones: concurrent measurement of thyroxine by dialysis and canine thyroid-stimulating hormone for assessment of hypothyroidism (Panciera, 1994; Peterson et al., 1997) Serologic testing for canine brucellosis: The rapid slide agglutination test (Synbiotics, San Diego, Calif.) is a good screening test that is accurate as early as 8-12 weeks after infection Negative results with this test are accurate; positive tests must be rechecked with a nonagglutination method The preferred nonagglutination method in the United States is the agar gel immunodiffusion (AGID) test available at Cornell University Ultrasonography of the scrotum Culture of seminal fluid: quantitative culture is performed and finding of >10,000 bacteria/mL of a single organism is considered significant Perform serum chemistry profile, complete blood count, and urinalysis to assess for systemic diseases
Oligozoospermia: a total number of spermatozoa in the ejaculate <300 million Dogs with a low number of spermatozoa in the ejaculate are not necessarily infertile A total of 250 million normally shaped spermatozoa must be introduced into the bitch over the fertile period from 3 days before to 4 days after ovulation to reliably effect pregnancy (Mickelsen et al., 1993)	Prostate disease Orchitis	Prostate diagnostic tests (see Box 61-3) Culture of seminal fluid Serology for canine brucellosis Measurement of serum thyroid hormones Serum chemistry profile, complete blood count, and urinalysis to assess for systemic disease
Teratozoospermia: <80% normally shaped spermatozoa in the ejaculate	Orchitis Testicular neoplasia Contaminated semen collection equipment Prostate disease	Culture of seminal fluid Ultrasonography of the scrotum Re-collection with different equipment Prostate diagnostic tests
Asthenozoospermia: <70% progressively motile spermatozoa in the ejaculate	As for oligozoospermia	As for oligozoospermia

D. Evaluate the percentage of morphologically normal spermatozoa.
   1. Place a drop of undiluted semen on one end of a glass slide, smear it out as for a blood smear, and allow it to air dry.
   2. Examine the slide under oil immersion (×100 objective of the light microscope) and evaluate 100 spermatozoa.
   3. The normal percentage of morphologically normal spermatozoa is >80%.

IV. Perform serological testing for canine brucellosis (see Table 61-1).

V. Cases refractory to standard diagnosis and therapy may benefit from testicular fine-needle aspirate or biopsy.
   A. Testicular fine-needle aspiration requires that the dog be sedated.
      1. Using a 20-gauge needle on a 10-mL syringe, insert it on the testicular midline, and apply suction while the needle is directed in several directions (Dahlbom et al., 1997).
      2. Submit the sample for histological examination.
      3. Ongoing spermatogenesis, inflammation, and neoplasia may be identified.
      4. Because testicular architecture is not maintained, complete information about spermatogenesis is not obtained with this technique.
   B. Testicular biopsy is performed with the animal under general anesthesia.
      1. Exteriorize the testis through a prescrotal incision.
      2. Incise through the tunica albuginea with a scalpel blade, and shave off the tissue that bulges through the incision.
      3. Place the tissue in modified Bouin's or Zenker's fixatives rather than formalin.
      4. Evaluate for the presence of the hierarchy of spermatogenesis within the seminiferous tubule, as well as for inflammation and neoplasia.

Treatment

I. Behavioral causes of poor libido may be overcome.
   A. Administer gonadotropin-releasing hormone (GnRH) at 1 to 2 μg/kg IM 1 hour before attempted breeding or semen collection (Purswell, 1994).
   B. This method is not to be used routinely in valuable stud dogs, because frequent artificially enhanced serum testosterone concentrations may exert negative feedback on the pituitary, producing an eventual decline in serum testosterone concentration and reduced spermatogenesis.

II. Retrograde ejaculation is treated with sympathomimetic drugs (e.g., pseudoephedrine 4 to 5 mg/kg PO 1 and 3 hours before attempted breeding or semen collection) to effect antegrade ejaculation (Root et al., 1994).

III. Treatment of prostate disease varies with the specific abnormality present (see Chapter 53).

IV. Canine brucellosis is not curable in dogs, and no recommended treatment exists for infertility caused by *B. canis*.
   A. Euthanize *Brucella*-positive male dogs housed in a kennel situation.
   B. Individually housed dogs may be treated by performing castration and administering tetracycline 30 mg/kg PO BID for 28 days and streptomycin 20 mg/kg IM SID for 14 days.
   C. Antibiotic therapy induces remission but does not eradicate the organism.
   D. Canine brucellosis is a zoonotic disease, so caution owners of *Brucella*-positive dogs of possible human transmission, especially if pediatric, geriatric, or immunosuppressed persons live in the household.

V. Start thyroid supplementation.
   A. Supplement with thyroxine 0.01 to 0.02 mg/kg PO BID.
   B. Recheck serum concentration of thyroxine 4 to 6 weeks after treatment is instituted.
   C. Hypothyroidism may be hereditary in dogs, so advise owners that dogs with hypothyroidism are not good candidates for breeding.

Monitoring of Animal

I. Prognosis for return to fertility varies with the cause.
   A. Behavioral causes of lack of normal copulation or ejaculation may be overcome with administration of GnRH (as described previously) or circumvented by use of artificial insemination.
   B. The prognosis is better for dogs with poor semen quality than for dogs with azoospermia.
   C. The prognosis is better for dogs with normal testicular size and consistency than for dogs with testicular atrophy or fibrosis.

II. A definitive prognosis for future fertility may be made after testicular biopsy. If spermatogenic cells are absent from the seminiferous tubules, or if a significant percentage of the seminiferous tubules are atrophied or fibrotic, then infertility is irreversible in that animal.

III. Brucellosis is an irreversible cause of infertility.

IV. Hypothyroidism may be a reversible cause of infertility with proper supplementation with thyroxine; however, dogs with hypothyroidism are not good candidates for breeding.

DISORDERS OF PREGNANCY

Pregnancy Loss

Definition

I. Early embryonic death (death of the fetuses with subsequent resorption in the first half of gestation) is indistinguishable from lack of conception.

II. Abortion (fetal death with expulsion of the fetus and placental tissues) occurs in the second half of gestation.

III. Birth of stillborn pups or retention of nonviable pups in the uterus without onset of parturition can also be defined as pregnancy loss.

Causes

I. Bacterial causes
   A. *Brucella canis* may cause pregnancy loss
      1. Transmission usually occurs by ingestion of aborted tissues or urine excreted from infected males or females (Carmichael and Joubert, 1988).
      2. Transient lymphadenopathy and colonization of many tissues occurs, especially in the reproductive tract (Johnson and Walker, 1992).
      3. The classic presentation is abortion late in gestation.
      4. Birth of stillborn or weak pups and persistent discharge of purulent vaginal discharge may also be seen.
      5. Infertile bitches infected with canine brucellosis may be asymptomatic.
   B. Miscellaneous bacteria implicated in canine pregnancy loss include *Campylobacter* spp., *Salmonella* spp., *Escherichia coli*, and *Streptococcus* spp. (Johnston and Raksil, 1987).

II. Viral causes
   A. Canine herpesvirus
      1. Canine herpesvirus can be transmitted by aerosol, via licking, or venereally.
      2. Most infected adult animals are asymptomatic or have mild vesicular lesions of the genitalia.
      3. Animals at greatest risk are naive bitches exposed to the virus in the last 3 weeks of gestation.
      4. Necrotizing placentitis develops, with subsequent birth of stillborn, macerated, mummified, or weak pups of various sizes, often all within the same litter (Poste and King, 1971).
   B. Other viruses: parvovirus and canine distemper virus

III. *Mycoplasma* spp. and *Ureaplasma* spp.
   A. *Mycoplasma* spp. and *Ureaplasma* spp. are ubiquitous organisms that lack a rigid cell wall.
   B. They have been associated with infections of the reproductive tract and pregnancy loss and also are part of the normal vaginal flora (Doig et al., 1981).

IV. Protozoal causes *(Toxoplasma gondii)*
   A. Toxoplasmosis infection is uncommon in dogs and is a very uncommon cause of pregnancy loss.
   B. Pups have been experimentally infected with toxoplasmosis transplacentally.
   C. Dogs that lose pregnancies from toxoplasmosis may be clinically ill from systemic disease (Dubey et al., 1990).

V. Hypoluteoidism and hypolutemia
   A. Hypoluteoidism is a hypothesized cause of pregnancy loss in dogs.
   B. The corpora lutea are the sole sources of progesterone, which is required throughout pregnancy.
   C. If the corpora lutea fail prematurely, then progesterone concentrations decline and pregnancy loss occurs.

Clinical Signs

I. Most bitches have nonspecific clinical signs, including anorexia, lethargy, and fever.

II. Signs specific to the reproductive tract include exudation of purulent or bloody vaginal discharge from the vulva.

Diagnosis

I. Diagnostic testing both of the bitch and any pups is beneficial in determining the cause of pregnancy loss (Box 61-4) (Purswell, 1992).

II. *Mycoplasma* spp. and *Ureaplasma* spp. are difficult to grow in culture, and differentiating pathologic from nonpathologic isolates is also difficult.

III. Hypoluteoidism is diagnosed by measurement of serum progesterone concentrations during pregnancy.
   A. Weekly measurement of serum progesterone concentration is recommended in bitches with a history of possible hypoluteoidism, for the first 6 to 8 weeks after breeding.
   B. If serum progesterone falls to <10 ng/mL, then daily monitoring of serum progesterone concentration is recommended.
   C. Treatment is instituted with progesterone supplementation if serum progesterone concentration falls to <5 ng/mL.

Treatment

I. Canine brucellosis is not curable in dogs.
   A. Antibiotic therapy can be tried, but the infection usually persists and the dog may exhibit bacteremia when stressed months to years after therapy.
   B. Brucellosis is a zoonotic disease and may be reportable in the state or country where the disease is diagnosed.
   C. Neutering minimizes shedding of the organism in urine.
   D. Eradication of canine brucellosis in a kennel may require euthanasia of affected animals.

II. Treatment of the bitch for a bacterial cause of pregnancy loss often is not useful at the time she is aborting.
   A. Even if the cause can be identified, the pups are not viable; therefore pregnancy loss is allowed to continue, with monitoring to ensure its completion and normal uterine involution.
   B. Antibiotic therapy to prevent sepsis in the bitch is instituted as needed.
   C. *Mycoplasma* spp. and *Ureaplasma* spp. infections can be treated with tetracycline, which is contraindicated during pregnancy, and with enrofloxacin, which is not approved for use during pregnancy.

III. Treatment of the bitch with canine herpesvirus rarely is necessary.
   A. Treat viremic pups by increasing environmental temperature to decrease replication of the virus within the pups.
   B. An infected bitch should not lose more than one litter to canine herpesvirus, apparently because she retains enough memory cells to allow an adequate immune response if she is reexposed to the virus.

IV. Bitches with documented hypoluteoidism are treated with progesterone (in oil) 2 mg/kg IM every 3 days, or with

Box 61-4

Diagnostic Scheme for Pregnancy Loss in Dogs

Is the Bitch Pregnant and, If So, Are the Pups Viable?

Abdominal ultrasonography is the diagnostic method of choice for this assessment, but radiographs may be used after 45 days from breeding to give some idea of fetal viability.

Yes

1. Serological testing for canine brucellosis is performed (see Table 60–3).
2. Serum progesterone concentration is measured. Serum progesterone concentration of <10 ng/mL at midgestation, and <5 ng/mL anytime before the last 2 to 3 days of gestation, is suggestive of poor luteal function.
3. A sample of the vaginal discharge of the bitch is submitted for aerobic culture, and empirical treatment is instituted with amoxicillin-clavulanate at 14 mg/kg PO BID.
4. Continuing viability of the pregnancy is monitored weekly, preferably with abdominal ultrasonography.
5. If nonviable pups are passed, they are submitted for necropsy.

No

1. If the pups are not viable, expulsion of the pups is allowed to continue, and the bitch is monitored with abdominal ultrasonography and/or abdominal palpation to ensure complete loss of the pregnancy and normal involution of the uterus. Expulsion of uterine contents may be augmented with oxytocin or prostaglandin $F_2\alpha$.
2. A sample of the vaginal discharge of the bitch is submitted for aerobic culture.
3. Serologic testing for canine brucellosis is performed.
4. Any nonviable pups passed or stillborn pups are submitted for necropsy. Pups that died from canine herpesvirus have pathognomonic hemorrhagic lesions on the major abdominal organs. Contents of the stomach can be cultured to identify what organisms were in the pup's amniotic fluid.
5. Serologic testing for canine herpesvirus may be performed on the bitch, but the antigenicity of the virus is poor, so low titers do not indicate lack of exposure.

altrenogest *(Regumate)* 0.088 mg/kg PO SID (Purswell, 1991; Eilts, 1992).

A. Therapy must be withdrawn (to mimic the normal decline in progesterone) in the last 2 to 3 days of gestation.
B. Bitches receiving altrenogest may have poor milk production in early lactation.

Monitoring of Animal

I. All breeding bitches are tested for canine brucellosis twice yearly, even if they are not actively being bred.
II. The poor antigenicity of canine herpesvirus and the variability of titers because of environmental and host factors preclude regular serologic testing as a means of defining naive and exposed dogs (Ronsse et al., 2004).
III. In dogs with a history of pregnancy loss from bacterial infections, obtain quantitative culture of the cranial vagina early in proestrus, with administration of appropriate antibiotic therapy throughout proestrus and estrus while the cervix is open.
IV. Cleanliness of the environment must be assessed.
V. Bitches with a history of hypoluteoidism are monitored via weekly serum progesterone assays during subsequent pregnancies.
   A. Serum progesterone concentrations of <10 ng/mL at midgestation or <5 ng/mL anytime before the last 2 to 3 days of gestation are suggestive of poor luteal function.
   B. Empiric administration of progesterone to pregnant dogs is not desirable, because progestogens are teratogenic and nonviable pups need to be expelled.

Dystocia

Definition

Dystocia comes from the Greek words *dys*, meaning abnormal, and *tokos*, meaning birth, and is abnormal parturition.

Causes

I. Maternal causes
   A. Uterine inertia
      1. Primary uterine inertia is lack of initiation of second-stage labor by the bitch.
      2. Secondary uterine inertia is the lack of progression of second-stage labor as the uterine muscle fatigues.
   B. Obstruction of passage, as might be seen in a bitch with an artificially narrowed birth canal after pelvic fracture
   C. Abnormality of pregnancy, such as uterine torsion
II. Fetal causes
   A. Developmental abnormality, such as hydrocephalus
   B. Obstruction of passage from relative or absolute oversize of the pup
   C. Malpresentation
      1. Both cranial (head and extended forelimbs) and caudal (tail and extended hind limbs) presentation is normal in the dog.
      2. Examples of malpresentation include breech presentation (caudal presentation with the hind limbs flexed) and cranial presentation with only one or neither forelimb extended.
III. Breeds at increased risk for dystocia: Pekingese, Chihuahua, Scottish terrier, dachshund, Yorkshire terrier, miniature

poodle, Pomeranian, and English bulldog (Gaudet and Kitchell, 1985)

Clinical Signs

I. An obvious malpresentation is present.
II. The bitch has been in first-stage labor for >12 hours, in weak and intermittent second-stage labor for >4 hours, or in hard second-stage labor for >30 minutes before delivering any pups.
III. It has been >2 hours since the last pup was born.
IV. Abnormal vaginal discharge is present.
  A. Frank blood indicates hemorrhage.
  B. Black or green discharge indicates placental separation and is most valuable as an indicator before the first pup is born.
V. The pregnancy is a high-risk one (e.g., former pelvic fracture, predisposed breed, known single-pup litter).

Diagnosis

I. At the minimum, diagnosis of dystocia requires a good history, a physical examination including a digital vaginal examination, and a lateral abdominal radiograph.
II. Abnormalities that may be noted on physical examination are as follows:
  A. The bitch appears systemically ill.
  B. Abnormal vaginal discharge is present (see previous discussion).
  C. Digital vaginal examination findings are abnormal (no pup in the birth canal or vagina, very large pup palpable in birth canal or vagina, obvious malpresentation).
III. Abnormalities are found on radiography.
  A. Extremely large pup(s)
  B. Dead pups: gas within or around fetuses, collapse of axial skeleton and/or skull
  C. Large number of pups remaining in a fatigued bitch
IV. Obtain an abdominal ultrasound if viability of the pups is in question.
  A. Fetal heart rate of <150 beats per minute is indicative of fetal distress.
  B. Lack of visible movement or heart beats at term is indicative of fetal death.
V. Measure serum calcium.
  A. Serum calcium <7 mg/dL is diagnostic of hypocalcemia.
  B. Hypocalcemia causes dystocia by prohibiting normal muscle contraction.
VI. Evaluate labor with an external whelping monitor, which may suggest a decrease in fetal viability or show an abnormal pattern of uterine contractions (Whelp Watch; Vet Watch Corporation [888-200-8044]).

Treatment

I. Manipulation
  A. If a pup is palpable within the birth canal, then manipulation may allow it to pass.
  B. Use caution when manipulating pups, because limb dislocation and skin tearing may occur.
  C. Clamps, forceps, and other instruments have been described for relief of dystocia but must be used with extreme caution.
II. Pharmacological therapy
  A. Oxytocin causes uterine contractions and contributes to cervical dilatation.
    1. It also promotes placental separation.
    2. Oxytocin is not to be used unless the cervix is open (pup or significant vaginal discharge passed) and no present obstruction exists (as determined by abdominal radiography).
    3. The recommended dose is 2 to 5 IU SC, IM.
    4. If no response to oxytocin is seen after three doses (administered at 20- to 30-minute intervals), then institute some other form of therapy (Wallet Darvelid and Linde-Forsberg, 1994).
  B. Hypocalcemic bitches with no signs of eclampsia other than dystocia may benefit from parenteral calcium gluconate at 5 to 10 mL SC, IM.
  C. Oxytocin and calcium are often given together, because calcium may potentiate the effects of oxytocin.
  D. Some reports suggest that bitches in dystocia may respond to parenteral dextrose; however, hypoglycemia has not been reported as a cause of dystocia in the bitch.
III. Surgical therapy
  A. Surgical treatment of dystocia is via cesarean section.
  B. Use anesthetic agents with a short half-life and agents that can be reversed in the pups.
    1. Premedicate with atropine 0.04 mg/kg IM.
    2. Examples of suitable induction agents include thiopental 4 to 8 mg/kg IV (to effect) or oxymorphone 0.1 to 1.0 mg/kg IV (to effect).
    3. Intubate and maintain on inhalant anesthesia; isoflurane is the inhalant anesthesia of choice.
  C. No contraindications exist to ovariohysterectomy at the time of cesarean section.
  D. Ovariohysterectomy at the time of cesarean section is recommended if uterine rupture has occurred or if the owner has no further plans to breed the bitch.

Monitoring of Animal

I. The prevention of dystocia requires good client education.
II. Feed the bitch a well-balanced diet and provide consistent exercise throughout pregnancy.
III. Stress good breeding management to optimize litter size.
  A. Vaginal cytological examination and measurement of serum progesterone concentration allow determination of ovulation day.
  B. Optimal litter size is achieved by breeding 2 days after ovulation.
IV. Provide the bitch with a stress-free, sanitary whelping environment.

Pseudocyesis

Definition

I. Pseudocyesis is mammary development, lactation, and behavior typical of whelping, nursing, and mothering in nonpregnant bitches at the end of diestrus.
II. The term *false pregnancy* is a misnomer.

A. All bitches undergo a hormonal false pregnancy, with luteal production of progesterone for an approximately 2-month diestrus, regardless of breeding or pregnancy status.
B. The terms *pseudocyesis* or *false whelping* more accurately describe this phenomenon.

III. Pseudocyesis is a normal reproductive phenomenon in dogs and is not associated with reproductive tract disease.

Causes and Clinical Signs

I. All bitches produce luteal progesterone for approximately 2 months after ovulation, which causes mammary development.
II. The abrupt decline in serum progesterone at the end of diestrus stimulates release of prolactin from the anterior pituitary, with subsequent mothering behavior and lactation.
III. Onset of pseudocyesis can be triggered by withdrawal of exogenous progestogen therapy or by a decline in endogenous progesterone after ovariohysterectomy during diestrus.
IV. Physical changes of pseudocyesis include distention of the mammary glands and exudation of serous fluid or normal milk from the mammae.
V. Behavioral changes include nesting behavior, mothering of inanimate objects, and possible aggression.

Diagnosis

I. Diagnosis of pseudocyesis is based on a history of having been in estrus approximately 2 months before presentation, as well as the presence of the previously mentioned clinical signs.
II. If breeding occurred, or if the owner is unsure if the bitch was bred, then perform abdominal radiography to rule out pregnancy and imminent whelping.
III. Diagnose secondary mastitis if the mammary glands are enlarged, hot, and painful (see Chapter 60).

Treatment

I. Spontaneous remission occurs in most cases within 2 to 3 weeks of onset of clinical signs.
A. Do not milk out the mammary glands, because increased intramammary pressure inhibits prolactin release and continuing milk production.
B. Wrapping the mammary glands with an elastic bandage may hasten this pressure effect and protects the distended glands from trauma.

II. Megestrol acetate *(Ovaban)* at 2.5 mg/kg PO SID for 8 days is the only therapy approved for treatment of pseudocyesis in dogs.
A. Signs resolve with treatment but very often recur when the drug is withdrawn.
B. Side effects of progestogen therapy include increased appetite and changes in temperament.
C. Progestogens are not given to bitches with a history of mammary neoplasia, diabetes mellitus, or pyometra.
D. The author does not recommend the use of megestrol acetate for treatment of pseudocyesis in dogs.

III. Testosterone cypionate at a dose of 0.5 to 1.0 mg/kg IM may decrease milk production in dogs.
IV. Prolactin inhibitors decrease milk production in dogs.
A. Bromocriptine is administered at a dose of 30 μg/kg PO SID for 16 days, with the most common side effect being emesis.
B. Cabergoline is administered at a dose of 1.5 to 5.0 μg/kg PO SID for 2 to 8 days, with emesis as a rare side effect.

V. Ovariohysterectomy is not curative of a given episode of pseudocyesis but prevents subsequent episodes.
VI. Short-term tranquilization may be necessary in aggressive animals.
A. Diazepam is the drug of choice.
B. Phenothiazine tranquilizers (e.g., acepromazine) and butyro-phenone tranquilizers (e.g., haloperidol) are not recommended, because they may stimulate prolactin release and worsen clinical signs.

Monitoring of Animal

I. Pseudocyesis is not associated with uterine disease and may, in fact, be a historical indicator of normal ovarian function in the bitch.
II. Age at onset of pseudocyesis is variable, and a given bitch may not exhibit signs of pseudocyesis after every estrous cycle.
III. Increased incidence of pseudocyesis in a given bitch may be associated with predisposition to malignant mammary neoplasia, presumably because of inflammatory changes and release of free radicals within the distended mammary tissue (Verstegen and Onclin, 2003).

POSTPARTUM DISORDERS

Eclampsia

Definition

I. Eclampsia is hypocalcemia arising from inadequate stores of usable calcium in the extracellular compartment.
II. Eclampsia is also known as *postpartum hypocalcemia* and *puerperal tetany*.

Causes and Pathophysiology

I. Hypocalcemia occurs most commonly in small breed dogs nursing large litters, especially at peak lactation (2 to 3 weeks postpartum) (Kaufman, 1986).
II. Eclampsia can also occur during parturition and may precipitate dystocia.
III. The disorder develops because the bitch's body is incapable of drawing enough calcium from intracellular sources, such as bone, and cannot ingest enough oral calcium to meet the excessive demands of lactation.
IV. Supplementation with oral calcium during pregnancy may predispose bitches to eclampsia during peak lactation.
V. Excessive calcium intake during pregnancy causes down-regulation of the bitch's own calcium regulatory system and subsequent clinical hypocalcemia when calcium demand is high.

Clinical Signs

I. Eclampsia is characterized by progressive neurologic changes, with initial tremors followed by ataxia and disorientation, collapse with seizures, and, finally, coma and death (Drobatz and Casey, 2000).
II. Elevated body temperature (>40.5° C [105° F]) may be present.

Diagnosis

I. Putative diagnosis is made by signalment (small breed dog, nursing large litter), history (2 to 3 weeks postpartum), and clinical signs as described previously.
II. Confirmatory diagnosis requires demonstration of total serum calcium concentration <7 mg/dL.

Differential Diagnosis

I. Differential diagnoses for seizures in dogs include idiopathic epilepsy, meningoencephalitis, and toxicities (see Chapter 22).
II. Evaluate dogs for hypoglycemia that do not respond to empiric treatment with calcium.

Treatment

I. Mild tremors, ataxia, and disorientation in the lactating bitch
   A. Provide 10% calcium gluconate 0.2 to 0.4 mL/kg IM, SC.
   B. Dispense oral calcium carbonate or calcium gluconate (1 to 3 g/day) with concurrent vitamin D.
   C. Puppies may continue to nurse unless signs worsen or recur.
II. Severe tremors, ataxia or disorientation, or seizures in a bitch at peak lactation
   A. Administer 10% calcium gluconate 1 to 10 mL IV, to effect, while ausculting the heart.
   B. Stop administration of calcium if any cardiac abnormality is evident.
   C. If hyperthermia is present, then gradually cool the bitch.
   D. Provide a depot of 10% calcium gluconate 0.2 to 0.4 mg/kg IM, SC, and dispense oral calcium carbonate or calcium gluconate (1 to 3 g/day), with concurrent vitamin D, when the animal is discharged.
   E. Remove pups from the bitch for 24 hours, or permanently if signs recur during the same lactation.

Monitoring of Animal

I. If signs worsen or recur, then the puppies are removed from the bitch and either hand raised (<4 weeks of age) or weaned (>4 weeks of age).
II. Bitches with a history of eclampsia may benefit from oral calcium supplementation during lactation after subsequent whelpings.

Metritis

Definition

I. Metritis is a primary bacterial infection of the uterus that occurs postpartum.
II. Metritis is not synonymous with pyometra, which is primary cystic endometrial hyperplasia with secondary bacterial infection that occurs during or after diestrus.

Causes and Clinical Signs

I. Metritis is caused by an ascending infection with vaginal aerobic organisms after normal parturition, or after abortion, fetal infection, dystocia, and/or retention of placentas.
II. Clinical signs include fever, anorexia, depression, neglect of pups, and exudation of foul-smelling purulent discharge from the vulva.

Diagnosis

I. Cytological examination of the vulvar discharge: inflammation, contains numerous polymorphonuclear leukocytes (some of which may be degenerative) and bacteria
II. Aerobic culture and sensitivity of the vulvar discharge to guide antibiotic therapy
III. Complete blood count to demonstrate neutrophilia with a left shift (common)
IV. Abdominal radiographs or ultrasonography to diagnose retention of placentas and/or fetuses
V. Serological examination for canine brucellosis

Differential Diagnosis

I. Other causes of purulent vulvar discharge in the postpartum bitch include brucellosis and vaginitis.
II. Rule out other causes of uterine disease (see Chapter 57).

Treatment

I. Administer an appropriate antibiotic, based on culture and sensitivity testing, for 14 days.
II. While awaiting culture results, start on a broad-spectrum antibiotic, such as ampicillin at 20 mg/kg PO TID.
III. Evacuate the uterine contents by administration of oxytocin at 1 IU/kg IM or prostaglandin $F_2\alpha$ *(Lutalyse)* at a dose of 0.25 mg/kg SC.
IV. Perform ovariohysterectomy on bitches that become septic (as evidenced by worsening clinical signs, hypoglycemia, and positive blood cultures) and on bitches that are not intended for future breeding.
V. Bitches with mineralized retained fetal tissue may require hysterotomy or ovariohysterectomy for its removal.

Monitoring of Animal

I. Vaginal discharge resolves within 3 weeks postpartum or 2 weeks after institution of appropriate antibiotic therapy.
II. Properly treated, metritis should have no effect on future fertility of bitches left intact.

Subinvolution of Placental Sites

Definition

Subinvolution of placental sites (SIPS) is exudation of serosanguineous, noninflammatory vulvar discharge beyond the time normal postpartum lochia generally is present (>3 weeks postpartum).

Causes and Pathophysiology

I. Histological examination of placental sites in affected bitches reveals eosinophilic protrusions of nodular epithelium with necrosis and hemorrhage from failure of normal thrombosis and occlusion of endometrial blood vessels.
II. Underlying cause is unknown.

Clinical Signs

I. SIPS is most common in young bitches after whelping their first litter.
II. Clinical presentation is of an apparently healthy bitch with prolonged exudation of serosanguineous vulvar discharge.

Diagnosis and Differential Diagnosis

I. SIPS is diagnosed by ruling out other causes of persistent vulvar discharge, such as metritis and canine brucellosis.
II. Perform cytological examination of the vulvar discharge.
  A. Vulvar discharge characteristic of SIPS is noninflammatory.
  B. It contains noncornified vaginal epithelial cells, occasional healthy polymorphonuclear leukocytes, and mucoid proteinaceous debris.
III. Perform culture of the vulvar discharge.
  A. Because the vagina of the normal bitch is not sterile, ask the laboratory for a quantitative culture.
  B. Moderate to heavy growth of a single organism is significant and leads to a diagnosis of infection of the reproductive tract, not SIPS.
IV. Perform serological examination for canine brucellosis, which also produces persistent vaginal discharge.
V. Perform abdominal palpation, radiography, and/or ultrasonography.
  A. Assess uterine size and evaluate for retained fetuses or placentas.
  B. The presence of excessive intrauterine fluid or retained tissues from parturition suggest metritis is present, not SIPS.
VI. Perform a complete blood count to assess hematocrit, white blood cell count, and cell differential count.
  A. Chronic exudation of serosanguineous discharge may be excessive enough to cause a regenerative anemia.
  B. Neutrophilia with a left shift is suggestive of metritis, not SIPS.
VII. Definitive diagnosis of SIPS requires histopathology of uterine tissue and is rarely, if ever, performed in the bitch.

Treatment

I. If the bitch is not intended for future breeding, then ovariohysterectomy is performed.
II. If the bitch is to be left intact, then monitoring is recommended.

Monitoring of Animal

I. Evaluate cytological findings of the vulvar discharge weekly.
  A. If the vulvar discharge becomes cytologically purulent, then perform aerobic vaginal culture.
  B. Next, treat with an appropriate antibiotic (based on culture and sensitivity testing) for 14 days.
II. Monitor hematocrit weekly, because bitches rarely become anemic to an extent requiring transfusion of whole blood.
III. The serosanguineous vulvar discharge of SIPS may persist until onset of the subsequent proestrus.
IV. SIPS rarely recurs after subsequent whelpings.

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CHAPTER 62

Disorders of Feline Reproduction

Milan B. Hess

NORMAL PATTERNS

Estrous activity

I. The breeding season extends from mid January to August in the Northern Hemisphere.
II. On average, queens cycle every 2 to 3 weeks during this period.
III. Queens may also cycle during nonseasonal months because of consistent household lighting (Herron, 1977; Stabenfeldt and Shille, 1977).
IV. Behavioral changes result from repeated waves of follicular growth and regression.
  A. The growth phase consists of proestrus and estrus (average 6 to 7 days).
    1. The condition is marked by increased vocalization and rubbing behavior, crouching and elevation of hindquarters, hind limb treading, and subsequent acceptance of a male.
    2. Plasma estradiol levels range from 25 to >80 pg/mL (Shille et al., 1979).
  B. The regression phase (average 8 to 9 days) is denoted by sexual nonreceptivity.
    1. The condition is also termed *interestrus*.
    2. Plasma estradiol concentrations are usually <15 pg/mL.

Pregnancy and Pseudopregnancy

I. The queen is considered an induced ovulator, requiring coitus or mechanical stimulation of the cervix and/or cranial vagina for luteinizing hormone (LH) release from the pituitary gland.
II. Spontaneous ovulation also occurs (Lawler et al., 1993).
  A. If pregnancy results after ovulation is induced, then progesterone production occurs for approximately 65 to 66 days.
  B. If pregnancy fails to occur after ovulation is induced, then a pseudopregnant state of approximately 40 to 50 days ensues.

Clinical Evaluation

I. In addition to a thorough physical examination, obtain information regarding reproductive behavior, past reproductive history, breed-related traits, and sibling and offspring fertility.
II. Consider the following parameters:
  A. Queen
    1. Vaginal cytology contributes little to the clinical workup.
    2. Hormonal profiles, appropriate serology, ultrasonography, and evaluation of the uterus at surgery are key.
  B. Tom
    1. Evaluate the scrotum for evidence of dermatitis and determine the presence of both testicles.
    2. Ascertain mobility of testes within the scrotal sac.
    3. Evaluate the testes for symmetry, texture, size, and shape.
    4. A semen sample is collected if necessary.

INFERTILITY IN THE QUEEN

Definition

I. Failure of the queen to cycle normally
II. Failure of the queen to breed or conceive after mating with a fertile tom

Causes and Pathophysiology

I. Persistent anestrus
  A. Inadequate photoperiod
    1. Queens housed indoors may not receive adequate intensity or duration of light, which may result in unpredictable ovarian cycles and anestrus.
    2. Approximately 12 to 14 hours of daylight are required for normal cyclicity.
  B. Progesterone-secreting ovarian cyst or neoplasm
    1. Persistently elevated progesterone may inhibit ovarian activity.
    2. This can result in anestrus (Johnston et al., 2001).
  C. Abnormality of sexual differentiation
    1. Queens with persistent anestrus that are phenotypically normal may have abnormal karyotypes, such as XO, XX/XY, or XY (Johnston et al., 2001).
    2. Persistent anestrus can be associated with pseudohermaphrodite disorders.
  D. Estral behavior after previous ovariohysterectomy (OHE)
    1. Queens that have undergone OHE occasionally are presented for estrus behavior.
    2. Confirmation of ovarian tissue is accomplished by treating with human chorionic gonadotropin (HCG)

or gonadotropin-releasing hormone (GnRH) during periods of estrus behavior, then measuring serum progesterone 7 to 10 days later.
3. Progesterone concentration >1.0 ng/mL indicates the presence of luteal tissue and confirms the presence of ovarian tissue.

II. Persistent estrus
A. A careful history is required to discriminate between persistent estrus and normal cyclic estrus behavior.
B. Persistently elevated plasma estradiol concentrations can result in prolonged estrus behavior (Feldman and Nelson, 1996).
C. Queens with estradiol-producing ovarian cysts or neoplasms can display persistent estrus.

III. Copulation failure
A. Sexual partner discrimination can result in the queen's refusal to mate with the tom (Schmidt, 1986).
B. Young or inexperienced queens may refuse to mate with the tom.
C. Vestibular and vaginal abnormalities may prevent normal intromission.

IV. Ovulation failure
A. Multiple copulations are necessary to induce a sufficient LH surge and ovulation in the queen.
B. Anovulatory cycles occur in the majority of queens that copulate with the tom only once (Schmidt, 1986).

V. Infectious causes
A. Infection of the reproductive tract is a common cause of infertility in the queen.
B. *Escherichia coli* is frequently isolated from the uterus in many queens with cystic endometrial hyperplasia (CEH).
C. Feline panleukopenia, feline infectious peritonitis (FIP), feline leukemia virus, and feline herpesvirus 1 are potential causes of infertility in the queen (Johnson, 1998).

VI. CEH-pyometra complex
A. As in the bitch, pyometra is a diestral disease and develops during progesterone domination (Dow, 1962; Kenney et al., 1987).
B. Pyometra can occur in the queen during the luteal phase, resulting from a copulation-induced ovulation or spontaneous ovulation.

VII. Anatomic abnormalities of the female reproductive tract
A. Nonpatent uterine tubes
B. Infantile tracts
C. Segmental hypoplasias and aplasias

Clinical Signs

I. Queens with persistent anestrus will fail to cycle during the normal breeding season when exposed to an adequate duration and intensity of light.
II. Queens with true persistent estrus will remain continuously in estrus for prolonged periods; normal estrus durations should not exceed 19 days (Shille et al., 1979).
III. Queens that fail to display estrus despite normal ovarian function have historical anestrus with no other clinical signs.
IV. Queens that are presented for ovulation failure may have a history of inadequate copulatory stimulus.
V. CEH-pyometra complex may be present.
A. Vaginal discharge
B. Lethargy
C. Weight loss
D. Unkempt hair coat
E. Abdominal distention
F. Polyuria/polydipsia

Diagnosis

I. Detailed medical and reproductive histories, as well as a complete physical examination, are imperative.
II. Routine screening tests such as blood chemistries, complete blood count, urinalyses, feline leukemia virus testing, and feline immunodeficiency virus testing are indicated in all cases of infertility.
III. Reproductive hormone analyses can be useful in determining the presence or absence of hormonally active ovarian cysts or neoplasms.
A. Normal fluctuations in hormone concentrations make interpretation of pathologic conditions difficult.
B. Hormone concentrations must be assessed repeatedly and interpreted in light of other clinical findings.
C. Measurements of estradiol may help identify follicular ovarian cysts and estrous cycles in queens suspected of having unobserved estrus cycles.
D. Pathologic increases in estradiol concentrations, however, may be less than the detectable levels of some assays.
E. Therefore measurement of plasma estradiol concentrations may have no diagnostic value (Johnson, 1998).
F. Serum progesterone concentrations can help distinguish between stages of the estrous cycle.
1. Progesterone concentrations are at basal levels until ovulation in the normal queen.
2. After ovulation, serum progesterone concentrations are >1.5 ng/mL for the duration of the luteal phase (Johnson, 1998).
3. Serum progesterone concentrations that remain elevated for longer than 40 to 45 days in the nonpregnant queen indicate a progesterone-producing ovarian cyst or neoplasm (Johnston et al., 2001).

IV. Karyotyping may reveal abnormalities in chromosomal number or chromosomal sex.
V. Exploratory laparotomy may be required to identify anatomic abnormalities within the reproductive tract.
VI. Biopsy and culture of the uterus and ovarian biopsy may be necessary to diagnose bacterial infections, CEH, ovarian cysts, and ovarian neoplasms.
VII. Ultrasonographic examination of the reproductive tract is a useful diagnostic tool.
A. Thickening of the nonpregnant uterine lining and fluid within the uterine lumen indicates pyometra, with or without CEH.
B. Large cystic or masslike structures associated with the ovaries in the queen with abnormal estrous cycles are consistent with ovarian cysts or neoplasms.

VIII. Culture and cytological examination of vaginal discharge is recommended.
  A. Used to determine appropriate antibiotic therapy
  B. *Escherichia coli*, hemolytic *Streptococcus* spp., and *Staphylococcus* spp. most frequently isolated (Kenney et al., 1987)

Treatment and Monitoring

I. Persistent anestrus
  A. Exposure to 12 to 14 hours of daily light will induce estrus in those queens with anestrus associated with insufficient photoperiod (Michel, 1993).
  B. Housing the queen with cycling females or a fertile male may induce estrus in a queen with historical anestrus.
  C. Surgical excision of progesterone-producing ovarian cyst or neoplasm may be required.
II. Persistent estrus
  A. Attempt luteinization of follicular cyst with 250 to 500 IU HCG IM or 25 μg GnRH IM (Johnston et al., 2001).
  B. Surgical excision of ovarian cyst or neoplasm is frequently curative.
III. Copulation and ovulation failure
  A. Allow the queen and tom to copulate multiple times daily during estrus and monitor for the "after reaction" by the queen, indicating intromission has occurred (Schmidt et al., 1983).
  B. Artificial insemination may be required in the case of the queen that persistently refuses the tom.
    1. Historically, surgical insemination is recommended but transcervical insemination is possible.
    2. Intravaginal insemination is also successful but requires significantly more sperm to obtain conception rates similar to surgical insemination conception rates (Zambelli and Cunto, 2005).
  C. Induce ovulation after natural service or artificial insemination.
    1. Administer 250 IU HCG IM or 25 μg GnRH IM.
    2. Give the HCG 15 to 30 hours before insemination (Tanaka et al., 2000).
IV. CEH-pyometra complex
  A. OHE is indicated if the queen is not part of a breeding program or is systemically ill.
  B. Medical management using prostaglandin $F_2\alpha$ can be attempted in young and otherwise healthy, hospitalized queens with an open-cervix pyometra.
    1. Administer 0.1 to 0.25 mg/kg SC SID to TID.
    2. Treatment continues 24 hours beyond resolution of the clinical signs.
    3. Supportive fluids and antibiotic therapy are indicated in queens displaying signs of systemic illness.

FETAL RESORPTION AND ABORTION

Definition

I. Fetal loss in utero
II. Premature parturition and delivery of immature fetuses

Causes and Pathophysiology

I. Viral diseases most frequently reported
  A. Feline leukemia virus
  B. Feline herpesvirus 1 (Smith, 1997)
  C. Feline immunodeficiency virus: abortion under experimental conditions (Ueland and Nesse, 1992; Sellon et al., 1994)
  D. FIP (Grahn, 1991)
II. Taurine deficiency (Sturman et al., 1986; Dieter et al., 1993)

Clinical Signs

I. Resorption may go unnoticed, especially if the pregnancy has gone undiagnosed.
II. Expelled fetuses and vaginal discharge may be seen with late-term abortions.
III. Queens may begin to cycle again if the litter is lost during the physiologic breeding season.

Diagnosis

I. Serological testing for viral disease
II. Ultrasonographic examination to detect fluid in the uterine lumen or thickening of the wall
III. Exploratory laparotomy
  A. To obtain biopsy and culture samples of the reproductive tract
  B. To identify gross abnormalities of the uterus and ovaries
IV. Abortion screening on any fetus to detect chromosomal, developmental, or infectious causes

DYSTOCIA

Definition

I. Difficult birth
II. Inability to expel kitten from birth canal

Causes and Pathophysiology

I. Uterine inertia and fetal malpresentation are the most frequently reported causes of dystocia in the queen (Ekstrand and Linde-Forseberg, 1994; Gunn-Moore and Thrusfield, 1995).
  A. Uterine inertia
    1. Primary uterine inertia is the failure to initiate labor at term.
    2. Secondary uterine inertia is the failure to progress once labor is initiated (uterine fatigue).
  B. Fetal malpresentation
    1. Both anterior and posterior presentations are normal in the queen.
    2. Common malpresentations include true breech, forward flexion of one hindlimb, flexion of head or neck, simultaneous presentation of two kittens, and transverse presentations (Ekstrand and Linde-Forsberg, 1994).
II. Dystocia is significantly more prevalent in purebred queens than mixed-breed queens.

III. Dolichocephalic and brachycephalic head types have higher rates of dystocia compared with mesocephalic head types (Gunn-Moore and Thrusfield, 1995).
IV. Less common causes of dystocia in the queen include narrowed birth canal, oversized fetuses, and fetal malformation.
V. Dystocia from uterine torsion occurs uncommonly in the queen.

Clinical Signs

I. Gestation length that is >71 days from the first breeding is abnormal.
II. Serum progesterone concentration <2 ng/mL in a near-term queen with no signs of labor is consistent with primary uterine inertia.
III. Failure to deliver a fetus after 20 to 30 minutes of straining, or failure to deliver a fetus within 15 minutes of entering the birth canal, is consistent with dystocia.
IV. The presence of uteroverdin (greenish-black vaginal discharge) before delivery of a fetus is abnormal and indicates separation of the placenta from the uterus and significant fetal compromise.
V. Copious hemorrhagic vaginal discharge or significant maternal distress indicates dystocia.
VI. Hypovolemic shock and abdominal pain indicate uterine torsion; there may be only hours between normal birth and uterine torsion (see Chapter 57).

Diagnosis

I. Clinical signs and history
II. Ultrasonography
  A. To determine fetal viability and heart rate
  B. Fetal stress: heart rate <190 to 200 beats per minute
III. Abdominal radiography of fetus (or fetuses)
  A. Fetal size
  B. Number of fetuses
  C. Position of fetuses
IV. Laparotomy necessary to diagnose uterine torsion
V. Digital vaginal examination to identify fetus in vagina

Treatment

I. Surgical intervention (cesarean section) is indicated for evidence of fetal stress, a uterine tear, uterine torsion, or primary uterine inertia.
  A. OHE is preferred if the queen is not intended for use in a breeding program.
  B. OHE is indicated for a uterine tear or uterine torsion resulting in significant uterine compromise or with the presence of decomposing fetuses.
II. Oxytocin therapy is used cautiously because it can cause placental separation and fetal compromise.
  A. Oxytocin is contraindicated in the presence of fetal malpresentation, obstruction of the birth canal, and fetal or maternal compromise.
  B. The dose is 1 to 3 IU oxytocin SC, IM repeated in 20 to 30 minutes if necessary.

INFERTILITY IN THE TOM

Definition

I. Failure to breed queens of known estrous activity
II. Failure to cause conception after mating to queens of known fertility

Causes and Clinical Signs

I. Noninfectious disorders
  A. Behavior
    1. A dominant or aggressive queen may discourage mating behavior in an inexperienced male.
    2. Previous negative breeding may inhibit normal behavior for future matings.
    3. This is exaggerated by uninterrupted housing in a restricted environment (Christiansen, 1984).
    4. Poor libido may have a genetic basis in Persian cats and is worse during immaturity and senescence.
  B. Physical abnormalities
    1. Persistent penile frenulum
    2. Hair rings at the base of the penis
    3. Retrograde ejaculation
    4. Hypoplastic or degenerate testicles
  C. Semen quality
    1. Causes of reduced sperm quality or quantity have not been extensively investigated.
    2. Known causes include the following:
      a. Age: immaturity and senescence
      b. Intersex conditions such as the tortoiseshell male XXY karyotype
      c. Testicular hypoplasia
  D. Cryptorchidism and abdominal testicle
    1. Normal reproductive behavior in toms possible
    2. Infertile from failure of spermatogenesis if bilateral
II. Infectious causes
  A. Chronic illness may affect libido and/or semen quality.
  B. Reproductive tract infections are not commonly associated with infertility.
  C. Orchitis has been observed in association with FIP virus (Stein, 1991; Johnston et al., 2001).

Diagnosis

I. Diagnosis is based on findings of a detailed reproductive history, general physical examination, and examination of the reproductive organs.
II. Evaluation of a semen sample may be necessary for diagnosis.
  A. Collection of semen may be accomplished manually by training to an artificial vagina (AV) or via electroejaculation (EE).
    1. The volume of semen ranges from 0.01 to 0.12 mL when collected by AV and from 0.001 to 0.738 mL when using EE (Johnston et al., 2001).
    2. Ejaculate concentration varies based on collection technique.
    3. Normal sperm motility is at least 60%, with at least 70% morphologically normal sperm.

   B. Postcoital vaginal smears are not optimal for evaluating semen.
III. Test for feline leukemia virus, feline immunodeficiency virus, and urinary tract disease, and measure serum thyroxine.
IV. Serum testosterone concentrations can be used to differentiate between a castrated and cryptorchid animal.
   A. Serum testosterone concentration is >1000 pg/mL in an intact tom.
   B. Because of the episodic release of testosterone, however, GnRH or HCG stimulation is recommended before sampling.
   C. Serum testosterone concentration should increase at least twofold by 1 to 2 hours after administration of 25 μg GnRH IM or 250 IU HCG IM in an intact tom.
   D. Castrated animals show no response to GnRH or HCG stimulation.
V. Karyotyping can be used to evaluate for potential chromosomal anomalies.

Treatment

I. Management changes can be instituted.
II. House the tom and queen together only for breeding.
III. Consider artificial insemination.
IV. Artificial insemination is becoming more common in cats, but the procedure is not routine in most veterinary practices.

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CHAPTER 63

Introduction

A. Eric Schultze

HEMOLYMPHATIC SYSTEM COMPONENTS

I. Hematopoietic tissues (blood and bone marrow)
   A. In adult mammals, blood cells are produced in the bone marrow and released into the blood.
   B. In the fetus, blood cell production occurs in the yolk sac, liver, spleen, and eventually in bone marrow.
II. Hemostatic system
   A. Composed of vessels, platelets, coagulation factors and inhibitors, and fibrinolytic factors/proteins
   B. Necessary for vascular integrity, to cease hemorrhage, and to maintain blood fluidity
III. Lymphoid system
   A. Composed of lymph nodes, spleen, thymus, bone marrow, and lymphatic vessels
   B. Develops and maintains cellular and humoral immune responses to foreign antigens, microbial agents, and virally infected and transformed cells

DISORDERS OF RED BLOOD CELLS (ERYTHROCYTES)

I. Erythrocytes transport oxygen from lungs to tissues and carbon dioxide from tissues to the lungs.
II. Abnormalities of erythrocytes may be quantitative or qualitative.
   A. Anemia is a decrease in functional erythrocyte mass defined by decreased packed cell volume, hemoglobin concentration, and/or the total erythrocyte count.
   B. Classification of anemia as regenerative or nonregenerative is helpful in refining a diagnosis, determining prognosis, and monitoring response to treatment.
      1. Regenerative anemias are usually the result of blood loss or hemolysis.
      2. Nonregenerative anemias occur as a result of reduced or defective erythrocyte production and may have extramarrow or intramarrow causes, or both.
   C. Polycythemia is defined by a relative or absolute increase in the erythrocyte mass.
      1. Relative polycythemia: plasma volume decreased secondary to vomiting, diarrhea, or other causes of volume contraction
      2. Absolute polycythemia: true red blood cell mass increased from polycythemia vera or occurring secondary to physiologically appropriate or inappropriate stimuli
III. Tests used to evaluate the erythron are frequently performed serially and include the complete blood count, reticulocyte count, and bone marrow aspirate or core biopsy.

DISORDERS OF WHITE BLOOD CELLS (LEUKOCYTES)

I. Functions of white blood cells (WBCs) include the following:
   A. Neutrophils engulf or destroy microorganisms and transformed cells, modulate acute inflammatory reactions, and control granulopoiesis.
   B. Lymphocyte functions include humoral and cell-mediated immunity.
   C. Monocytes phagocytose and kill microorganisms, engulf and digest foreign materials and dead cells, secrete inflammatory mediators, participate in immune recognition and tissue remodeling, and produce cytokines and several colony-stimulating factors.
   D. Eosinophils destroy parasites, modulate hypersensitivity reactions, and promote inflammation.
   E. Basophils participate in immunoglobulin E–mediated inflammatory reactions, initiate plasma lipolysis, and participate in immune surveillance.
II. Disorders of leukocytes may be quantitative, qualitative, or both.
   A. Quantitative abnormalities are detected by smear evaluation and confirmed by actual counting of leukocytes in blood.

B. Accurate interpretation of leukocyte numbers is best made using an absolute count (% leukocyte type × total leukocyte count).
C. Some qualitative abnormalities may be observed with blood smear morphology and confirmed with leukocyte function tests.

III. The total WBC count and the relative and absolute differential WBC counts, coupled with the blood smear morphology, are collectively called the *leukogram*.
IV. Leukograms provide valuable information regarding pathologic and physiologic WBC responses to several stimuli, severity of disease, prognosis, and response to treatment.
V. Tests to assess the leukon are often performed serially and include complete blood counts and bone marrow aspirate or core biopsies.

MYELOPROLIFERATIVE DISORDERS

I. Myeloproliferative disorders (MPDs) occur from unregulated proliferation of one or more nonlymphoid hematopoietic cell lines.
A. Acute MPDs are characterized by large numbers of poorly differentiated blast cells of one or more nonlymphoid hematopoietic cell lines in the bone marrow, blood, or tissues.
B. Chronic MPDs are characterized by marked proliferation and some partial differentiation of the abnormal nonlymphoid hematopoietic cell line.

II. Myelodysplastic syndromes are a vague group of bone marrow disorders characterized by abnormal development of one or more nonlymphoid hematopoietic cell lines that result in various cytopenias; these disorders are often called *preleukemias.*
III. Diagnosis is based upon examination of serial complete blood counts, with or without serial bone marrow aspirates and/or core biopsies; special cytochemical stains of blood and/or bone marrow may be required to identify the cell of origin.

PLATELET DISORDERS AND VON WILLEBRAND DISEASE

I. Platelets
A. Anucleate fragments of megakaryocyte cytoplasm
B. Cause primary hemostasis

II. Abnormalities in platelets
A. Quantitative or qualitative
B. Congenital or acquired (more common)

III. Quantitative disorders of platelets
A. Thrombocytopenia may have many causes.
B. Thrombocytosis may arise from reactive thrombocytosis, neoplasia, and/or select splenic disorders.

IV. Qualitative disorders of platelets
A. Inherited platelet defects (uncommon): basset hound thrombopathia, Chédiak-Higashi syndrome, Glanzmann's thrombasthenia of Great Pyrenees
B. Acquired disorders of platelets (common): drug therapy, liver disease, uremia, infectious agents

V. von Willebrand disease
A. It is the most common inherited, extrinsic platelet disorder of the dog.
B. It occurs from decreased concentrations of all multimers of von Willebrand factor (vWF) (Type I), decreased concentrations of vWF high-molecular-weight multimers (Type II), or undetectable concentrations of vWF multimers of all sizes (Type III).
C. Clinical signs are intermittent mucosal bleeding and prolonged bleeding postsurgery.
D. Diagnosis is by evaluation of blood vWF antigen concentration, molecular techniques, and/or platelet aggregation studies.

DISORDERS OF COAGULATION AND FIBRINOLYSIS

I. Coagulation factors
A. Soluble proteins and cofactors
B. When activated, cause conversion of soluble fibrinogen to an insoluble fibrin clot

II. Abnormalities in coagulation/fibrinolytic factors
A. Quantitative or qualitative
B. Congenital or acquired (more common)

III. Characteristics of hemorrhages
A. Petechial and mucosal hemorrhages suggest platelet disorders.
B. Large hemorrhages into joints or body cavities suggest coagulation disorders.

DISORDERS OF LYMPH NODES, LYMPHATICS, AND SPLEEN

I. Lymph nodes and lymphatic vessels filter the lymph and provide an avenue for lymphocytes to respond in immune challenges.
II. The spleen removes effete erythrocytes and other damaged cells from circulation, produces lymphoid and plasma cells, functions in the immunologic defense system, and acts as a reservoir for certain cell types.
III. Congenital abnormalities include aplasia or hypoplasia of lymph nodes, lymphatic vessels, or spleen, with resultant decreased function (immune or phagocytic).
IV. Acquired abnormalities include inflammation, hyperplasia, or neoplasia of lymph nodes, lymphatics, or spleen.
V. Diagnosis is dependent upon a combination of history, physical examination, laboratory assessment, cytological examination, surgical biopsy, diagnostic imaging, and/or exploratory laparotomy.

TRANSFUSION MEDICINE

I. Indications for whole blood or component therapy include anemia, coagulopathy, selective cytopenias, and/or hypoproteinemia.

II. Whole blood or its components (packed erythrocytes, plasma, and platelets) may be administered depending upon the animal's need.
III. Cross-matching of blood is recommended for safe transfusions; typing of the donor and recipient animals is also helpful.
IV. Careful, periodic screening of the donor animals for infectious agents is essential for safety.

PRINCIPLES OF ONCOLOGY

I. Neoplasia is a growth of abnormal cells that proliferates independently of physiologic control.
II. Neoplastic conditions may be benign or malignant.
III. Neoplastic growths may have a genetic or acquired origin.
IV. Diagnosis of neoplasia is dependent upon a combination of history, physical examination findings, laboratory analysis, biopsy, diagnostic imaging, and endoscopy/bronchoscopy.
V. Treatments for neoplasia are numerous and depend upon the individual tumor cell type.
VI. Treatments include chemotherapy, surgery, radiation, biological response modifiers, photodynamic therapy, hyperthermia, or palliative therapy.

PARANEOPLASTIC SYNDROMES

I. Paraneoplastic syndromes (PNS) are defined as neoplasia-associated alterations in tissue structures and/or functions that occur at sites distant from a neoplasm.
II. Many PNS are systemic in nature, occur before actual detection of the tumor, and can induce more morbidity than the tumor.
III. Examples include humoral hypercalcemia of malignancy, hypoglycemia, hyperhistaminemia, cachexia, hypertrophic osteopathy, fever of unknown origin, inappropriate secretion of antidiuretic hormone, and hyperviscosity syndrome.

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CHAPTER 64

Disorders of Red Blood Cells

Dina A. Andrews

CLASSIFICATION AND LABORATORY INTERPRETATION OF ERYTHROCYTE ABNORMALITIES

Definition and Causes

I. The red blood cell (RBC, erythrocyte) transports oxygen (O_2) and carbon dioxide (CO_2), buffers hydrogen ions, maintains vascular integrity, and participates in coagulation.
II. Clinical signs occur when RBC mass is decreased (anemia), increased (polycythemia), or when there are significant red cell morphologic abnormalities that impair normal RBC function.
III. An anemia may be regenerative or nonregenerative (Figure 64-1).
  A. A regenerative anemia occurs when RBC mass is reduced in the presence of a functional bone marrow able to produce and release RBCs.
  B. A nonregenerative anemia occurs when RBC mass is reduced because of a poorly or nonresponsive bone marrow or there is an inability to release RBCs peripherally.
  C. Anemia is a secondary process caused by decreased RBC production, increased destruction, or blood loss.
IV. Polycythemia is defined as increased red cell mass.
  A. Relative polycythemia occurs secondary to dehydration and is more common than absolute polycythemia.
  B. Absolute polycythemia may be a primary myeloproliferative disease or secondary to changes in erythropoietin concentrations.
V. Hereditary RBC anomalies recognized by changes in RBC shape or RBC indices may lead to a clinical manifestation of disease (Table 64-1).
  A. Increased nucleated RBCs in schnauzers
  B. Increased packed cell volume (PCV) in greyhounds
  C. Microcytosis in Japanese fighting dogs (Akita, Shiba inu)
  D. Microcytosis in dogs with portosystemic shunts

Clinical Signs

I. Clinical manifestations of anemia are dependent on duration and severity.
  A. General clinical signs include pallor, lethargy, tachypnea, and tachycardia.
  B. Hemolytic anemias can cause icterus, hemoglobinemia, and hemoglobinuria.
  C. Sources of blood loss include melena, epistaxis, petechiae, ecchymosis, hematuria, and hematemesis.
  D. Many anemias are subclinical and not identified unless a routine PCV or complete blood count (CBC) is performed.
II. Polycythemia is characterized by deep red to purple congested mucus membranes with mild cyanosis.

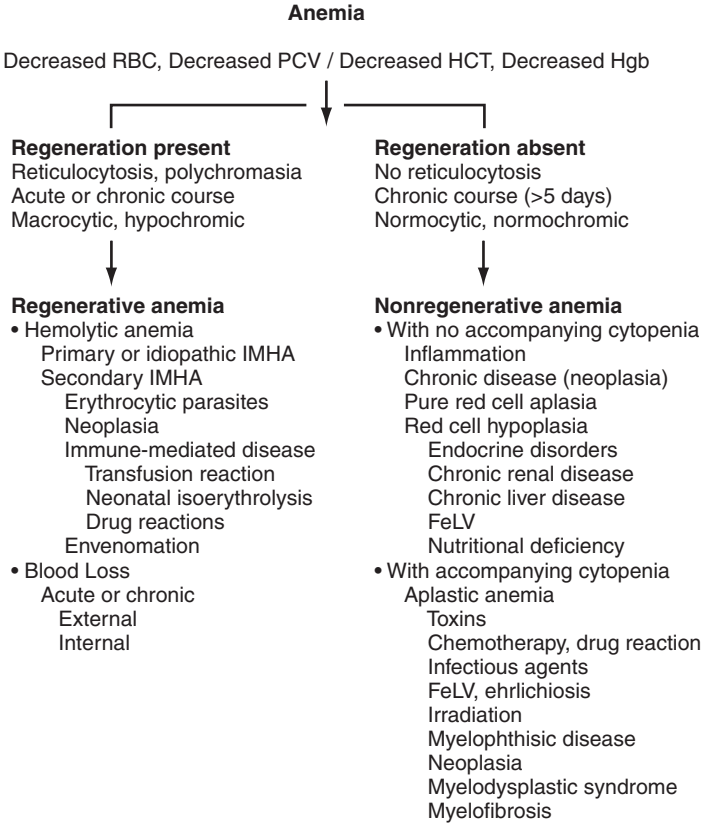

FIGURE 64-1 Anemia classifications and differential diagnoses. *RBC,* Red blood cell; *PCV,* packed cell volume; *HCT,* hematocrit; *Hgb,* hemoglobin; *IMHA,* immune-mediated hemolytic anemia; *FeLV,* feline leukemia virus.

TABLE 64-1

Hereditary Erythrocyte Defects

DEFECTS	AFFECTED BREEDS	CLINICAL CHARACTERISTICS	DIAGNOSTIC TESTS
Enzyme Defects			
PK deficiency	Dogs: Basenji, West Highland white terrier, beagle, American Eskimo, miniature poodle Cats: Abyssinian, Somali	Regenerative hemolytic anemia; icterus; osteosclerosis in dogs <5 years; myelofibrosis, liver cirrhosis Hemolytic anemia, splenomegaly	PCR-based DNA testing R-PK enzyme activity assay
PFK deficiency	English springer spaniel, American cocker spaniel, mixed breed dogs	Hyperventilation, excitement-induced (alkalemic) hemolytic crisis	PCR-based DNA testing PFK enzyme activity assay
Cb_5R deficiency	Dogs: isolated reports in the Chihuahua, borzoi, English setter, cock-a-poo mixed breeds Cats: DSH	Cyanosis, slight polycythemia, exercise intolerance	Cb_5R enzyme activity Methemoglobin spot test or measurement
Porphyria	Siamese cats, DSH cats	Photosensitivity, severe anemia, and renal disease in a Siamese cat Discoloration of the teeth and urine	Red fluorescence of teeth, urine, and body fluids when exposed to UV light
RBC Membrane Abnormalities			
Hereditary spherocytosis: spectrin deficiency	Golden retrievers originating from Netherlands	Severe hemolytic anemia, osmotic fragility of RBCs, spherocytes present	Osmotic fragility test Spectrin quantitation
Stomatocytosis	Alaskan malamute, miniature and standard schnauzers, Drentse Patrijshonds	Chondrodysplasia Clinically normal Hypertrophic gastritis	High numbers of stomatocytes on PBS Concurrent breed-specific clinical manifestations
Macrocytosis	Miniature and toy poodles	Clinically normal	Macrocytosis, normal PCV, hypersegmented PMNs
Nonspherocytic hemolytic anemia	Beagle	Clinically normal or chronic mild anemia	Unknown defect
Increased osmotic fragility	Cats: Abyssinian, Somali Dogs: English springer spaniel	Macrocytosis with moderate to severe anemia	Unknown defect Increased osmotic fragility of RBCs

Modified from Giger U: Hereditary blood diseases. p. 955. In Feldman BF, Zinkl JG, Jain NC (eds): Schalm's Veterinary Hematology. 5th Ed. Lippincott Williams & Wilkins, Philadelphia, 2000.

PK, Pyruvate kinase; *PCR,* polymerase chain reaction; *DNA,* deoxyribonucleic acid; *R-PK,* red blood cell isoform of pyruvate kinase; *PFK,* phosphofructokinase; *Cb_5R,* cytochromic b_5 reductase; *DSH,* domestic shorthair; *UV,* ultraviolet; *RBC,* red blood cell; *PBS,* peripheral blood smear; *PCV,* packed cell volume; *PMN,* neutrophil.

Diagnosis

I. Routine laboratory tests for characterizing red cell mass
   A. PCV and hematocrit (HCT) are used interchangeably.
      1. PCV is the percentage of whole blood composed of erythrocytes obtained using a microhematocrit tube and centrifuge.
      2. The HCT is a calculated value generated by automated machines after determining the mean erythrocyte size and RBC count.
      3. PCV and HCT must be interpreted relative to total plasma protein (TP).
         a. Dehydration (increased TP) falsely increases RBC mass.
         b. Overhydration (decreased TP) falsely underestimates RBC mass.
   B. Hemoglobin concentration (Hgb) is measured by a colorimetric method (cyanmethemoglobin) or by direct measurement of the optical density of oxyhemoglobin in a population of lysed RBCs.
      1. Hgb × 3 should approximate the PCV.
      2. Hgb can be falsely increased with hemolysis, lipemia, or Heinz bodies.
   C. Total RBC numbers can be obtained using a manual hemocytometer, although there may be a large margin of error; automated hematology analyzers count RBCs based on cell size or light scatter and are very accurate.

TABLE 64-2

Evaluating Absolute Reticulocyte Number

DEGREE OF REGENERATION	DOG	CAT (AGGREGATE FORM)
Normal or nonregenerative	<60,000/μL	<15,000/μL
Mild	60,000-150,000/μL	15,000-50,000/μL
Moderate	150,000-300,000/μL	50,000-100,000/μL
Marked	>300,000/μL	>100,000/μL

Modified from Tvedten H, Weiss D: Erythrocyte disorders. p. 31. In Willard MD, Tvedten H, Turnwald GH (eds): Small Animal Clinical Diagnosis by Laboratory Methods. 3rd Ed. WB Saunders, Philadelphia, 1999.

D. Total plasma protein is determined with a refractometer.

II. Reticulocyte enumeration
   A. A quantitative measure of reticulocytes (immature, anuclear RBCs) in circulation is the most important determinant in identifying a regenerative anemia (Table 64-2).
   B. Reticulocytes have retained intracytoplasmic organelles that precipitate when stained with new methylene blue (NMB) or brilliant cresyl blue (BCB), forming a reticulum recognized under light microscopy.
   C. A reticulocyte percentage (RP) >1% is indicative of regeneration although this does not correct for the degree of anemia and can be misleading (see corrected reticulocyte percent, below).
      1. Peripheral blood is mixed 1:1 with NMB or BCB, and reticulocytes are counted per 1000 RBCs; nucleated RBCs are not counted.
      2. In the dog, any RBC with a stainable reticulum is counted as a reticulocyte (mature to RBC in approximately 24 hours).
      3. Cats have two types of reticulocytes.
         a. Aggregate reticulocytes have large aggregates of RNA and are the best indicator of marrow activity.
         b. Punctate reticulocytes have a few dots of reticulum and can circulate for 10 to 12 days before full maturation. They assess the cumulative regenerative response and are commonly not enumerated.
   D. An absolute reticulocyte count (reticulocytes/μL) is most accurate and calculated by multiplying the RBC count (RBC/μL) by the RP present.
   E. A corrected reticulocyte percentage (CRP) corrects for the degree of anemia without requiring a RBC count.
      1. CRP = reticulocyte % × PCV ÷ normal PCV, where PCV in dog = 45%, and in cat = 37%.
      2. A CRP >1% supports regeneration.
   F. A reticulocyte production index (RPI) is used in the dog to compensate for younger reticulocytes (>24-hour maturation time) in circulation in response to a severe anemia.
      1. RPI = reticulocyte percentage × (HCT ÷ 45) × (1 ÷ maturation time).
         a. Maturation time varies depending on HCT.
         b. Maturation times are as follows: HCT 45% = 1 day, HCT 35% = 1.5 days, HCT 25% = 2.0 days, HCT 15% = 2.5 days.
      2. An RPI >1.0 = mild regeneration.
      3. An RPI >3 = marked regenerative response.

III. Peripheral blood smear evaluation
   A. The severity of the anemia (mild, moderate, severe) can be estimated by evaluating the decrease in RBC density in a peripheral smear.
   B. The degree of polychromasia reflects responsiveness of the bone marrow.
      1. Polychromatophils are large, blue-staining RBCs identified in the monolayer portion of a peripheral blood smear (Wright's, Diff-Quik stain).
      2. The degree of polychromasia correlates well with reticulocytosis.
      3. Normal dogs have approximately 1% polychromatophils and normal cats have approximately 0.5%.
   C. Identification of RBC morphologic abnormalities can elucidate the pathogenesis of the anemia (Table 64-3).

IV. RBC indices
   A. Mean cell volume (MCV) is the average size of the RBC expressed in femtoliters (fL).
      1. MCV can be directly determined by automated hematology analyzers or calculated by (HCT × 10) ÷ RBC ($\times 10^6$).
      2. A population of small RBCs = microcytic, normal RBCs = normocytic and large RBCs = macrocytic.
   B. Mean corpuscular hemoglobin concentration (MCHC) quantifies hemoglobin relative to the volume of packed erythrocytes.
      1. MCHC (g/dL) = (Hb concentration × 100) ÷ HCT
      2. RBCs with normal Hgb are normochromic and RBCs with decreased Hgb are hypochromic.
      3. Hyperchromic RBCs do not spontaneously occur.
      4. Increased MCHC is caused by in vivo or in vitro hemolysis, lipemia or Heinz body formation.
   C. The red cell distribution width (RDW) is obtained by an automated hematology analyzer.
      1. The RDW correlates with the size distribution of RBCs.
      2. Anemias with a large population of macrocytes or microcytes have an increased width.

V. Bone marrow examination: aspirate or core biopsy
   A. Indicated if there are no peripheral signs of RBC regeneration (reticulocytosis, polychromasia)
   B. Indicated if the degree of the reticulocyte response is not consistent with the degree of anemia

VI. Classification schemes for anemia
   A. Bone marrow responsiveness (Table 64-4)
      1. Regenerative anemia: anemia with a concurrent reticulocytosis/polychromasia
      2. Nonregenerative anemia: anemia without a concurrent reticulocytosis/polychromasia

TABLE 64-3

Red Blood Cell Morphological Changes of Clinical Significance

CHANGES	DESCRIPTION	CLINICAL SIGNIFICANCE
Shape Change		
Spherocytes	Small, dense, spherical-shaped cells with lack of central pallor	IMHA: extravascular hemolysis Fragmentation anemia Acanthocytosis (liver disease)
Ghost cells	Remnant membranes of RBCs	IMHA: intravascular hemolysis
Eccentrocytes	Eccentrically placed clear areas with displaced hemoglobin	Oxidative damage
Keratocytes	Two uniform hornlike projections	Oxidative damage
Dacryocytes	Tear shaped	Myelofibrosis
Schistocytes	Irregularly shaped, small fragments	DIC Iron deficiency anemia
Acanthocytes	2-10 irregularly shaped, blunt-ended projections	Liver disease Hemangiosarcoma
Target cells	Extra round outfolding of membrane in middle of cell	Usually with polychromasia Possibly liver disease
Agglutination	Three-dimensional clumping of RBCs	IMHA
Rouleaux	Coin stacking or linear chains of RBCs	Increased plasma proteins owing to inflammation
Size Change		
Anisocytosis	Variation in RBC size	Associated with polychromasia
Macrocytes	Large RBCs	Associated with polychromasia FeLV
Microcytes	Small RBCs	Iron-deficiency anemia Fragmentation anemia
Inclusions		
Basophilic stippling	Small, variably sized blue dots	Associated with polychromasia Lead poisoning
Howell-Jolly bodies	Single, small round remnants of nuclear material	Associated with polychromasia If no polychromasia, decreased splenic function
Heinz bodies	Refractile protuberances from membrane	Oxidative injury
Nucleated RBCs	RBCs with retained nucleus	Should be in low numbers with polychromasia present If no polychromasia, consider bone marrow injury, lead poisoning, myeloproliferative disease, hyperadrenocorticism
Color change		
Polychromatophils	Large blue RBCs	Associated with polychromasia
Hypochromic cells	Lack of hemoglobination	Iron deficiency

IMHA, Immune-mediated hemolytic anemia; *RBC,* red blood cell; *DIC,* disseminated intravascular coagulation; *FeLV,* feline leukemia virus.

B. Morphological classification based on RBC indices (population size, shape)
   1. Macrocytic, hypochromic: regenerative anemia
   2. Normocytic, normochromic: nonregenerative anemia
   3. Macrocytic normochromic: early regenerative response or defective erythropoiesis, especially with feline leukemia virus (FeLV)
   4. Microcytic hypochromic: iron deficiency
   5. Microcytic normochromic: iron deficiency, portosystemic shunts

C. Severity of anemia
   1. Can help identify the underlying clinical processes
   2. Dictates the aggressiveness of treatment (Table 64-5)

TABLE 64-4

Regenerative and Nonregenerative Response to Anemia

LABORATORY PARAMETERS	REGENERATIVE	NONREGENERATIVE
Reticulocytes		
Absolute count	>60,000/μL	<60,000/μL
Percentage	>1% dog, >0.5% cat	<1%
Corrected reticulocyte percentage	>1	<1
Reticulocyte production index	>1	<1
Peripheral blood smear	Polychromasia	Lack of polychromasia
	Anisocytosis	Lack of anisocytosis
	± nRBCs (low numbers)	No nRBCs detected unless bone marrow damage, lead poisoning or myeloproliferative disease present
	± Howell-Jolly bodies	Scattered to none present
	± Basophilic stippling	None present
	± Macrocytes	Normal-sized RBCs
	± Hypochromic cells	Normal pallor
	± Target cells	Normal shape
RBC indices	Macrocytic, hypochromic	Normocytic, normochromic
Bone marrow aspirate, biopsy	Erythroid hyperplasia	Normal to erythroid hypoplasia

nRBCs, Nucleated red blood cells; *RBCs,* red blood cells.

TABLE 64-5

Classifying the Severity of Anemia and Potential Causes

SEVERITY	DOG	CAT	POTENTIAL CAUSES	ACTION
Mild	PCV = 30% to 37%	PCV = 20% to 26%	Inflammatory disease, early iron deficiency, endocrinopathies, statistical chance of normal Consider age of animal, breed differences, sample error (clotting)	Repeated PCV Evaluate for underlying disease
Moderate	PCV = 20% to 29%	PCV = 14% to 19%	Hemolytic anemias, severe blood loss, chronic renal failure, chronic iron deficiency	Examine peripheral blood smear for parasites, RBC morphological abnormalities Assess clinical signs for need of transfusion; if PCV < 15%, whole blood transfusion is indicated Institute supportive care (fluids, plasma expanders) to restore circulating blood volume Evaluate for underlying diseases
Severe	PCV = 13% to 19%	PCV = 10% to 13%		
Very severe	PCV < 13%	PCV < 10%		

Data from Tvedten H, Weiss DJ: Classification and laboratory evaluation of anemia. p. 143. In Feldman BF, Zinkl JG, Jain NC (eds): Schalm's Veterinary Hematology. 5th Ed. Lippincott Williams & Wilkins, Philadelphia, 2000.

PCV, Packed cell volume; *RBC,* red blood cell.

REGENERATIVE ANEMIAS

Hereditary Causes of Hemolytic Anemia

See Table 64-1.

Immune-Mediated Hemolytic Anemia

Definition

I. Immune-mediated hemolytic anemia (IMHA) is a clinical condition where immunoglobulin (Ig) G and/or IgM antibodies bind to RBC surface antigens.
II. This reaction initiates RBC destruction via the complement system (intravascular destruction) and the mononuclear-phagocyte system (extravascular destruction).

Causes

I. Idiopathic or primary IMHA has no apparent underlying disorder and is more common in dogs than cats (Giger, 2005; Kohn et al., 2006).
II. Secondary IMHA is more common than primary IMHA and can be caused by the following:
  A. Erythrocytic parasites
  B. Neoplasia: hemangiosarcoma, lymphosarcoma (Gunn-Moore et al., 1999; Mellanby et al., 2004)
  C. Immune-mediated diseases: systemic lupus erythematosus, recent vaccination (Duval and Giger, 1996)
  D. Neonatal isoerythrolysis (Barker, 2000)
  E. Transfusions (Melzer, 2003; Castellanos et al., 2004)
  F. Drug reactions: penicillins, trimethoprim-sulfa, cephalosporins (Bloom et al., 1988), and carprofen (Mellor et al., 2005)
  G. Envenomation: bee sting (Noble et al., 1999)

Pathophysiology

I. Idiopathic or primary IMHA is caused by autoantibodies on RBCs, most frequently glycophorins in the RBC membrane (Barker, 1995).
II. Secondary IMHA occurs when a drug or antigen binding directly or indirectly to the RBC induces an antigenic state.
III. Removal of RBCs from circulation is by extravascular or intravascular hemolysis.
  A. The degree of hemolysis caused by the bound antibody depends on the quantity, specificity, complement-fixing ability, and binding to tissue macrophages.
  B. Resident macrophages in the spleen and/or liver represent the primary site of extravascular destruction and spherocyte formation.
  C. Macrophages phagocytose IgG, IgM, and complement-coated RBCs with partial (spherocyte formation) or full phagocytosis of RBCs.
  D. IgM and IgG (lesser extent) coated RBCs readily activate the complement system, with lysed RBCs forming ghost cells (Gehrs and Friedberg, 2002).
  E. Intravascular hemolysis is not as frequent as extravascular hemolysis because of regulatory RBC proteins that control complement activation.
IV. Moderate to severe tissue injury from hypoxia and thrombus formation is often present with IMHA (McManus and Craig, 2001).

Clinical Signs

I. Signalment
  A. Cocker spaniels are consistently overrepresented.
  B. English springer spaniels, poodles, Old English sheepdogs, bichon frise, collie breeds, and miniature pinschers are at increased risk (McManus and Craig, 2001; Miller et al., 2004).
  C. Age is variable, ranging from 2 to 12 years (mean 6.9 ± 2.9 years).
  D. Gender is highly variable; some reports favor females, whereas others show no difference.
II. Signs of anemia
  A. Pale mucous membranes
  B. Weakness, exercise intolerance
  C. Fever
III. Fulminant hemolysis
  A. Jaundice, severe pallor, hemoglobinuria
  B. Splenomegaly
  C. Disseminated intravascular coagulation (DIC), frank hemorrhage

Diagnosis

I. Complete blood count
  A. PCV, RBC, and Hgb are often severely decreased (PCV <20%, McManus and Craig, 2001).
  B. Hgb value may not be decreased to the same degree as PCV and RBC owing to intravascular hemolysis increasing the MCHC.
  C. Reticulocyte counts >60,000/μL are often seen after 3 days of anemia.
  D. IMHA can be nonregenerative if the immune response is directed at RBC precursors.
  E. Moderate to severe leukocytosis with a left shift and lymphopenia (inflammation and stress) are common.
II. Peripheral blood smear (Bain, 2005)
  A. Marked regenerative anemia: decreased RBC smear density, anisocytosis, polychromasia, macrocytes and hypochromic RBCs
  B. Evidence of intravascular and extravascular RBC destruction
    1. Spherocytes are partially phagocytosed RBCs.
    2. Ghost cells are empty RBC membranes.
  C. Agglutination (antibody-mediated three-dimensional clumping) versus rouleaux (nonspecific adherence of RBCs)
    1. Blood is mixed well with normal saline at a 1:5 ratio and placed on a glass slide.
    2. If the RBCs remain clumped, it is agglutination.
    3. If the cells disperse, rouleaux is present.
  D. Neutrophil toxicity common
III. Coagulation profiles
  A. Many dogs with IMHA are in a hypercoagulable state and at risk for developing DIC.

B. Cats do not appear at high risk for thromboembolic disease.

IV. Biochemistry profile and urinalysis: hemoglobinemia, hemoglobinuria, hyperbilirubinemia, bilirubinuria with severe hemolysis

V. Coombs test (direct antibody test)
   A. Detects IgG, IgM, and complement on RBC membranes with species-specific reagents.
   B. Antisera and RBC-associated immunoglobulin or complement result in macroscopic and/or microscopic agglutination in a positive Coombs test.
   C. In cats where spherocytes are difficult to identify because of lack of central pallor, the Coombs test can be helpful (Kohn et al., 2006).

VI. Bone marrow aspirate and core biopsy
   A. It is not commonly performed if there is peripheral evidence of a regenerative anemia.
   B. With a regenerative anemia, erythroid hyperplasia (decreased myeloid to erythroid [M:E] ratio) is present, although a concurrent leukocytosis may bring the M:E ratio into the normal range (erythroid and myeloid hyperplasia).
   C. In a nonregenerative hemolytic process, ineffective erythropoiesis (abrupt maturation arrest) supports immune-mediated destruction of immature RBCs (rubricyte, metarubricyte, prorubricyte).

Differential Diagnosis

I. Definitively eliminate all secondary causes of IMHA.

II. Examination of the peripheral blood smear is essential to identify parasites or RBC morphologic changes (schistocytes, acanthocytes, lack of spherocytes).

III. IMHA may be Coombs negative, as low numbers of antibodies may be washed off during the assay.

Treatment

I. Corticosteroids are the initial treatment of choice for IMHA (McCullough, 2003).
   A. Give prednisone or prednisolone 1 to 2 mg/kg PO BID for 2 weeks until the hematocrit increases or there is evidence of regeneration.
   B. When a response is identified, decrease dose by 25% every 2 to 4 weeks and taper over a 3-month period.

II. Use immunosuppressive drugs in combination with prednisone if there is a lack of response to prednisone therapy, severe hemolysis, or autoagglutination.
   A. Azathioprine *(Imuran)*
      1. A loading dose in dogs of 1.4 to 2.2 mg/kg PO SID is given for 4 to 7 days, followed by QOD tapering when remission is assured.
      2. One report documented increased survivability of dogs when ultra-low–dose aspirin (0.5 mg/kg PO SID) was administered with azathioprine (Weinkle et al., 2005).
      3. Azathioprine is not recommended in cats.
   B. Cyclophosphamide *(Cytoxan)*
      1. Many protocols are available for dogs and cats.
         a. Single IV or oral dose of 200 mg/m^2 initially
         b. Maintenance dose of 50 mg/m^2 PO or IV SID for 4 consecutive days of each week; discontinued when PCV increases significantly
         c. Alternative maintenance dose of 75 to 90 mg/m^2 PO SID
      2. Administration must be done cautiously because of increased risk of death and potential for side effects, such as myelosuppression, and hemorrhagic cystitis (Grundy and Barton, 2001; Mason et al., 2003; Burgess et al., 2000).
   C. Cyclosporine A
      1. Dose in dogs is 10 mg/kg PO SID or 6 mg/kg PO BID.
      2. Trough concentrations of 100 to 300 ng/mL should be maintained and serum concentrations measured every 2 to 4 weeks.
      3. Discontinue treatment when dog has been in remission for at least 2 weeks.
      4. Drugs using the cytochrome P450 pathway in the liver (e.g., diazepam, phenobarbital, erythromycin, piroxicam) may affect cyclosporine concentrations in the blood and cause vomiting, diarrhea, and anorexia.

III. Alternative treatments and supportive care include the following:
   A. Danazol *(Danocrine)* may be considered.
      1. Clinical response may take 3 weeks, so the drug is started with prednisone.
      2. Dosages in dogs range from 3 to 12 mg/kg PO BID and are gradually reduced after the animal is weaned off prednisone (Miller, 1997).
   B. Human gammaglobulin 0.5 to 1.5 g/kg IV as a 12-hour continuous infusion (CRI) may improve short-term survival (Scott-Moncrieff et al., 1997).
   C. Heparin can be administered if there is evidence of DIC or thromboembolism.
      1. Initial dose is 200 IU/kg IV followed by 75 to 125 U/kg SC TID to QID or a CRI of 15 to 20 IU/kg/hr IV.
      2. Prolongation of the activated partial thromboplastin time by 1.5 to 2.0 × normal or an increase in the activated clotting time by 15 to 20 seconds is recommended.
   D. Transfusions of whole blood, packed cells, or oxygen-containing whole blood substitutes can be initiated for severe anemia (see Chapter 71).

Monitoring of Animal

I. Measure PCV SID initially to determine response to treatment.
   A. If PCV is increasing with evidence of strong reticulocytosis, it can then be measured once or twice weekly.
   B. To assess the tapering of immunosuppressive drugs when remission is evident, measure PCV on a weekly basis.

II. Weekly monitoring of liver enzyme activity, renal function, white blood cell count and platelet count is warranted if cytotoxic drugs are used.

Erythrocytic Parasites

Definition

I. A hemolytic anemia is caused by epicellular or intracellular erythrocyte parasites.
II. RBC destruction is commonly extravascular from immune complexes attached directly to the parasite or from the exposure of novel RBC antigens that activate the immune system.

Causes

I. Hemotrophic *Mycoplasma* spp.
  A. *Mycoplasma felis* (formerly *Haemobartonella felis*) in cats
  B. *Mycoplasma canis* (formerly *Haemobartonella canis*) in dogs
II. *Babesia* spp.
  A. *Babesia canis vogeli* and *Babesia gibsoni* in dogs
  B. *Babesia felis* in cats (not reported in United States)
III. *Cytauxzoon felis*

Pathophysiology

I. Hemotrophic mycoplasmal agents are epicellular parasites of RBCs.
  A. *M. felis* is probably transmitted through a blood-sucking ectoparasite, with blood transfusions oral ingestion of infected blood, transmission to newborns by infected queens and cat bites as possible alternative modes of transmission (Woods et al., 2005).
    1. Parasitic incubation takes 7 to 30 days.
    2. Parasitemia is cyclical and can last for months.
    3. RBC destruction occurs from increased rigidity of infected RBCs, with sequestration in the spleen (Messick, 2004).
    4. Cats can recover by mounting an immune response, but a carrier state ensues.
  B. *M. canis* is transmitted by the brown dog tick, *Rhipicephalus sanguineus*, and via infected blood.
    1. The organism is nonpathogenic unless a splenectomy was done or other splenic dysfunction (neoplasia) is present.
    2. Organism is closely related to *M. felis* (Birkenheuer, 2002).
II. Babesiosis is a tick-borne disease caused by an intracellular protozoan parasite.
  A. *B. canis* is probably transmitted by the brown dog tick, *R. sanguineus.*
  B. The vector of *B. gibsoni* is unknown.
  C. Canine RBCs are infected by sporozoites in the saliva of a feeding tick.
  D. Asexual reproduction and binary fission of the organism causes RBC lysis.
  E. Incorporation of parasite antigens into the RBC surface induces opsonizing antibodies, with removal of RBCs by macrophages.
III. Cytauxzoonosis is a tick-borne protozoal disease of cats (Meinkoth and Kocan, 2005).
  A. The parasite is transmitted from bobcats to domestic cats (dead end hosts) via the tick, *Dermacentor variables*.
  B. The organism has a complex lifecycle with a tissue (schizogenous) phase followed by an intraerythrocytic phase that occurs late in infection.
  C. In the tissue phase, macrophages become engorged with schizonts obstructing vessels in major organs, resulting in severe clinical signs and rapid death.
  D. If the cat survives the tissue phase, merozoites from ruptured macrophages infect RBCs causing a severe hemolytic anemia.

Clinical Signs

I. Hemotrophic mycoplasmal agents
  A. *M. felis*
    1. Nonspecific signs of hemolytic anemia such as splenomegaly, fever, weakness and pallor are often present.
    2. Concurrent disease (FeLV), immunosuppression or splenectomy predispose to acute infection.
  B. *M. canis:* hemolytic disease in a compromised animal
II. Babesiosis
  A. *B. canis* is most common along the Gulf Coast and in the southern, central, and southwestern states.
  B. *B. gibsoni* is found worldwide and occurs most often in American Staffordshire and American pit bull terriers (Macintire et al., 2002).
  C. Dogs <1 year of age are most likely to show clinical illness.
III. Cytauxzoonosis
  A. Sudden onset of fever (39.8° to 40.1° C [103.8° to 104.2° F]), lethargy, jaundice, anorexia, dyspnea, and pallor are caused by rapid multiplication during the tissue phase.
  B. The incubation period is 5 to 20 days, with a rapid course of illness and death (approximately 5 days).
  C. Most cases are presented March to September (Birkenheuer et al., 2006; Greene, 2006).
  D. It occurs in central and southeastern states, and was recently documented in the Midatlantic states (North Carolina, South Carolina, Virginia) (Birkenheuer et al., 2006).
  E. History of tick exposure or living near a wooded area is common.

Diagnosis

I. Hemotrophic mycoplasmal agents
  A. *M. felis*
    1. Mild to severe regenerative anemia (with increased Howell-Jolly bodies, nRBCs) occurs.
    2. Autoagglutination is often present.
    3. An underlying disease (e.g., FeLV, feline immunodeficiency virus [FIV]) may cause a nonregenerative anemia.
    4. Organism is present <50% of time on RBCs owing to cyclic parasitemia and appears as small, blue-staining rods, coccoid, and ring forms.
    5. Blood smears should be made from an ear prick and in the absence of EDTA.

6. Polymerase chain reaction (PCR) tests are currently used to identify infection.

B. *M. canis*
1. Organism forms chains and Y-shaped branches of cocci across the surface of the RBC.
2. PCR tests can be used to identify the organism (Brinson and Messick, 2001).

II. Babesiosis
A. Examination of buffy coat or ear prick peripheral blood smear increases the chance of identifying low numbers of RBCs infected with 2 to 5 μm, paired, pyriform-shaped, light-blue organisms with an eccentric nucleus *(B. canis),* or 1 to 3 μm, round forms *(B. gibsoni).*
B. Indirect fluorescent antibody test and enzyme-linked immunosorbent assay (ELISA) are used for serologic screening of infection.
C. PCR tests are available for identification of the organism (Birkenheuer et al., 2005).

III. Cytauxzoonosis
A. Intraerythrocytic piroplasms, characterized by 1 to 5 μm, bluish-staining organisms with a "signet ring" or "safety pin" appearance, occur late in the disease process.
B. Cytological or histopathologic examination identifies the schizogenous tissue phase and allows for a definitive diagnosis early in the disease.
C. Normocytic, normochromic nonregenerative anemia (PCV 24 ± 5.5%) that is mild relative to the severity of icterus occurs, along with neutropenia and thrombocytopenia (Birkenheuer et al., 2006).
D. Increased serum bilirubin and bilirubinuria are common.
E. Infected cats are at increased risk for DIC.

Differential Diagnosis

I. Most RBC parasites are overdiagnosed because of stain artifacts, Howell-Jolly bodies, basophilic stippling, platelets overlying RBCs, and refractile elements on RBCs.
II. Investigate all infected animals for an underlying disease (e.g., FeLV, FIV, neoplasia).
III. If additional cytopenias are observed, test for ehrlichiosis.

Treatment

I. Hemotrophic mycoplasmal agents
A. Treat *M. felis* with doxycycline 5 mg/kg PO BID for 3 weeks or enrofloxacin 5 mg/kg PO SID (if doxycycline is not tolerated).
1. Both drugs have been used concurrently in refractory cases.
2. Blood transfusion is indicated for severe anemia.
3. Prednisone at 2 mg/kg PO BID is used to control hemolytic anemia.
4. Recovered cats remain carriers but seldom relapse with clinical disease once the HCT returns to normal.

B. Treat *M. canis* with doxycycline 5 mg/kg PO BID for 3 weeks.
1. Dogs become latent carriers.
2. Do not use treated dogs for blood transfusions.

II. Babesiosis
A. Give imidocarb dipropionate *(Imizol)* at 7.5 mg/kg IM once, but dogs may become carriers.
B. Give immunosuppressive doses of prednisone (1 to 2 mg/kg PO BID) for 2 to 3 weeks to control hemolytic anemia.
C. Supportive care may be required to correct dehydration, anemia, and acidosis.
D. *B. gibsoni* infection has been cleared using a combination of atovaquone 13.3 mg/kg PO TID with a fatty meal and azithromycin 10 mg/kg PO SID in one study (Birkenheuer et al., 2004).

III. Cytauxzoonosis
A. Mortality rate is extremely high, even with adequate therapy.
B. Supportive care (IV fluids) and heparin therapy are indicated for DIC.
C. Imidocarb dipropionate 5.0 mg/kg IM (two injections given 1 to 2 weeks apart) has had some success (Greene et al., 1999; Birkenheuer et al., 2006).

Monitoring of Animal

I. Use serial CBCs to monitor response to treatment.
II. Institute preventative ectoparasite control.

Acquired Erythrocyte Metabolic Defects

Definition

I. Indirect and direct oxidative damage to RBC membranes and the hemoglobin molecule form Heinz bodies and eccentrocytes, with secondary hemolytic anemia.
II. Lack of energy (adenosine triphosphate [ATP]) production leads to oxidative damage and the inability to reduce methemoglobin back to a nontoxic form.
III. Metabolic derangements in cats (e.g., diabetes, hyperthyroidism, and cancer) induce oxidative damage but usually are not associated with a clinically relevant anemia.

Causes

I. A variety of naturally occurring and manufactured hemolytic agents cause indirect and direct oxidative injury.
A. Certain foods: Allium family (onions and garlic)
B. Drugs and chemicals
1. Acetaminophen
2. Benzocaine-containing products
3. Propylene glycol: additive in wet cat foods
4. Methylene blue: historically used as a urinary analgesic
5. Naphthalene: moth balls
6. Propofol
7. Phenazopyridine: urinary analgesic
8. Vitamin K_3: dosages >1.25 mg/kg/day
9. DL-Methionine: for feline urologic syndrome
10. Skunk musk: contains thiols and other oxidizing agents

II. Zinc
A. Nuts and bolts

B. United States pennies minted since 1983
C. Zinc oxide dermatologic creams

III. Feline Heinz bodies
A. Normal cats may have increased numbers of Heinz bodies that are of little clinical significance.
B. Cats with metabolic derangements such as ketoacidotic diabetes mellitus, hyperthyroidism, and lymphoma have high numbers of Heinz bodies, with a minimal decrease in PCV.

IV. ATP depletion in RBCs
A. Hypophosphatemia from diabetes mellitus, hepatic lipidosis, enteral and parenteral hyperalimentation, and oral administration of phosphate binding antacids
B. Pseudohypophosphatemia from hemolysis and conjugated bilirubinemia
C. Pyruvate kinase (PK) and phosphofructokinase (PFK) deficiency (see Table 64-1)

Pathophysiology

I. Oxidative injury
A. Overwhelming oxidative insult results in the formation of one or multiple oxidative changes in the RBC.
1. Heinz body formation
a. An oxidative agent overwhelms the RBC reductive pathways, forming irreversibly denatured hemoglobin molecules (hemichromes) that aggregate to form Heinz bodies.
b. Sulfhydryl groups on the globin portion of hemoglobin can also oxidize and form Heinz bodies.
2. Eccentrocyte formation
a. Direct or indirect oxidation of RBC membrane proteins results in cross-linking.
b. The two membrane surfaces adhere to one another.
3. Methemoglobin formation
a. Severe oxidative insults overwhelm the RBCs' capability to reduce iron back to a usable state.
b. When methemoglobin predominates, transportation of oxygen is inhibited.
B. Extravascular hemolysis removes oxidatively damaged RBCs.
1. Heinz bodies cluster the intracellular portion of band 3, an integral RBC membrane protein, thereby altering the RBC surface; this is a signal for macrophages to remove the damaged RBC.
2. Damaged RBCs are less deformable and enhance removal by macrophages in the spleen.
3. Heinz bodies are "pitted" by the spleen, causing the formation of spherocytes, RBC fragments (schizocytes), or both.
C. Heinz body formation occurs in healthy cats because of higher numbers of sulfhydryl groups on the hemoglobin molecule, which potentiates oxidative injury.
1. Normal feline splenic architecture reduces the pitting function of the macrophage system (Blue and Weiss, 1981).
2. Cats with metabolic derangements have increased numbers of Heinz bodies likely caused by elevations of β-hydroxybutyrate.

II. Hypophosphatemia
A. It depletes concentrations of RBC ATP,2,3-bisphosphoglycerate, and reduced glutathione.
B. This decreases RBC deformability, increases osmotic fragility, and increases susceptibility to oxidative injury.

Clinical Signs

I. Oxidative injury is associated with the following:
A. Heinz body and eccentrocytic anemia
1. Severity of anemia is dependent on dose of offending agent and duration of oxidative injury.
2. Lethargy, pale mucous membranes, tachypnea and tachycardia are often seen.
B. Methemoglobinemia
1. Oxygen depletion can cause tachypnea, dyspnea, and tachycardia.
2. Mucous membranes, blood, and urine may appear brown.
C. Signs of underlying systemic illnesses in older cats

II. Hypophosphatemic cases often have a concurrent myopathy with cardiovascular dysfunction, weakness, ataxia, and seizures.

Diagnosis

I. Confirmation of oxidative injury
A. Heinz bodies stain as peripheral pale, refractile protuberances (Wright's stain) or as light greenish to dark blue small spherical structures (NMB stain) on the RBC.
B. Eccentrocytes have a clear region on one portion of the cell and a region of concentrated hemoglobin on the other.
C. Methemoglobinemia may be detected via two techniques.
1. Spot test involves the following:
a. One drop of animal and control blood is dropped on white filter paper and exposed to air.
b. The control spot turns red from oxygenation, whereas the methemoglobin blood remains brown, indicating methemoglobin concentration exceeds 10% of total hemoglobin (Giger, 2005; Harvey, 2000).
2. Commercial laboratories can quantify methemoglobin spectrophotometrically.

II. Documentation of hypophosphatemia
A. Serum phosphate <2.5 mg/dL can cause hemolysis in the dog and cat.
B. Clinical signs, hemolysis, or serum phosphate concentrations <1.5 mg/dL require treatment.
C. Serum phosphate concentrations often overestimate total body phosphate stores.

III. Presence of heavy metal in gastrointestinal tract on radiography

IV. Zinc toxicosis
A. Serum zinc concentrations >2.0 ppm
B. Liver biopsy zinc concentrations >70.0 ppm

Differential Diagnosis

I. Rule out other underlying causes of hemolytic anemia.
II. In an aged cat with systemic disease, the anemia may not be entirely from Heinz body production; other causes of the anemia (blood loss) must be considered.

Treatment

I. Oxidative injury (see also Chapter 127)
  A. Immediate removal of the oxidative agent
  B. Use of antioxidants
    1. Severe methemoglobinemia can be treated with one slow IV injection of methylene blue (0.2 mg/kg), although its use remains controversial, because it can aggravate oxidant-induced hemolysis (Harvey and Keitt, 1983; Giger, 2005).
    2. In cats with acetaminophen intoxication, give *N*-acetylcysteine *(Mucomyst)* at an initial dose of 140 mg/kg PO or IV, followed by seven treatments of 70 mg/kg PO TID (Giger, 2005).
    3. Dietary antioxidant supplementation is controversial, and only bioflavonoid administration (*Proanthozone* 10 mg/cat/day PO) has demonstrated any protective effect (Allison et al., 2000; Hill et al., 2001; Hill et al., 2005).
    4. Intravenous fluids, transfusions, and supportive care are required in severe cases.
II. Hypophosphatemia
  A. For severe hypophosphatemia, give sodium or potassium phosphate at 0.01 to 0.03 mmol/kg/hr IV (maximum 0.06 mmol/kg/hr), with concurrent monitoring of serum calcium and phosphorus concentrations QID to ensure calcium homeostasis is maintained (Giger, 2005).
  B. Treat mild hypophosphatemia with oral administration of skim milk or commercial diets enriched in phosphorus.

Monitoring of Animal

I. Oxidative injury
  A. A CBC and review of a peripheral blood smear are used to assess response to therapy and decreased oxidative injury.
  B. Animals with resolving methemoglobinemia have clinical resolution of hypoxia.
  C. Serum zinc concentrations can be monitored for resolution of toxicity.
  D. With early removal of inciting oxidative insult and supportive care for the hemolytic crisis, the prognosis is favorable for a full recovery.
II. Hypophosphatemia
  A. Hypocalcemia, acute renal failure, and dystrophic soft tissue calcification can occur with intravenous sodium or potassium phosphorus administration.
  B. Immediate correction with calcium gluconate and cessation of phosphate administration is recommended (Giger, 2005).
  C. If the animal survives the initial insult with appropriate treatment and adequate supportive care, and the underlying cause is corrected or managed, the prognosis can be favorable.

Microangiopathic Hemolytic Anemia

Definition

I. Mechanical damage to RBCs occurs from turbulent shear forces of blood in altered organs.
II. Fragmentation of RBCs develops from intravascular fibrin strands.

Causes

I. DIC
II. Vasculitis
III. Neoplasia: especially hemangiosarcoma
IV. Altered rheologic blood flow: heartworm disease, heart valve disease, IV catheters
V. Acanthocytosis: associated with liver disease

Pathophysiology

I. Direct erythrocyte trauma can be caused by fibrin strands produced as a consequence of DIC.
II. RBCs are fragmented, or fibrin strands cause direct intravascular hemolysis.
III. Organs altered by vasculitis, neoplasia, etc. have tortuous, narrowed vessels with high shear forces that fragment RBCs during their circulation.
IV. Acanthocytes frequently have blebs sheared off, leading to fragmentation.

Clinical Signs and Diagnosis

I. Clinical signs are variable and associated with a primary disease process.
II. Identification of the primary disease process (DIC, neoplasia, liver disease, etc.) is imperative.
III. Examination of peripheral blood smear identifies small, irregularly shaped RBC fragments (schistocytes or schizocytes).
IV. With acute DIC, thrombocytopenia is also present.

Differential Diagnosis

I. Chronic iron-deficient states
II. Zinc toxicity

Treatment

I. Identification and treatment of the underlying disease process are the primary goals.
II. Supportive care and treatment for DIC may be indicated.

Monitoring of Animal

I. Examination of a peripheral blood smear is the most sensitive method of detecting schistocytes.
II. Even a few schistocytes are significant.

Blood Loss Anemia

Definition

I. Loss of blood externally (e.g., gastrointestinal tract, urinary tract, trauma) or internally (e.g., hemoperitoneum, hemothorax) lead to anemia.
II. Blood loss can be acute or chronic.

Causes

I. Hemorrhage
  A. Vascular damage from trauma or changes in vascular architecture (neoplasia)
  B. DIC
  C. Thrombocytopenia (platelet count <30,000/μL)
  D. Congenital or acquired (rodenticide poisoning) coagulation factor deficiency
II. Iatrogenic causes
  A. Repeated phlebotomies
  B. Surgery
  C. Parasitism: hookworms, whipworms, fleas, ticks

Pathophysiology

I. Acute blood loss
  A. Acutely, total blood volume is decreased, but PCV and TP are constant, as proportional amounts of RBCs and protein are lost.
  B. Within 2 to 3 hours, blood volume is restored by movement of interstitial fluid, which dilutes RBC mass, decreases PCV, and causes hypoproteinemia.
  C. The anemia causes hypoxia that stimulates erythropoietin production by the kidney.
  D. Erythroid hyperplasia in the bone marrow takes 3 to 5 days to fully develop, although peripheral signs of regeneration (polychromasia) can be present within 48 hours.
  E. Regenerative responses can be robust unless there has been significant loss of iron.
  F. In the dog, the hemogram should return to normal within 1 to 2 weeks after an acute hemorrhagic episode.
II. Chronic blood loss
  A. Blood loss occurs over weeks to months.
  B. Early erythroid response is regenerative because of adequate body stores of iron.
  C. Over time, iron deficiency occurs with small and hypochromic RBCs produced.

Clinical Signs

I. Acute blood loss
  A. Tachypnea, tachycardia, hypovolemic shock, and death
  B. Visible signs of external hemorrhage
  C. Epistaxis, petechiation, and ecchymosis, suggesting a platelet problem
  D. Hemothorax, hemoperitoneum, and hemarthrosis, suggesting a coagulopathy
II. Chronic blood loss
  A. Clinical signs may be nonspecific, and animals may tolerate extremely low PCV values.
  B. Pale mucous membranes, exercise intolerance, fatigue, melena, and hematuria are possible.
  C. Pica is often present in iron-deficient states.
  D. Evidence of external parasitism (e.g., fleas, ticks) may be noted.

Diagnosis

I. Peripheral signs of regeneration are dependent on the time elapsed since the hemorrhage.
II. Early in the process, a normocytic, normochromic anemia may be mistaken for a nonregenerative anemia.
III. Hallmark findings are anemia and hypoproteinemia, with early evidence of bone marrow responsiveness (developing polychromasia, increasing reticulocytes) by 48 hours.
IV. Regenerative anemia (reticulocytosis, polychromasia) is seen after 3 to 5 days, with maximal response within 4 to 7 days.
V. Bone marrow responsiveness may be dampened by limited iron stores.
VI. Coagulation profile, von Willebrand factor assay, platelet count, and buccal mucosal bleeding time may determine the cause of bleeding.
VII. If blood loss is chronic, a microcytic, hypochromic anemia occurs owing to depleted iron stores.

Differential Diagnosis

I. Other causes of regenerative anemia
II. Investigation into cause of underlying blood loss

Treatment

I. Acute blood loss
  A. Administer IV fluids, hetastarch, hemoglobin solutions, or transfusions of whole blood to restore circulating blood volume (see Chapter 71).
  B. Iron supplementation is usually not necessary.
II. Chronic blood loss
  A. Treatment of the underlying disease is essential.
  B. Iron supplementation is indicated.
    1. Give ferrous sulfate 10 mg/kg PO SID in food for several weeks to months.
    2. If a gastrointestinal disorder prevents oral iron administration, give iron dextran complex (50 mg iron/mL) IM.
      a. Initially, inject a small dose is to test for hypersensitivity.
      b. Give a maximum dose of 2 mL IM SID.

Monitoring of Animal

I. A competent bone marrow requires 2 weeks to restore blood volume after acute blood loss.
II. With resolution of the primary problem and supplementation with iron, it takes months to repopulate RBC mass with normal erythrocytes in cases of chronic blood loss.

NONREGENERATIVE ANEMIAS

Definition

I. PCV is decreased with no evidence of marrow response (lack of polychromasia or reticulocytosis).
II. An anemia is nonregenerative only if it has been present >3 days, which allows enough time to allow the bone marrow to respond.

Causes

I. Nonregenerative anemia with no other accompanying cytopenia

A. Inflammation and/or chronic disease: most common causes
B. Pure red cell aplasia
   1. Immune-mediated
   2. Treatment with recombinant human erythropoietin (rhEPO)
C. Red cell hypoplasia
   1. Endocrine disorders: hypothyroidism, hypoadrenocorticism, hyperestrogenism
   2. Chronic renal insufficiency
   3. Chronic liver disease
   4. FeLV
   5. Nutritional deficiencies: iron from chronic blood loss or a milk diet in young kittens

II. Nonregenerative anemia with other accompanying cytopenias or aplastic anemia
A. Bone marrow toxicity from chemotherapy or drug reaction (Weiss, 2005a)
B. Infectious agents: FeLV, parvovirus, acute ehrlichiosis
C. Irradiation: therapeutic, environmental
D. Myelophthisic disease (Weiss, 2005b)
E. Neoplasia: primary hematopoietic, metastatic
F. Myelodysplastic syndrome (Hisasue et al., 2001)
G. Myelofibrosis (Weiss and Smith, 2002)

Pathophysiology

I. Nonregenerative anemia with no other cytopenias
A. Inflammation and/or chronic disease
   1. Pathogenesis is multifactorial and influenced by induction of inflammatory cytokines (tumor necrosis factor, interleukin [IL]-1α, IL-1β, interferon-γ).
      a. Reduced uptake of iron by gastrointestinal tract from decreased synthesis of transferrin (negative acute phase protein), and iron sequestration in bone marrow
      b. Increased erythrocyte destruction
      c. Decreased erythropoietin secretion
      d. Decreased marrow response to erythropoietin
   2. Onset can be short (hours to days).
B. Pure red cell aplasia
   1. Most often an immune-mediated destruction of an erythroid precursor or a committed erythroid stem cell (Stokol et al., 2000, Weiss, 2002)
   2. Identified in dogs treated with rhEPO for chronic renal failure (Randolph et al., 2004)
C. Red cell hypoplasia
   1. Endocrine disorders
      a. Thyroid hormones and cortisol stimulate and facilitate RBC production.
      b. An estrogen-induced substance produced by thymic stromal cells causes severe bone marrow suppression.
   2. Chronic renal insufficiency
      a. Inadequate and impaired hematopoietic response to erythropoietin
      b. Decreased RBC lifespan owing to uremic toxins and underlying inflammation
   3. Chronic liver disease
      a. Acanthocyte formation can potentiate a fragmentation anemia (schistocytes).
      b. Altered liver production of coagulation proteins can lead to hemorrhage.
   4. FeLV: erythroid stem cells and progenitors selectively killed
D. Nutritional deficiencies
   1. Iron loss occurs from hemorrhage or decreased intake.
   2. RBCs continue to divide in the bone marrow until a critical concentration of Hgb is reached, producing small RBCs that eventually lack a full complement of Hgb (microcytic, hypochromic anemia).

II. Nonregenerative anemia with other cytopenias
A. Bone marrow toxicity from chemotherapy, drug reaction or irradiation kills stem cells and/or causes necrosis of the bone marrow.
B. Infectious agents (FeLV, parvovirus, acute ehrlichiosis) preferentially attack multipotent stem cells (Shelton and Linenberger, 1995).
C. Replacement of the bone marrow by primary hematopoietic neoplastic cells (leukemia), metastatic cancer cells or fibrocytes (myelofibrosis) may also be a cause.
D. Infection with FeLV can cause aplastic anemia, a myeloproliferative disorder or myelodysplastic syndrome.

Clinical Signs

I. General signs of anemia such as pallor, weakness, or lethargy may be noted with severe anemia.
II. If anemia is mild and longstanding, there may be no clinical signs.
III. Clinical signs related to primary disease problems are usually present.

Diagnosis

I. Nonregenerative anemia with no accompanying cytopenias
A. Inflammatory diseases
   1. PCV is mildly to moderately decreased (PCV ≥25% in cats; PCV ≥20% in dogs).
   2. Other changes include decreased serum iron concentration, normal or decreased total iron-binding capacity, normal or increased serum ferritin, and normal or increased stainable iron stores in the bone marrow.
   3. Inflammatory leukogram is identified on the CBC.
B. Pure red cell aplasia (Weiss, 2002)
   1. The median age in dogs is 6.5 years and most cats are <2 years of age (Stokol and Blue, 1999).
   2. Marked nonregenerative anemia (PCV <15%), with normal leukocyte and platelet counts is a typical finding.
   3. Bone marrow aspirate reveals absence of erythroid precursors with pure red cell aplasia, although erythroid precursors with maturation arrest may be found with simple nonregenerative immune-mediated anemia.
   4. Cats are often FeLV- and FIV-negative (Stokol and Blue, 1999).

C. Red cell hypoplasia
   1. Anemias can be mild to severe.
   2. Evidence of renal disease and liver disease or dysfunction may be detected on a biochemistry profile.
   3. FeLV can cause a mild to severe, often macrocytic, (MCV >50 fL) anemia, with atypical erythrocytes (megaloblasts) in the blood and bone marrow.

D. Nutritional deficiencies
   1. Early in an iron-deficient state, PCV may be mildly decreased, MCV is often normal, and there is regeneration with low numbers of microcytes in the circulation.
   2. Over time, high numbers of small RBCs are seen with decreased MCV and hypochromic cells.
   3. With severe iron depletion, a microcytic, hypochromic anemia occurs and is accompanied by schistocyte formation and concurrent fragmentation anemia.

II. Nonregenerative anemia with other cytopenias (Weiss et al., 1999)
   A. Anemias are commonly severe (PCV <15%), with no evidence of regeneration.
   B. Leukopenia and/or thrombocytopenia are common.
   C. Dacryocytes (tear-shaped RBCs) are seen with myelofibrosis.
   D. Bone marrow aspirate and core biopsy reveal pancytopenic aplasia, either as a primary lesion or from a space-occupying lesion (fibroblasts, neoplasia).

Differential Diagnosis

I. A healthy bone marrow with inadequate time to respond to anemia
II. Evidence of underlying chronic disorder

Treatment and Monitoring

I. Nonregenerative anemia with no accompanying cytopenia
   A. Identification and resolution of the underlying disorder are paramount.
   B. Iron administration is not beneficial in anemias of chronic inflammatory disease.
   C. Pure red cell aplasia may respond to immunosuppressive therapy with prednisone or prednisone and cyclophosphamide, with recovery taking weeks to months (Stokol and Blue, 1999; Weiss, 2002).
   D. If a true iron-deficient state exists, give ferrous sulfate 10 mg/kg PO SID in food for several weeks to months.
   E. If a gastrointestinal disorder prevents oral iron administration, give iron dextran complex (50 mg iron/mL) IM.
      1. A small dose is initially injected to test for hypersensitivity.
      2. A maximum dose of 2 mL is given IM SID.
   F. With hyperestrogenism, some dogs recover in 30 days but others develop severe, chronic aplasia.

II. Nonregenerative anemias with other cytopenias
   A. Treat the underlying cause and give supportive care.
   B. Prognosis is usually poor.

POLYCYTHEMIA

Definition

I. Increased circulating numbers of RBCs from physiologic changes or neoplasia
II. Classification of polycythemia
   A. Relative
      1. True RBC mass is unchanged, although PCV, Hgb concentration, and RBC counts are increased.
      2. Decreased plasma volume or splenic contraction causes erythrocytosis.
   B. Absolute
      1. RBC mass: truly increased, with elevated PCV, Hgb concentration, RBC count
      2. Primary or polycythemia vera (PV): a myelodysplastic syndrome characterized by clonal proliferation of neoplastic erythroid cells and high numbers of normal-appearing RBCs in the circulation (see Chapter 66)
      3. Secondary: physiologically appropriate or inappropriate

Causes

I. Relative polycythemia is the most common type and is caused by dehydration or fluid shifts that decrease plasma volume.
II. Physiologically appropriate erythrocytosis (increased PCV, in conjunction with decreased partial pressure of oxygen in arterial blood (Po_2) occurs in response to hypoxic conditions, such as congenital or acquired right-to-left heart shunts, cardiac failure, chronic pulmonary disease, hyperthyroidism, and high altitude.
III. Physiologically inappropriate erythrocytosis (increased PCV, normal Po_2) may be caused by renal cysts, renal neoplasia, metastatic diseases of the kidney, and nonrenal tumors that produce an erythropoietin-like substance.
IV. Primary polycythemia is a well-differentiated myeloproliferative disorder.

Pathophysiology

I. With relative polycythemia, dehydration causes an increase in blood components from decreased plasma volume.
II. Pain or excitement causes epinephrine-induced splenic contraction.
III. Appropriate secondary erythrocytosis occurs from increased production of erythropoietin that is triggered by tissue hypoxia.
IV. Inappropriate secondary erythrocytosis occurs when production of erythropoietin or an erythropoietin-like substance is triggered in the absence of hypoxia.
V. PV is a neoplastic proliferation of erythroid precursors that is erythropoietin independent and results in increased numbers of RBCs.

Clinical Signs

I. Relative polycythemia
   A. History of vomiting, diarrhea, or both
   B. Tacky or dry mucous membranes

II. Splenic contraction
   A. Commonly a history of excitement, anxiety, or pain
   B. More common in breeds with higher normal PCVs: greyhound, Afghan hound, saluki, whippet
III. Absolute polycythemia
   A. Congestion and deep red color of mucous membranes may be detected.
   B. Cyanosis may be present.
   C. Lethargy, blindness, and seizures may develop from decreased vascular perfusion and venous return to the heart.

Diagnosis

I. Secondary and appropriate polycythemia
   A. Reconfirm that erythrocytosis is present.
   B. Decreased Po_2 (<92% or 60 mm Hg) is required to trigger erythrocytosis (Campbell, 1990; Thrall, 2004).
   C Perform diagnostic imaging for pulmonary and heart diseases.
   D. Serum erythropoietin is commonly increased.
II. Secondary and inappropriate polycythemia
   A. Increased concentrations of erythropoietin are documented with normal Po_2 (>97%).
   B. Perform diagnostic imaging of the kidneys and obtain renal cytology or biopsy.
   C. With primary PV, the PCV is commonly >70%, with a normal Po_2.
      1. Diagnosis requires eliminating all other causes of erythrocytosis.
      2. Bone marrow aspirate and core biopsy identify erythroid hyperplasia with a normal maturation sequence.
      3. Serum erythropoietin is commonly normal or decreased.

Differential Diagnosis

I. Ensure erythrocytosis is a repeatable finding.
II. Rule out dehydration, as it is the most common cause of an increased PCV.

Treatment

I. Relative polycythemia: treatment of underlying disease and correction of dehydration
II. Absolute polycythemia
   A. Treat the underlying disease process.
   B. Phlebotomy is usually not indicated because the animal is hypoxic.
III. Primary PV
   A. Treat with repeated phlebotomies to bring PCV into the high-normal range.
   B. Remove 20 mL/kg blood, which results in a PCV decrease of approximately 15%.
   C. Give saline or plasma expanders to maintain circulating blood volume.
   D. With Primary PV, iron supplementation is often necessary.
   E. Oral hydroxyurea is indicated if phlebotomy is needed more often than every 4 to 8 weeks (Campbell, 1990).
      1. Dose in dogs is 15 mg/kg PO SID until the PCV normalizes.
      2. Check PCV every 7 to 14 days until normal and then every 4 months.

Monitoring of Animal

I. Monitor for hemostatic abnormalities, such as thrombosis and hemorrhaging.
II. PCV is monitored every 2 weeks, depending on the cause of the erythrocytosis and resolution of the underlying problem.
III. Many animals respond to treatment and survival time can be >1 year in most cases.

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CHAPTER 65

Disorders of White Blood Cells

Laura I. Boone

GENERAL CONSIDERATIONS

Leukogram Evaluation

I. The complete blood count (CBC) evaluates white blood cells (WBCs [leukocytes]), red blood cells (RBCs [erythrocytes]), and platelets.
II. The leukogram is composed of total, relative, and absolute differential leukocyte counts and morphology evaluation.
  A. Absolute differential leukocyte counts (total WBC × WBC type relative percent) are the preferred evaluation method and result in fewer interpretation errors.
  B. Canine and feline leukocytes are present in the following numeric order of prevalence in healthy animals: neutrophils, lymphocytes, monocytes, eosinophils, and basophils.
III. Published total leukocyte counts in health are 6000 to 17,000/μL in dogs and 5500 to 19,500/μL in cats (Mahaffey, 2003).
  A. These numbers are provided as guidelines; use the reference ranges provided by each laboratory to interpret the leukogram.
  B. Interpretation of the leukogram is based on the absolute leukocyte count (reported as numbers/μL) rather than the relative percentages.
  C. The absolute numbers of the various WBCs are altered by physiological, pathologic, or pharmacological processes.
  D. Increased numbers of leukocytes are denoted by the addition of the suffix "ilia" or "osis."
    1. *Neutrophilia* is defined as absolute neutrophil counts >12,000/μL in dogs and >12,500/μL in cats; it is the most common contributor to leukocytosis.
    2. *Monocytosis* is defined as absolute monocyte counts >1400/μL in dogs and >850/μL in cats.
    3. *Lymphocytosis* is defined as absolute lymphocyte counts >2900/μL in dogs and >7000/μL in cats.
    4. *Eosinophilia* is defined as absolute eosinophil counts >1300/μL in dogs and >750/μL in cats; it generally occurs with hypersensitivity reactions or parasitic infections.
    5. *Basophilia* is defined as absolute basophil counts >140/μL in dogs and >200/μL in cats.
    6. Basophilia is rare, is often accompanied by eosinophilia, and is associated with parasitic diseases (particularly dirofilariasis); hypersensitivity reactions; inflammation; neoplasia (basophilic leukemia, mast cell tumor/mastocytosis, lymphomatoid granulomatosis, essential thrombocythemia); and drug reactions (heparin, penicillin).
  E. Decreased numbers of leukocytes are denoted by the addition of the suffix "penia" or "cytopenia."
    1. *Neutropenia* is defined as absolute neutrophil counts of <2900/μL in dogs and <2500/μL in cats.
    2. *Lymphopenia* is defined as absolute lymphocyte counts <400/μL in dogs and <1500/μL in cats.
    3. Monocytopenia and basopenia occur infrequently and are of no clinical importance.
    4. Eosinopenia and basopenia are difficult to define, because the lower limit of normal in dogs and cats typically extend to 0/μL.
      a. Eosinopenia may occur with acute inflammation or infection.
      b. Eosinopenia also may follow endogenous corticosteroid release secondary to stress, trauma, or hyperadrenocorticism, and may be associated with exogenous corticosteroid or adrenocorticotropic hormone (ACTH) administration.
IV. Assessment of WBC morphology is extremely important.
  A. Altered WBC morphology and the presence of cytoplasmic inclusions are important indicators of physiological abnormalities or disease (Tables 65-1 and 65-2).
  B. Abnormal morphology does not always indicate abnormal or compromised cell function; normal morphology does not guarantee normal cell function.
  C. Characteristic and cyclical patterns of changes in WBC numbers over time are unique to certain disorders (e.g., canine cyclic hematopoiesis).

Peripheral Blood Neutrophil Pools

I. Neutrophils in peripheral blood randomly disperse into two interchangeable populations—the circulating and the marginated pools.
II. The circulating pool includes neutrophils located within the vasculature that are sampled with routine blood collection and quantified in the CBC.
III. The marginated pool is composed of neutrophils that are loosely attached to capillary and venule endothelial surfaces

TABLE 65-1

Morphological Alterations in Leukocytes

ALTERATION	CELL TYPE AFFECTED	KEY MORPHOLOGICAL FEATURE(S)	INTERPRETATION	CAUSES	REFERENCES
Hypersegmentation	Neutrophils	≥5 nuclear lobes	Increased vascular transit time	Increased endogenous (protracted stress, hyperadrenocorticism) or exogenous corticosteroid administration	Schultze (2000)
Hyposegmentation	Neutrophils	Round, bean- or horseshoe-shaped nuclei	Cellular immaturity or failure of the nucleus to segment (congenital or acquired)	Left shift: release of immature neutrophils or Pelger-Huët anomaly	Kociba (2000), Schultze (2000)
Toxic change	Neutrophils	Cytoplasmic abnormalities: Döhle bodies (basophilic, pale, angular, peripherally located inclusions), vacuolation, basophilia, toxic granulation, and/or giant neutrophils	Accelerated production of neutrophils and decreased neutrophil maturation time in the marrow Affected cells lack some functions (guarded prognosis) Can be a sensitive diagnostic aid for inflammation, systemic disease, or drug toxicity, as they may precede changes in neutrophil number and appearance of immature forms	Severe inflammation from localized or systemic infection, endotoxemia, sterile inflammation, or drug toxicity	Aroch et al. (2005)
EDTA artifact	Neutrophils	Cytoplasmic vacuolization, membrane irregularity, and pyknosis	Artifact (must be differentiated from toxic change)	Prolonged exposure to EDTA (delayed blood smear preparation)	Gossett and Carakostas (1984)
Reactive lymphocytes	Lymphocytes	Increased cell size, deeply basophilic cytoplasm, perinuclear clear zone, aggregated chromatin, and indistinct nucleoli	Antigenic stimulation	Many causes; occurs secondary to inflammation, infection, or recent immunization	Kociba (2000)
Large granular lymphocytes	Lymphocytes	Variable numbers of azurophilic to eosinophilic cytoplasmic granules Dogs: small granules clustered near the nucleus Cats: larger, evenly dispersed granules	Neoplasia or inflammation	Neoplasia or inflammation	Weider et al. (1991)

EDTA, Ethylenediamine tetraacetic acid.

TABLE 65-1

Morphological Alterations in Leukocytes—*cont'd*

ALTERATION	CELL TYPE AFFECTED	KEY MORPHOLOGICAL FEATURE(S)	INTERPRETATION	CAUSES	REFERENCES
Lymphocytes in Sézary syndrome	Lymphocytes	Large circulating neoplastic lymphocytes with intensely cleaved nuclei with prominent nucleoli	Neoplasia	Neoplasia	Foster et al. (1997)
Plasma cells	Lymphocytes	Characterized by basophilic cytoplasm, eccentrically placed nucleus with condensed chromatin, and prominent perinuclear Golgi zone	Rarely found in circulation	Antigenic stimulation from infection, inflammation, hypersensitivity reactions, systemic disease	Schultze (2000)
Degranulation or vacuolation of eosinophils (dogs)	Eosinophils	Complete or partial clearing of eosinophilic staining of granules	Artifact	Unknown, but not indicative of injury or abnormal function	Schultze (2000)

TABLE 65-2

Leukocyte Cytoplasmic Inclusions

INCLUSION	CELL(S) AFFECTED	KEY MORPHOLOGIC FEATURES	REFERENCES
Bacteria	Neutrophils, monocytes, eosinophils (rarely)	Dogs, cats: positively or negatively staining rods or cocci	Tvedten et al. (1990)
Hepatozoon spp. gametocytes	Neutrophils or monocytes	Dogs: oval, unstained to pale blue basophilic inclusions (5-10 μm)	Barton et al. (1985), Panciera et al. (2000)
Canine distemper virus	Leukocytes (particularly lymphocytes), red blood cells	Dogs: round to irregularly shaped, homogeneous, blue-gray to magenta, intracytoplasmic inclusions	McLaughlin et al. (1985)
Histoplasma capsulatum	Neutrophils, monocytes, eosinophils (rarely)	Dogs, cats: round to oval, uniform, basophilic yeast (2-4 μm) with dark central area and clear halo	Clinkenbeard et al. (1988a, 1988b)
Ehrlichia spp. morulae	*E. ewingii, E. equi,* or human granulocytotropic *Ehrlichia* spp.: neutrophils and eosinophils *E. canis:* monocytes, lymphocytes	Dogs: magenta to basophilic inclusion (2-6 μm) resembling a mulberry	Cowell et al. (1988), Rikihisa (2000)
Leishmania spp. amastigotes	Neutrophils	Dogs: 1-2 small, round to oval organisms with oval nucleus, basophilic ventral kinetoplast, and light blue cytoplasm	Schultze (2000)
Hemosiderin	Neutrophils and monocytes	Dogs: brown crystals (1-4 μm) that stain positively with Prussian blue stain; reported with immune-mediated hemolytic anemia	Gaunt and Baker (1986)

and, therefore, are not sampled during blood collection procedures.

Bone Marrow Neutrophil Production and Kinetics

I. Neutrophil production and maturation occurs in the bone marrow, with precursors progressing through stages, such as myeloblast, progranulocyte, myelocyte, metamyelocyte, band neutrophil, and mature segmented neutrophil.
II. Neutrophil precursors are divided into two pools based on their mitotic capabilities.
   A. The proliferation-mitotic pool is composed of myeloblasts, progranulocytes, and myelocytes.
   B. The storage-maturation pool (no cell division) is composed of metamyelocytes, band, and segmented neutrophils.
III. The marrow transit time (myeloblast to released segmented neutrophils) is 3.5 to 6 days.

ALTERATIONS IN WHITE BLOOD CELL NUMBERS AND MORPHOLOGY

Neutrophilia

See Box 65-1.

Neutropenia

Definition

I. Neutropenia is characterized by a neutrophil count below the lower limit of the reference range (<2900/μL in dogs and <2500/μL in cats) (Mahaffey, 2003).
II. It is common in dogs and cats and is often accompanied by leukopenia.
III. Neutropenia accompanied by anemia and thrombocytopenia indicates pancytopenia and is suggestive of bone marrow injury or effacement.

Causes and Pathophysiology

I. General mechanisms of neutropenia consist of decreased bone marrow production and tissue utilization exceeding marrow production and release (Box 65-2).
II. Neutropenia can be secondary to increased margination, sequestration, hemophagocytic syndrome, and immune-mediated damage to circulating neutrophils or granulocytic precursors in the bone marrow.
III. Neutropenia can be a negative prognostic indicator associated with increased mortality; the more severe the neutropenia, the greater the risk of infection (Aroch et al., 2005).
IV. Neutropenia resulting from tissue utilization in excess of marrow production can occur with severe, localized bacterial infections involving body cavities, the uterus, the respiratory or gastrointestinal (GI) tracts, or during generalized septicemia.
V. Neutropenia can be associated with neutrophil toxicity.
VI. Marrow suppression resulting in decreased leukocyte production may arise with the following:

Box 65-1

Causes of Neutrophilia*

Causes	Species Affected
Inflammation	
Infectious agents	
Bacteria: numerous species	Dog, cat
Fungi: numerous species	Dog, cat
Rickettsia: Rocky Mountain spotted fever	Dog
Viruses: canine distemper, feline rhinotracheitis, feline calicivirus	Dog, cat
Parasites: numerous species	Dog, cat
Protozoa: *Hepatozoon americanum*	Dog
Tissue necrosis	
Thrombosis/infarction	Dog, cat
Metabolic injury: uremia	Dog, cat
Physical injury: surgery, trauma, burns, frostbite	Dog, cat
Neoplasia	Dog, cat
Immune-mediated diseases	
Immune-mediated hemolytic anemia	Dog, cat
Polyserositis	Dog, cat
Polymyositis	Dog, cat
Rheumatoid arthritis	Dog, cat
Systemic necrotizing vasculitis	Dog (beagle)
Lupus erythematosus	Dog, cat
Physiologic leukocytosis: epinephrine release resulting from excitement, fear, exercise	Dog, cat
Corticosteroid-induced leukocytosis: increased endogenous or exogenous steroids, ACTH administration	Dog, cat
Neoplasia	
Leukemia: several types	Dog, cat
Paraneoplastic syndrome: benign and malignant tumors	Dog, cat
Genetic disorders: CD11b/CD18 leukocyte adhesion deficiency	Dog (Irish setter)
Drug administration: recombinant human or canine colony-stimulating factor	Dog, cat
Drug toxicity: early estrogen toxicosis	Dog
Miscellaneous	
Hemolysis	Dog, cat
Hemorrhage	Dog, cat
Toxemia/toxicity	
Blue-green algae toxicity	Dog
Botulism	Dog, cat
Endotoxemia	Dog, cat
Uremia	Dog, cat

ACTH, Adrenocorticotropic hormone.
*Absolute neutrophil counts >12,000/μL in dogs and >12,500/μL in cats (Mahaffey EA: Quality control, test validity, and reference values. p. 331. In Latimer KS, Mahaffey, Prasse KW (eds): Duncan and Prasse's Veterinary Laboratory Medicine: Clinical Pathology. 4th Ed. Iowa State University Press, Ames, 2003).

Box 65-2

Causes of Neutropenia*

Causes	Species Affected
Tissue utilization in excess of bone marrow release	
Infectious agents	
Acute endotoxemia, septicemia	Dog, cat
Bacteria: numerous species	Dog, cat
Rickettsia: *Ehrlichia canis*	Dog
Viruses: canine parvovirus, canine distemper virus, infectious canine hepatitis, FeLV, FIV	Dog, cat
Parasites: *Babesia canis*	Dog
Decreased bone marrow production	
Drug toxicity	
Estrogen toxicosis: iatrogenic, prolonged estrus, or Sertoli cell tumor–induced hyperestrogenism	Dog
Griseofulvin	Cat
Chloramphenicol	Cat
Idiosyncratic drug reactions	
Cephalosporins	Dog, cat
Noxzema skin creme	Dog, cat
Phenylbutazone	Dog
Trimethoprim-sulfadiazine	Dog
Phenobarbital	Dog
Thiacetarsamide	Dog
Methimazole	Cat
Myelodysplasia and myeloproliferative diseases	Dog, cat
Lymphoproliferative disease	Dog, cat
Myelophthisis	
Neoplasia: metastatic carcinoma	Dog
Granulomatous inflammation: disseminated *Histoplasma capsulatum*	Dog, cat
Myelofibrosis and osteopetrosis	Dog
Bone marrow necrosis	Dog, cat
Radiation	Dog, cat
Shifts from the circulating to marginated neutrophil pool	
Endotoxemia	Dog, cat
Anaphylaxis	Dog, cat
Congenital disorders	
Cyclic hematopoiesis	Dog (gray-coated collie)
Inherited vitamin B_{12} malabsorption	Dog (giant schnauzer)
Destruction/sequestration of neutrophils	
Immune-mediated neutropenia	Dog
Hemophagocytic syndrome	Dog

FeLV, Feline leukemia virus; *FIV,* feline immunodeficiency virus.
*Absolute neutrophil counts <2900/μL in dogs and <2500/μL in cats (Mahaffey EA: Quality control, test validity, and reference values. p. 331. In Latimer KS, Mahaffey, Prasse KW (eds): Duncan and Prasse's Veterinary Laboratory Medicine: Clinical Pathology. 4th Ed. Iowa State University Press, Ames, 2003)

A. Total body ionizing radiation
B. Myelosuppression with chemotherapeutic agents (see Chapter 72)
   1. Examples include cyclophosphamide, daunomycin, dimethyl myleran, doxorubicin, 6-thioguanine, azathioprine, cisplatin, carboplatin, chlorambucil, melphalan, methotrexate, mitoxantrone, and combination therapy with vincristine and L-asparaginase.
   2. The marrow neutrophil proliferation-mitotic pool is most sensitive to chemotherapeutics.
      a. Differentiated cells in the maturation-storage pool are unaffected, so release of mature neutrophils continues for 5 to 10 days.
      b. A neutropenic nadir often occurs during these 5 to 10 days as a result of decreased marrow production and the short (6-hour) lifespan of the circulating neutrophil.
   3. Chemotherapy-induced thrombocytopenia occurs in 1 to 2 weeks (circulating lifespan of platelets is 10 days).
   4. Anemia is uncommon.
C. Estrogen toxicosis in dogs
   1. Sources of estrogen exposure include the following:
      a. Diethylstilbestrol or estradiol cyclopentylpropionate therapy used for mismating, urinary incontinence, or infertility in females may be a cause.
      b. With exogenous estrogen therapy for perianal gland tumors in males, pancytopenia can occur with the neutropenia.
      c. Excessive endogenous estrogen with interstitial and Sertoli cell tumors (males) and granulosa cell tumors (females) can also be associated with pancytopenia.
   2. Sequential hematological abnormalities in canine estrogen toxicosis consist of the following:
      a. Immediate leukocytosis followed by rapid leukopenia
      b. Thrombocytosis followed by rapid thrombocytopenia
      c. Slow development of anemia and pancytopenia within 1 month
D. Prolonged (14 to 21 days) chloramphenicol therapy in cats: leukopenia and neutrophils with Döhle bodies
E. Idiosyncratic drug reactions with either neutropenia or pancytopenia
   1. Antibiotics: cephalosporins, trimethoprim-sulfadiazine
   2. Thiacetarsamide
   3. Griseofulvin
   4. Phenobarbital
   5. Phenylbutazone
   6. Albendazole
   7. Captopril
   8. Medicated skin cream *(Noxzema)*
   9. Methimazole
   10. Trimeprazine tartrate

F. Infectious causes of neutropenia or pancytopenia (see Chapters 112 and 115)
   1. Parvovirus infection of dogs and cats (feline panleukopenia)
   2. Feline leukemia virus (FeLV)
   3. Feline immunodeficiency virus (FIV)
   4. Canine ehrlichiosis

VII. Neutropenia or pancytopenia from significantly decreased hematopoiesis can result from the following:
   A. Reduction or complete effacement of the marrow space with bone marrow necrosis (rare) or myelophthisic disease
   B. Causes of myelophthisic disease in dogs and cats
      1. Myelofibrosis (see Chapter 66)
      2. Osteopetrosis: rare
      3. Myeloproliferative diseases or myelodysplasia (see Chapter 66)
      4. Multicentric lymphoma (lymphosarcoma [LSA]) (see Chapter 69)
      5. Disseminated granulomatous disease (e.g., systemic mycoses)
      6. Metastatic neoplasia

VIII. Neutrophils shift rapidly from the circulating to marginated pool, especially during episodes of anaphylaxis or endotoxemia in dogs (pseudoneutropenia).

IX. Hemophagocytic syndrome is a rare event.
   A. Hematology findings consist of cytopenias involving two or more of the hematologic cell lines and circulating fragments of erythrocytes.
   B. Bone marrow aspirate reveals increased numbers of macrophages containing phagocytized hematopoietic precursors, and predominantly erythroid precursors, with fewer neutrophils and platelets.

X. Uncommon causes of neutropenia include the following:
   A. Immune-mediated neutropenia can be idiopathic, drug-related, or associated with other immune-mediated diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus).
      1. Presumptive diagnosis can be made with clinical response to immunosuppressive doses of corticosteroids and with termination of therapy in cases of drug-related neutropenia.
      2. Definitive diagnosis requires demonstration of antineutrophil antibodies, which is difficult owing to fragility of the neutrophils and potential release of intracellular enzymes.
   B. Canine cyclic hematopoiesis, a genetic disorder specific for gray-coated collies, is characterized by continuous, abnormal 2- to 4-day cycles of neutropenia.
      1. Affected dogs exhibit recurrent infections by 8 weeks of age.
      2. Death usually occurs by approximately 3 years of age from septicemia or systemic amyloidosis.
   C. Inherited vitamin B_{12} (cobalamin) malabsorption in giant schnauzers results in failure to express the necessary receptor for normal intestinal cobalamin absorption.
      1. Cobalamin deficiency induces maturation abnormalities in hematopoietic precursors.
      2. Characteristic findings consist of neutropenia, neutrophil hypersegmentation, nonregenerative anemia, nucleated red blood cells (nRBCs) with nuclear:cytoplasmic asynchrony, thrombocytosis, and rare giant platelets.

Diagnosis

I. Perform routine CBCs to identify and monitor neutropenia and concurrent hematological abnormalities.

II. Question clients regarding the administration of chemotherapeutics, estrogen, or other hematotoxic compounds.

III. Serological and other tests are used for diagnosis of canine and feline viral and ehrlichial diseases (see Chapters 112 and 115).

IV. Bone marrow evaluation is a useful procedure in cases of neutropenia when the aforementioned causes of neutropenia or pancytopenia have been eliminated, and may reveal the following:
   A. Myeloproliferative disease: blast cells in circulation and in bone marrow samples; cytochemical stains required for definitive diagnosis (see Chapter 66).
   B. Myelofibrosis: obliteration of marrow spaces by increased fibrous connective tissue
   C. Myelodysplasia: peripheral cytopenias to pancytopenia, abnormal cellular morphology and/or maturation, and hypercellular bone marrow with or without blast cells
   D. Identification of bone marrow abnormalities in inherited vitamin B_{12} deficiency: decreased cellularity, hypersegmented neutrophils, giant neutrophil precursors, and erythroid dysplasia

V. Measure serum cobalamin concentrations in giant schnauzers with suspected inherited cobalamin malabsorption.

Treatment

I. Consider discontinuing or delaying chemotherapy in animals with neutrophil counts of <1000/μL, and starting prophylactic broad-spectrum antibiotics, because they are predisposed to sepsis (Kociba, 2000).

II. Lithium carbonate (11 mg/kg PO BID for 6 weeks) may reverse marrow hypoplasia and pancytopenia secondary to estrogen toxicosis in dogs (Hall, 1992).

III. Lithium carbonate at 21 to 26 mg/kg/day PO may partially alleviate neutropenia of canine cyclic hematopoiesis, but can have toxic effects at this latter dose (Campbell, 1985).

IV. Recombinant human granulocyte colony-stimulating factor (G-CSF, 2.5 to 10 μg/kg/day SC for 3 to 5 days) can be used for short-term management of neutropenia in dogs and cats, but neutralizing antibodies develop in cats and dogs within 14 and 21 days, respectively; therefore, long-term use is not recommended (Ogilvie, 2000; Phillips et al., 2005).

V. Parenteral administration of 1 mg cobalamin once monthly has resulted in temporary remission; no improvement occurs with oral therapy (Fyfe, 2000).

VI. Bone marrow transplantation and lentivirus-mediated G-CSF therapy have been used experimentally to treat or lessen the severity of canine cyclic hematopoiesis (Lothrop et al., 1988; Yanay et al., 2003).

Monitoring of Animal

I. Prognosis for recovery from neutropenia is dependent on the cause and reversibility of bone marrow damage.
II. Neutrophil counts usually rebound when chemotherapeutic agents are discontinued.
III. Recovery following estrogen toxicosis is possible but variable.
   A. Recovery may occur within 3 months.
   B. Pancytopenia may be permanent in some cases.
IV. Neutropenia associated with idiosyncratic drug reactions may resolve within 1 to 2 weeks after therapy is discontinued.
V. Neutropenia induced by infectious diseases carries a fair (FeLV) to good (ehrlichiosis) prognosis.
VI. Neutropenia associated with bone marrow necrosis and myelophthisic disease has a guarded prognosis, but recovery is possible with successful treatment of certain underlying causes, such as lymphoma.

Lymphocytosis

See Box 65-3.

Lymphopenia

See Box 65-4.

Monocytosis

See Box 65-5.

Box 65-3

Causes of Lymphocytosis*

Causes	Species Affected
Physiological leukocytosis: epinephrine response	Dog, cat
Chronic antigenic stimulation	
Infectious agents	
Bacteria: brucellosis	Dog
Mycoses: various species	Dog, cat
Rickettsia: *Ehrlichia canis,* Rocky Mountain spotted fever	Dog
Viruses: feline leukemia virus	Cat
Vaccine-induced (acute response)	Dog, cat
Hypoadrenocorticism	Dog
Lymphoid neoplasia	
Acute or chronic lymphocytic leukemia	Dog, cat
Lymphoma	Cat
Thymoma	Cat

*Absolute lymphocyte counts >2900/μL in dogs and >7000/μL in cats (Mahaffey EA: Quality control, test validity, and reference values. p. 331. In Latimer KS, Mahaffey, Prasse KW (eds): Duncan and Prasse's Veterinary Laboratory Medicine: Clinical Pathology. 4th Ed. Iowa State University Press, Ames, 2003).

Eosinophilia

See Box 65-6.

Circulating Mast Cells

Definition

Mast cells are rarely seen in peripheral blood smears, but can occur with certain conditions.

Causes

I. Inflammatory conditions (dogs): allergic dermatitis, trauma, regenerative anemia, parvovirus infection, or non–mast cell neoplasia.

Box 65-4

Causes of Lymphopenia*

Causes	Species Affected
Corticosteroid-induced	
Increased endogenous corticosteroid levels	
Acute severe stress: inflammation, infection, trauma	Dog, cat
Hyperadrenocorticism	Dog
Exogenous corticosteroid or ACTH administration	Dog, cat
Septicemia or endotoxemia	Dog, cat
Acute viral infections	
FeLV, panleukopenia, FIV	Cat
Canine parvovirus, coronavirus, distemper, infectious hepatitis	Dog
Loss of lymph fluid	
Chylothorax (see Chapter 19)	Dog, cat
Chyloperitoneum	Dog, cat
Lymphangiectasia	Dog, cat
Gastrointestinal disease	
Protein-losing enteropathy	Dog
Ulcerative or granulomatous enteritis	Dog, cat
Neoplasia	
Gastrointestinal lymphoma	Dog, cat
Enteric tumors	Dog, cat
Lymph node effacement	
Granulomatous inflammation: numerous etiologies	Dog, cat
Multicentric lymphoma	Dog, cat
Hereditary disorders	
Severe combined immunodeficiency	Dog†
Treatment-induced	
Immunosuppressive drugs	Dog, cat
Chemotherapeutic drugs	Dog, cat
Radiation	Dog, cat

ACTH, Adrenocorticotropic hormone; *FeLV,* Feline leukemia virus; *FIV,* Feline immunodeficiency virus.
*Absolute lymphocyte counts <400/μL in dogs and <1500/μL in cats (Mahaffey EA: Quality control, test validity, and reference values. p. 331. In Latimer KS, Mahaffey, Prasse KW (eds): Duncan and Prasse's Veterinary Laboratory Medicine: Clinical Pathology. 4th Ed. Iowa State University Press, Ames, 2003).
†Basset hound, Parson (Jack) Russell terrier, Cardigan Welsh corgi.

Box 65-5

Causes of Monocytosis*

Causes	Species Affected
Acute or chronic inflammation	
Protozoal, fungal, or parasitic diseases: numerous species	Dog, cat
Bacterial diseases, particularly intracellular organisms such as *Mycobacterium* spp. or *Brucella* spp.	Dog, cat
Viral diseases: feline infectious peritonitis, FeLV	Cat
Foreign-body reaction	Dog, cat
Tissue necrosis	Dog, cat
Immune-mediated diseases: hemolytic anemia, arthritis	Dog
Pyogranulomatous inflammation	Dog, cat
Neoplasia-associated inflammation	Dog, cat
Hemolysis	Dog, cat
Corticosteroid-induced leukocytosis	Cat
Rebound from neutropenia (may be first indicator of recovery)	
Recovery from neutropenia with inflammation, infection, systemic disease	Dog, cat
Congenital cyclic hematopoiesis of gray-coated collies	Dog
Recovery from feline panleukopenia or canine parvovirus	Dog, cat
Neoplasia	
Monocytic leukemia	Dog, cat
Myelomonocytic leukemia	Dog, cat
Malignant histiocytosis	Dog

FeLV, Feline leukemia virus.
*Absolute monocyte counts >1400/μL in dogs and >850/μL in cats (Mahaffey EA: Quality control, test validity, and reference values. p. 331. In Latimer KS, Mahaffey, Prasse KW (eds): Duncan and Prasse's Veterinary Laboratory Medicine: Clinical Pathology. 4th Ed. Iowa State University Press, Ames, 2003).

II. Canine or feline metastatic mast cell neoplasia
III. Mast cell leukemia
  A. Myeloproliferative disease
  B. Atypical mast cells in circulation and in aspirate or biopsy samples from bone marrow, liver, and spleen

Diagnosis

I. Occasional mast cells are seen in peripheral blood smears.
II. Differentiation of mast cell leukemia from other conditions requires examination of cellular morphological characteristics, cytochemical staining, and histological examination of tissues.

Treatment

I. When mast cells are seen in peripheral blood smears, the underlying disease should be identified and treated.
II. See Chapter 70 for further discussion of treatment of mastocytosis.

Box 65-6

Causes of Eosinophilia*

Causes	Species Affected
Parasitic disease	
Heartworm disease	Dog, cat
Nematodes: numerous species	Dog, cat
Trematodes: various species	Dog, cat
Ectoparasites	Dog, cat
Protozoa: *Babesia canis, Hepatozoon americanum, H. canis, Pneumocystis carinii*	Dog, cat
Mycoses: *Cryptococcus neoformans, Aspergillus fumigatus, Pythium* spp., *Blastomyces dermatitidis*	Dog, cat
Immediate or delayed hypersensitivity reactions	
Oral granuloma	Dog
Gastrointestinal eosinophilic granuloma	Dog
Ulcerative gastroenteritis	Dog, cat
Pulmonary granuloma	Dog
Pulmonary infiltrates with eosinophilia	Dog
Asthma	Cat
Panosteitis	Dog
Pyometra	Dog
Atopy	Cat
Feline eosinophilic granuloma complex	Cat
Food hypersensitivity	Cat
Eosinophilic keratitis	Cat
Canine eosinophilic granuloma	Dog
Neoplasia	
Eosinophilic leukemia	Cat
Myeloid leukemia	Dog
Lymphoma	Cat
Lymphomatoid granulomatosis	Dog
Paraneoplastic conditions	
Carcinomas: select types	Dog, cat
Sarcomas: select types	Dog, cat
Mast cell neoplasia	Dog, cat
Endocrine conditions	
Hypoadrenocorticism	Dog
Hyperthyroidism	Cat
Estrus	Dog
Tetracycline administration	Dog
Idiopathic hypereosinophilic syndrome	Dog (rottweiler), cat

*Absolute eosinophil counts >1300/μL in dogs and >750/μL in cats (Mahaffey EA: Quality control, test validity, and reference values. p. 331. In Latimer KS, Mahaffey, Prasse KW (eds): Duncan and Prasse's Veterinary Laboratory Medicine: Clinical Pathology. 4th Ed. Iowa State University Press, Ames, 2003).

Inflammatory Leukocytosis

Definition

I. Neutrophil supply released from the bone marrow exceeds the migration of neutrophils into sites of inflammation.
II. The end result is an increase in circulating mature and immature neutrophils.

Causes and Pathophysiology

I. Tissue demand for neutrophils exceeds the reserve of mature neutrophils in the bone marrow.
   A. Release of immature cells (left shift) in the following order: band cells, then metamyelocytes, then myelocytes
   B. Regenerative left shift
      1. It occurs with acute inflammation.
      2. It is characterized by increased numbers of WBCs (leukocytosis) that are predominantly mature neutrophils, with increased immature neutrophil precursors.
   C. Degenerative left shift
      1. The WBC count is normal to decreased with excessive numbers of immature relative to mature neutrophils.
      2. It is often seen with septicemia or endotoxemia.
      3. Prognosis is poor, because tissue demand is greater than neutrophil production in the bone marrow.

II. Neutrophilic responses vary with inflammation.
   A. Peracute inflammation
      1. Transient neutropenia develops within 1 to 3 hours.
      2. It is often in response to endotoxemia or severe infections, particularly those involving the peritoneum, lungs, or thorax.
   B. Acute inflammation
      1. Bone marrow responds within 4 to 6 hours to increased tissue demands, causing an accelerated release of neutrophils (mature and immature).
      2. The resulting inflammatory leukogram is characterized by leukocytosis, neutrophilia, and a regenerative left shift (generally >450 immature neutrophilic precursors/μL in dogs or >500 to 1000/μL in cats) (Schultze, 2000; Cowell and Decker, 2000).
   C. Chronic, prolonged (days to weeks) inflammation
      1. Characterized by leukocytosis with mature neutrophilia
      2. Results from expanded marrow production that exceeds tissue demand

Corticosteroid-Induced Leukocytosis (Stress Leukogram)

Definition and Causes

I. It is characterized by leukocytosis with mature neutrophilia, lymphopenia, and eosinopenia.
II. Concurrent monocytosis is common in the dog and infrequent in the cat.
III. It accompanies increased endogenous corticosteroid concentrations (severe stress or hyperadrenocorticism) or exogenous glucocorticoid or ACTH administration.

Diagnosis

I. A CBC demonstrates the characteristic leukogram.
   A. WBC counts from 15,000 to 25,000/μL (Schultze, 2000)
   B. Neutrophilia in the absence of a left shift
   C. Lymphocyte count <1000/μL (Latimer and Prasse, 2003)

II. Stress leukogram can also occur concurrently with an inflammatory leukogram (see Inflammatory Leukocytosis).

Extreme Neutrophilic Leukocytosis (Leukemoid Response)

Definition

I. Pronounced leukocytosis from dramatic neutrophilia (up to 100,000/μL in dogs or 75,000/μL in cats), with a significant but orderly left shift (Kociba, 2000).
II. Occasionally accompanied by eosinophilia or lymphocytosis

Causes and Pathophysiology

I. It results from inflammation or nonhematopoietic neoplasia.
II. It mimics granulocytic leukemia in cellular magnitude and composition.
III. Several causes exist.
   A. Inflammation
      1. Localized infections: pyometra, peritonitis, pyothorax, pancreatitis
      2. Hepatazoonosis
      3. Hemolysis secondary to immune-mediated hemolytic anemia
         a. Dogs: *Babesia canis*
         b. Cats: *Mycoplasma haemofelis, Mycoplasma haemominutum*
   B. Paraneoplastic conditions
      1. Production of hematopoietic-stimulating cytokines
      2. See Chapter 73
   C. Other causes
      1. Early estrogen toxicity
      2. Recombinant canine or human granulocyte-colony stimulating factor therapy
      3. Leukocyte adhesion protein deficiency in Irish setters

Diagnosis and Differential Diagnosis

I. Differentiate from chronic myelogenous leukemia (CML).
II. Both conditions have neutrophilic leukocytosis with a left shift, nonregenerative anemia, and increased myeloid: erythroid ratio, with orderly granulocytic maturation in the bone marrow.
III. Suspect CML with a disorderly left shift, neutrophil dysplasia, thrombocytopenia, decreased marrow megakaryocytes, and granulopoietic precursors in extramedullary sites (liver, spleen, and lymph nodes).
IV. Neutrophil toxicity, indicative of inflammatory conditions, drug toxicity, or systemic disease, is not typically a feature of CML.

Physiologic Leukocytosis

Definition

I. Transient leukocytosis from epinephrine release with excitement, fear, or exercise that is characterized by mature neutrophilia and lymphocytosis

II. Common in puppies and kittens
III. Uncommon in adult dogs
IV. Rapid neutrophilia
    A. Neutrophil count up to 39,000/μL in cats (Latimer and Prasse, 2003) that generally diminishes within 20 minutes
    B. Neutrophilia often accompanied by lymphocytosis (absolute lymphocyte counts usually <20, 000/μL) in young cats (Cowell and Decker, 2000)

Causes and Pathophysiology

I. Neutrophilia
    A. It results from cellular shifts from the marginated to circulating pool.
    B. It is of greater magnitude in cats (larger marginated pool).
II. Lymphocytosis: decreased migration into lymphoid tissue or increased mobilization from the thoracic duct
III. Monocyte and eosinophil numbers: unchanged or slightly increased

CONGENITAL DISORDERS OF WBCS

Morphologic and Functional Disorders

See Table 65-3.

Lysosomal Storage Diseases

Definition and Causes

I. Autosomal recessive genetic disorders characterized by multiple organ failure (Table 65-4)
II. Intracellular accumulation of incompletely degraded substrates from deficiency of the lysosomal enzyme required for their metabolism

Diagnosis

I. Examination of peripheral blood smears may reveal vacuolation or abnormal granules within leukocytes.
II. Radiography helps characterize bony malformations in animals with clinically evident skeletal abnormalities.
III. Identification of deficient lysosomal enzyme activity in plasma, leukocytes, or cultured skin fibroblasts can be attempted.
IV. The structures of lysosomal enzymes are highly conserved; therefore, techniques developed for detection of enzymatic deficiencies in humans can be used in dogs and cats.
V. Polymerase chain reaction (PCR)-based genomic screening can be used to identify some cases.
    A. Examples include dogs with fucosidosis, mucopolysaccharidosis (MPS) I, and MPS VII, and cats with MPS VI.
    B. Novel genetic mutations can occur with these diseases that may not be detected by the established testing procedures; therefore, a negative result does not eliminate a storage disease (Skelly and Franklin, 2002).
VI. Excessive urinary glycosaminoglycan excretion in animals with MPS can be detected by a urine spot test.

Treatment and Monitoring

I. Storage diseases are generally untreatable and progressive.
II. Bone marrow transplantation has resulted in clinical improvement in dogs with MPS I and cats with MPS VI.

NEOPLASIA

Myeloproliferative Disorders

See Chapter 66.

Acute Lymphoblastic Leukemia

Definition

I. Acute lymphoblastic leukemia (ALL) is characterized by progressive lymphoblastic infiltration of lymphoid organs and bone marrow.
II. Unlike lymphoma, the bone marrow is the primary tumor site.

Clinical Signs

I. Affected animals present with nonspecific signs of anorexia, lethargy, weight loss, vomiting, diarrhea, lameness, altered mentation, and intermittent fever.
II. Physical examination findings consist of pallor, hepatosplenomegaly, lymphadenopathy, and petechia.

Diagnosis

I. Lymphocytosis with circulating lymphoblasts
II. Anemia, thrombocytopenia, variable WBC counts, or pancytopenia
III. Possible absence (aleukemia) or only small numbers (subleukemia) of circulating lymphoblasts
IV. Possible bone marrow aspiration and/or biopsy findings
    A. Homogeneous population of large immature lymphocytes
    B. Replacement of normal nucleated cell population with 40% to 50% lymphoblasts
V. Possible clinical chemistry abnormalities
    A. Increased alanine and aspartate transferases (ALT, AST) and alkaline phosphatase (ALP) activities indicative of potential liver involvement
    B. Increased blood urea nitrogen concentration indicative of azotemia (prerenal or renal) or GI hemorrhage
    C. Hypercalcemia uncommon

Differential Diagnosis

I. ALL is difficult to differentiate from multicentric lymphoma with bone marrow or blood involvement (stage V disease).
II. Unlike advanced lymphoma, ALL often occurs without lymphadenopathy, is poorly responsive to chemotherapy, and has a more rapid and progressive disease course.
III. Differentiation from acute myeloproliferative diseases (see Chapter 66) requires cytochemical and immunohistochemical staining of bone marrow preparations.
IV. Lymphocytosis with mature, well-differentiated lymphocytes distinguishes chronic lymphocytic leukemia (CLL) from ALL (see below).

TABLE 65-3

Morphological and Functional Disorders of Canine and Feline Leukocytes

DISORDER	INHERITANCE	CAUSE	SPECIES	APPEARANCE/CLINICAL SIGNS	DIAGNOSIS	TREATMENT	REFERENCES
Cyclic hematopoiesis	Autosomal recessive	Stem cell abnormality	Gray-coated collie, collie-mix dogs	Continuous abnormal hematological cycles Decreased neutrophil number and function: recurrent bacterial infections, defective platelet aggregation, systemic amyloidosis	Serial CBCs every 3-6 weeks: cyclic neutropenia and anemia Clinical signs: hair coat color dilution	Broad-spectrum antibiotics for sepsis Lithium carbonate 21-26 mg/kg/day PO (potential side effects) rhG-CSF 5 µg/kg SC BID (watch for neutralizing antibodies) Bone marrow transplantation is curative	Campbell (1985), Lothrop et al. (1988), Niemeyer and Lothrop (2000)
Inherited vitamin B_{12} (cobalamin) malabsorption	Autosomal recessive	Failure to express intestinal intrinsic factor cobalamin complex receptor (cubilin)	Inbred giant schnauzer	Nuclear chromatin maturation abnormalities, neutropenia, nonregenerative anemia	Decreased serum cobalamin concentration Classic hematological abnormalities	Parenteral administration of megadose cobalamin (1 mg IM) monthly No improvement with oral cobalamin	Fyfe (2000)
Birman cat neutrophil granulation anomaly	Autosomal recessive	Fine azurophilic granules similar to progranulocyte granules	Birman cat	Prominent neutrophil granulation	Serial CBCs Differentiate from MPS VI, MPS VII, and toxic change	None; neutrophils function normally	Hirsch and Cunningham (1984)
Canine leukocyte adhesion deficiency	Autosomal recessive	Deficient expression of CD18 (subunit of B_2 integrins)	Irish setter	Recurrent infections, marked neutrophilia, chronic anemia Bone marrow myeloid hyperplasia	Flow cytometry for neutrophil CD18 expression	Antibiotics alleviate signs but not infection Affected animals usually die	Andreason and Roth (2000)
Pelger-Huët anomaly	Uncertain inheritance Acquired secondary to sepsis, drugs, MPD, viral infections	Failure of the mature nucleus to form true filaments	Cats, dogs	Peanut-shaped nuclei in granulocytes, monocytes, or megakaryocytes	Serial CBCs	None; neutrophils function normally	
Chédiak-Higashi syndrome	Autosomal recessive	Failure of granule fusion	Persian cats	Yellow-green eyes Smoke-blue hair color Hypopigmentation of eyes, skin, hair	CBC: neutropenia, abnormal granules Prolonged bleeding times Abnormal platelet aggregation	Temporary improvement with rhG-CSF Bone marrow transplant	Meyers (2000)

CBC, Complete blood count; *rhG-CSF,* recombinant human granulocyte-colony stimulating factor; *IM,* intramuscularly; *MPS,* mucopolysaccharidosis; *MPD,* myeloproliferative disease.

TABLE 65-4

Lysosomal Storage Diseases of Dogs and Cats

DISEASE	ENZYME DEFICIENCY	BREEDS AFFECTED	WHITE BLOOD CELL ABNORMALITIES	CLINICAL SIGNS
Mannosidosis	α-D-Mannosidase	English springer spaniel DSH, Persian cat	Lymphocyte, neutrophil, eosinophil, monocyte cytoplasmic vacuolization	Neurological and skeletal abnormalities Retarded growth Facial dysmorphism (flattened features)
Fucosidosis	α-L-fucosidase	English springer spaniel	Lymphocyte vacuolization	Behavioral changes Ataxia Hearing and vision loss
MPS I	α-L-iduronidase	Plott hound DSH cats	Basophilic to metachromatic (pink-purple) neutrophil cytoplasmic granules Lymphocyte granulation or vacuolization	Skeletal abnormalities Facial dysmorphism Dwarfism Corneal opacities Neurologic abnormalities
MPS VI	Arylsulfatase B	Siamese and DSH cats Miniature pinscher	See MPS I	See MPS I
MPS VII	β-Glucuronidase	Dogs, cats	See MPS I	See MPS I
GM_1 gangliosidosis	β-D-Galactosidase	Siamese, DSH cats Beagle, English springer spaniel, Portuguese water dog, mixed breed dog	Lymphocyte vacuolization	Ataxia Visual deficits
GM_2 gangliosidosis	β-D-Hexosaminidase	Korat and DSH cats Japanese spaniel	Neutrophil granulation Lymphocyte and/or eosinophil vacuolization	Corneal clouding Muscle wasting Cerebral and/or cerebellar dysfunction

DSH, Domestic short hair; *MPS,* mucopolysaccharidosis.

V. Eliminate other causes of pancytopenia via bone marrow examination.

Treatment and Monitoring

I. Treat ALL using established protocol treatments for canine or feline lymphoma (Fan, 2003; Couto, 2001)
   A. Use of vincristine and L-asparaginase therapy together may result in neutropenia.
   B. Prognosis is poor, as treatment-induced remission is short and survival is generally less than a few months.
II. Initiate broad-spectrum antibiotic therapy in animals with fever or neutropenia (<1000/μL).
III. For animals with anemia and/or thrombocytopenia, consider fresh whole blood, packed RBCs, platelet-rich plasma, or platelet concentrate transfusions (see Chapter 71).

Chronic Lymphocytic Leukemia

Definition and Causes

I. Chronic lymphocytic leukemia (CLL) is characterized by lymphocytic leukocytosis, with a predominance of small lymphocytes.
II. There is no reported association between CLL and FeLV infection in cats.
III. Most cases of CLL in dogs are of T-cell origin.
IV. CLL is rare in cats.

Clinical Signs

I. Possibly asymptomatic
II. Nonspecific signs: lethargy, anorexia, weight loss, vomiting, diarrhea, polyuria/polydipsia, lameness
III. Physical examination: hepatosplenomegaly, peripheral lymphadenopathy, pallor

Diagnosis

I. CBC findings
   A. Persistent marked lymphocytosis
   B. Lymphocyte counts: >1,000,000/μL in dogs and up to 250,000/μL in cats (Workman and Vernau, 2003)
   C. Concurrent hematological findings: nonregenerative, normocytic, normochromic anemia, thrombocytopenia, neutropenia, or pancytopenia from myelophthisis
   D. Findings in cats: not well characterized
II. Bone marrow aspirate and/or biopsy samples: >30% small mature lymphocytes

III. Serum biochemistry results
  A. They can indicate multiple organ involvement.
  B. Serum and urine electrophoresis is indicated in dogs with hyperglobulinemia, as a monoclonal gammopathy occurs in up to 30% of dogs with hyperglobulinemia.
IV. Immunophenotyping procedures (Burnett et al., 2003)
  A. It uses PCR amplification of cellular DNA from peripheral blood.
  B. It identifies neoplastic populations of circulating small lymphocytes based on unique rearrangements of the T cell receptor γ (T-cell lymphoma) or immunoglobulin (B-cell lymphoma) sequences.
  C. It helps to differentiate CLL from other nonneoplastic causes of persistent lymphocytosis, which can be difficult.

Differential Diagnosis

I. Other causes of persistent lymphocytosis
  A. Transient leukocytosis (epinephrine response)
  B. Immune-mediated or other chronic, systemic diseases
  C. Chronic ehrlichiosis, Rocky Mountain spotted fever and babesiosis infections (dogs), and toxoplasmosis (cats)
II. Large granular lymphocyte (LGL) leukemia
  A. LGL leukemia in cats is uncommon, may accompany lymphoma, and involves the alimentary tract or mesenteric lymph nodes.
  B. In dogs, LGL leukemia presents as either ALL or CLL.
III. Acute lymphoblastic leukemia
IV. Multicentric lymphoma

Treatment and Monitoring

I. Treatment for CLL is not often required, especially in the absence of bone marrow involvement and hematological abnormalities (anemia or other cytopenias), or evidence for multiorgan involvement (lymphadenopathy, splenomegaly, enzyme abnormalities).
II. Chemotherapy is not recommended until the development of clinical signs, cytopenias, or marked lymphocytosis (generally defined as 60,000 to 100,000/μL).
III. A combination protocol of oral chlorambucil and prednisone is effective dogs and cats (Workman and Vernau, 2003).
  A. Treatment in dogs involves the following:
    1. Chlorambucil: 0.2 mg/kg or 6 mg/m^2 PO SID for 7 to 14 days, then 0.1 mg/kg or 3 mg/m^2 PO SID, then long-term maintenance at 2.0 mg/m^2 QOD
    2. Prednisone: 30 mg/m^2 PO SID for 7 days, followed by 20 mg/m^2 for 7 days and 10 mg/m^2 QOD
  B. Treatment in cats involves the following:
    1. Chlorambucil: 0.2 mg/kg or 2 mg/cat QOD
    2. Prednisone: 1 mg/kg SID
  C. Dosages are modified based on clinical response.
  D. Monitor CBCs weekly for the first month and monthly thereafter.
  E. Prognosis is variable and depends on the extent of disease and response to therapy.

Sézary Syndrome in Dogs

Definition and Cause

I. Lymphoproliferative disease in dogs (uncommon) and cats (rare)
II. Characterized by cutaneous lymphoma and a circulating population of large neoplastic T lymphocytes with intensely cleaved or indented nuclei and prominent nucleoli

Clinical Signs

I. Ulcerative dermatitis, pruritus, anorexia, alopecia, and peripheral lymphadenopathy
II. Hematologic abnormalities
  A. Lymphocytic leukocytosis with abnormal lymphocyte morphology
  B. Possible monocytosis, neutrophilia, and nonregenerative, normocytic, normochromic anemia

Diagnosis

Dermal-epidermal infiltration by neoplastic lymphocytes in skin biopsy samples combined with the presence of circulating neoplastic lymphocytes.

Treatment and Monitoring

I. Chemotherapeutic protocols for canine lymphoma can be tried.
II. Prognosis is poor.

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CHAPTER 66

Myeloproliferative Disorders

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MYELODYSPLASTIC DISORDERS

Definition and Classification

I. Primary myelodysplastic syndrome (MDS) consists of irreversible, acquired clonal (neoplastic) disorders of multipotential hematopoietic cells unrelated to concurrent diseases, nutritional deficiency, or drug-induced toxicosis.
II. Animals with MDS ("preleukemia") often suffer from chronic debilitation that may continue unchanged or evolve into acute myeloid leukemia (AML).
III. Myelodysplastic disorders are morphologically divided into subtypes (Table 66-1) relative to the percentage of myeloblasts in the bone marrow and the myeloid-to-erythroid (M:E) ratio.
   A. MDS-refractory cytopenia (MDS-RC) and MDS-excess blasts (MDS-EB) have an M:E ratio >1.0.
   B. The subtype MDS-erythroid predominance (MDS-Er) refers to feline cases with an M:E ratio ≤1.0 (Raskin, 1996; Jain et al., 1991), but has also been considered a variant of MDS-RC in dogs (Weiss, 2005).
IV. MDS-EB may be considered a form of oligoblastic leukemia that often behaves as an antecedent of AML and has a worse prognosis (McManus and Hess, 1998; Weiss, 2005).

Clinical Signs

I. Chronic infections with fever
II. Lethargy related to anemia
III. Anorexia
IV. Hemorrhage

Diagnosis

I. The peripheral blood indicates cytopenia of one or more cell lines, with ineffective hematopoiesis.
II. Abnormal morphology (dyshematopoiesis) must be observed in either the erythroid, granulocytic, or megakaryocytic cells.
   A. Dysplasia in the erythroid line may involve macrocytosis, megaloblastosis with asynchrony of maturation, nuclear fragmentation, unequal cell division, sideroblastosis, or siderocytosis.
   B. The granulocytic line may exhibit giant forms, nuclear hypersegmentation, hyposegmentation, or abnormal cytoplasmic granulation as evidence of dysmyelopoiesis.
   C. Dysplastic changes involving platelets include giantism, hypergranularity, or hypogranularity.
   D. Dwarf or micromegakaryocytes with asynchrony of maturity are common signs of dysthrombopoiesis.
III. Despite the altered development of these precursors (from increased apoptosis), the bone marrow is generally hypercellular, with blast forms accounting for <30% of nucleated cells.
IV. Myelofibrosis is often present in the marrow of cats with MDS (Blue, 1988).
V. Feline leukemia virus infection is common in cats with MDS (Hisasue et al., 2001)

Differential Diagnosis

I. The main differential diagnosis is secondary MDS, which includes cobalamin or folate deficiencies, drug-induced toxicosis, or concurrent immune-mediated or neoplastic diseases.
II. Other myeloid neoplasms, such as chronic granulocytic leukemia (CGL), chronic myelomonocytic leukemia (CMMoL), and chronic monocytic leukemia (CMoL), have <30% blast cells in the bone marrow and may have dyshematopoiesis.

Treatment and Monitoring

I. Because the condition may persist for long periods without significant clinical disease, the goal of treatment is often supportive, with antibiotics and blood transfusions.
II. A few cases have been treated, but with limited success.
   A. Dogs: human recombinant erythropoietin at 100 U/kg SC QOD for 10 days and prednisone at 2 mg/kg PO SID initially (Boone et al., 1998)
   B. Dogs: low doses of aclarubicin at 5 mg/m^2 IV SID for 5 days (Miyamoto et al., 1999)
   C. Cats
      1. Several treatment protocols were used for 16 cats (Hisasue et al., 2001).
      2. Whole blood transfusion was used to improve clinical signs in 15 cats.
      3. Prednisolone 1 to 4 mg/kg PO, IM SID was used in combination with other drugs for 13 cats.
      4. Low-dose cytarabine 0.7 to 1.4 mg/kg SC SID or cytarabine ocfosfate 2 to 4 mg/kg PO SID for 2 to 4 weeks was used along with prednisolone in nine cats.

TABLE 66-1

Myeloproliferative Disorders

TYPES AND SUBTYPES	MORPHOLOGICAL CHARACTERISTICS
Myelodysplastic disorders	Myeloblasts <30% of ANC; peripheral cytopenias and dyshematopoiesis common; may evolve into acute myeloproliferative disorder
MDS-Er (cats)	M:E ratio ≤1, myeloblasts <5% of ANC
MDS-RC (cats/dogs)	M:E ratio >1, myeloblasts <5% of ANC
MDS-EB (cats/dogs)	M:E ratio >1, myeloblasts ≥5% of ANC
Acute undifferentiated leukemia	Requires electron microscopy and/or immunophenotyping
Acute myeloid leukemia*	Blast cells ≥30% of ANC
Acute myeloblastic leukemia	
Without maturation	Type I myeloblasts ≥90% of ANC
With maturation	Types I-II myeloblasts ≥30% and ≤90% of ANC; also granulocytes ≥10% and monocytes ≤20% of NEC
Acute myelomonocytic leukemia	Myeloblasts and monoblasts ≥30% of ANC; also of differentiated granulocytes and monocytes ≥20% of NEC each
Acute monocytic leukemia	
Without maturation	Monoblasts and promonocytes ≥80% of NEC
With maturation	Promonocytes and monocytes ≥30% to ≤80% of NEC
Acute erythroleukemia	Erythroid cells >50% of ANC (M:E <1), myeloblasts and monoblasts ≥30% of NEC
With erythroid predominance	Erythroid cells >50% of ANC, rubriblasts, myeloblasts, and monoblasts ≥30% of ANC
Acute megakaryoblastic leukemia	Megakaryoblasts >30% of ANC
Chronic myeloproliferative diseases	Myeloblasts <30% of ANC; also mild to moderate hematodysplasia; may evolve into acute myeloproliferative disorder
Chronic granulocytic leukemia	Marked neutrophilia
Eosinophilic leukemia	Marked eosinophilia
Basophilic leukemia	Marked basophilia
Chronic myelomonocytic leukemia	Persistent monocytosis
Chronic monocytic leukemia	Persistent monocytosis
Polycythemia vera	Erythropoietin-independent erythrocytosis
Essential (primary) thrombocythemia	Thrombopoietin-independent thrombocytosis
Chronic idiopathic myelofibrosis	Anemia with leukoerythroblastosis, extramedullary hematopoiesis, splenomegaly, and marrow fibrosis
Related myeloproliferative disorders	Derived from hematopoietic stem cell
Malignant histiocytosis	Cytopenia and erythrophagia are common; pleomorphic histiocytes with multinucleated giant cells
Mast cell leukemia	Multiple cell lines affected; pleomorphic mast cells in size and nuclear features; erythrophagia possible

MDS, Myelodysplastic syndrome; *ANC,* all nucleated cells in bone marrow, excluding lymphocytes, plasma cells, macrophages, and mast cells; *M:E,* myeloid-to-erythroid; *NEC,* nonerythroid cells (ANC minus erythroid).
*Classification of canine and feline acute myeloid leukemia by blast cell type and percentage based upon modification of FAB system by the Animal Leukemia Study Group (Jain NC, Blue JT, Grindem CB et al: Proposed criteria for classification of acute myeloid leukemia in dogs and cats. Vet Clin Pathol 20:63, 1991).

5. Cyclosporin A at 2.5 to 5 mg/kg PO SID with prednisolone was used in one cat.
6. Daunorubicin 20 mg/m^2 IV SID for 3 days in 3 weeks, cytarabine at 100mg/m^2 SC SID for 4 days in 3 weeks, vincristine at 0.025 mg/kg IV weekly, and prednisolone were tried in three cats with advanced disease.

III. Animals with >5% marrow myeloblasts have shorter survival times and poorer responses to treatment (Couto and Kallet, 1984; Hisasue et al, 2001; Weiss and Smith, 2000).

ACUTE MYELOID LEUKEMIAS

Definition and Classification

I. AMLs are malignant, clonal proliferations of immature nonlymphoid hematopoietic cells resulting in the accumulation of blast cells in the bone marrow, peripheral blood, visceral organs, and lymph nodes.

II. *Aleukemic, subleukemic,* or *occult leukemias* are terms for acute leukemias in which blast cells are not observed, or are observed in low numbers in the peripheral blood, respectively.

III. AML is subclassified in animals according to the hematopoietic lineage of the blast cell population.
IV. In humans, AMLs have recently been reclassified under the World Health Organization (WHO) according to specific genetic abnormalities, therapy-related leukemias, presence of multilineage dysplasia, or leukemias with no evidence of genetic mutations, history of therapy, or dysplasia (Harris et al., 1999).
V. Under the WHO classification system, blast cell percentage for the diagnosis of acute leukemia decreased from 30% to 20% and use of the French-American-British (FAB) alpha-numeric system (AML: M1-M7) has been discarded (Harris et al., 1999; Vardiman et al., 2002).
VI. Classification of AML is based on the Animal Leukemia Study Group report, which standardized the diagnosis of AML for evaluation of clinical prognosis and treatment in dogs and cats (Jain et al., 1991).
   A. Cytomorphology by light microscopy, cytochemical staining, and immunophenotyping are used to identify the lineage of blast cells for subclassification of AML.
   B. The human WHO classification system has not yet been evaluated in animals; however, in recognition of this new system, the AML: M1-M7 numbering system is not used in this chapter.
   C. Subtypes of canine and feline AML described by the Animal Leukemia Study Group are as follows (see Table 66-1):
      1. Acute undifferentiated leukemia: lack morphological and cytochemical evidence of lineage for either lymphoid or myeloid cell types
      2. Acute myeloblastic leukemia without maturation
      3. Acute myeloblastic leukemia with maturation
      4. Acute promyelocytic leukemia (not identified in animals)
      5. Acute myelomonocytic leukemia
      6. Acute monocytic leukemia
         a. Acute monocytic leukemia without maturation
         b. Acute monocytic leukemia with maturation
      7. Acute erythroleukemia and/or acute erythroleukemia with erythroid predominance
      8. Acute megakaryoblastic leukemia

Diagnosis

I. Animals typically exhibit an acute onset and rapid progression of clinical signs related to peripheral blood abnormalities and organ or lymph node infiltration by leukemic cells.
II. Hematological findings include either leukopenia or leukocytosis with a disorderly left shift, nonregenerative anemia with or without macrocytosis and nucleated red blood cells (normoblastemia), and thrombocytopenia.
   A. Circulating blast cells may or may not be present.
   B. A significant monocytosis is usually present in acute monocytic leukemia.
   C. Morphological abnormalities in both marrow and circulating cells may include giant forms, granulocyte hypersegmentation, erythroid nuclear fragmentation and abnormal cell division, asynchronous maturation of erythroid cells, and hypogranular platelets.
III. Specific serum biochemical abnormalities suggest organ infiltration by neoplastic cells.
IV. Blast cells are sometimes seen in peripheral blood, lymph nodes, liver, spleen, occasionally kidneys, and cerebrospinal fluid.
V. Blast cells have round to indented nuclei, prominent single to multiple nucleoli, a high nuclear-to-cytoplasmic ratio, and basophilic cytoplasm.
VI. Definitive diagnosis requires identification of blast cell lineage and their percentages in bone marrow, blood, or both using morphological examination, cytochemical staining, and immunophenotyping.
   A. Cytochemical stains are species specific (Raskin and Valenciano, 2000).
   B. Submission of samples to a veterinary reference laboratory for cytochemical staining and interpretation by a board-certified clinical pathologist is recommended.
   C. Cytochemical staining is most useful for identification of myeloid, monocytic, and megakaryocytic neoplasms; good lymphocytic and erythroid cytochemical markers are lacking.
   D. Immunophenotyping (immunocytochemistry, immunohistochemistry, and flow cytometry) using antibodies that recognize specific enzymes or structural epitopes on the leukemic cells is also used to differentiate AML and acute lymphoid leukemia (ALL) and to subclassify AML.
   E. Other diagnostic tests used to identify or confirm blast cell lineage include ultrastructural analysis by electron microscopy and in vitro blast cell differentiation (Modiano et al., 1998).
   F. Use of a diagnostic algorithm derived from flow cytometry light scatter patterns (without use of monoclonal antibodies) to provide a preliminary classification of acute leukemia has also been evaluated and may provide more rapid evaluation of leukemias, although refinement of the algorithmic process is still needed (Fernandes et al, 2002).
   G. Genetic studies in animal leukemias have detected chromosomal abnormalities, although more information is needed regarding karyotypic, molecular DNA abnormalities, and their association with therapy and prognosis.

Differential Diagnosis

I. The primary and most significant differential diagnosis of AML is ALL.
II. In dogs and cats, lymphoid leukemia has a better response to chemotherapy and prognosis compared with AML; therefore, accurate differentiation is crucial.
III. Although morphological criteria can be used for differentiation, cytochemical staining, immunophenotyping, or both are recommended to distinguish between AML and ALL.

Treatment

I. AML has an extremely poor prognosis, with survival times ranging from days to <3 months in treated animals.
II. Supportive therapy is administered as needed.
III. Chemotherapy for AML, if attempted, is instituted as soon as possible after definitive diagnosis because of the rapid clinical course.
   A. Various combinations of cytotoxic agents, including doxorubicin, cyclophosphamide, vincristine, cytosine arabinoside, 6-thioguanine, busulfan, melphalan, and prednisone, have been used.
   B. Common side effects of these agents include leukopenia and thrombocytopenia resulting from myelosuppression, and gastrointestinal (GI) toxicity resulting in vomiting, anorexia, and diarrhea (see Chapter 72).

CHRONIC MYELOPROLIFERATIVE DISEASES

Chronic Granulocytic Leukemia

Definition and Classification

I. In animals, chronic granulocytic leukemia (CGL) and chronic myelogenous leukemia (CML) are synonymous and refer to a form of chronic myeloproliferative disease (MPD) characterized by a neoplastic proliferation within the granulocytic (neutrophilic) cell line.
II. CGL may terminate in a "blast crisis" with proliferation of immature blast cells and development of acute leukemia.
III. In humans, CML is characterized by a specific genetic translocation to form the BCR-ABL fusion gene or Philadelphia chromosome within pluripotential stem cells resulting in proliferations of neutrophils as well as other leukocytes, and to which targeted gene therapy is now available (Vardiman et al, 2002).
   A. A true clonal proliferation of neutrophils (chronic neutrophilic leukemia) is considered rare in people.
   B. Similar genetic abnormalities, as identified in human CML, have not been identified in animals.

Diagnosis

I. CGL is rare in animals; however, an increased risk has been reported in dogs exposed to high doses of radiation (Dungworth et al., 1969).
II. The hallmark of CGL is a marked and persistent leukocytosis consisting primarily of bands and segmented neutrophils, although a disorderly left shift may be present.
   A. White blood cell (WBC) counts may range to >100,000 cells/μL.
   B. Abnormal morphological features or dysplasia, such as giant bands, hypersegmentation, pyknosis, and nuclear fragmentation, are absent or uncommon.
III. Other laboratory findings are variable and include nonregenerative anemia ± normoblastemia, monocytosis, eosinophilia, basophilia, thrombocytopenia, and thrombocytosis.
IV. Bone marrow aspirates usually reveal a hypercellular marrow with a moderate to markedly increased M:E ratio; increased numbers of promyelocytes, neutrophilic myelocytes, and myeloblasts; but the latter cells are <30% of all nucleated cells.
   A. Bone marrow interpretation is often that of a leukemoid response.
   B. Bone marrow histopathologic examination is recommended to monitor the degree of fibrosis that may occur in later stages of CGL.
V. Although infiltration of liver, spleen, and other organs by leukemic cells is common, serum biochemical profiles are generally normal to mildly altered.
VI. Pseudohypoglycemia may occur from increased in vitro utilization of glucose by the excessive numbers of circulating granulocytes.
VII. Aspirates or biopsy of lymph nodes and visceral organs often reveal granulocytic infiltration and extramedullary hematopoiesis.
VIII. Rarely, a solid tumor of leukemic granulocytes (chloroma) is found.

Differential Diagnosis

I. The primary differential diagnosis for CGL is a leukemoid reaction (see Chapter 65) related to inflammation and manifested by marked neutrophilia with a left shift back to early precursors (progranulocyte or later).
II. Conditions associated with leukemoid reactions include pyogenic infections; immune-mediated hemolytic anemia; and neoplasms associated with necrosis, sepsis, production of hematopoietic growth factors (paraneoplastic neutrophilia), or metastasis to the bone marrow.
III. Exclusion of inflammatory diseases through appropriate clinical and diagnostic testing is used to rule out a leukemoid reaction and confirm suspected CGL.
IV. Laboratory criteria useful in the differentiation of CGL include the following (Fine and Tvedten, 1999):
   A. Persistent leukocytosis and left shift without evidence of neutrophil toxicity
   B. Macrocytic anemia accompanied by normoblastemia without a reticulocytosis
   C. Cytological evidence of granulocytopoiesis in lymph nodes and organs
   D. Histopathologic findings of granulocytic perivascular infiltration in liver, spleen, and other organs

Treatment

I. Treatment is somewhat controversial, because untreated animals may survive weeks to years, and the success of chemotherapy in prevention of a terminal blast crisis is uncertain.
II. Survival times of years can occur in treated animals, and reduction in numbers of circulating blasts via chemotherapy may decrease clinical signs and improve quality of life.
   A. Protocol 1: hydroxyurea 20 to 25 mg/kg PO BID until the WBC count decreases to 15,000 to 20,000 cells/μL,

then tapered to 10 to 12 mg/kg PO SID or to 50 mg/kg PO every 3 to 4 days (Young and MacEwen, 1996)

B. Protocol 2: hydroxyurea 50 mg/kg PO SID for 14 days until the WBC count is within normal reference range, then tapered to QOD and then to every 3 days (Leifer et al., 1983; Fine and Tvedten, 1999)
C. Side effects of hydroxyurea: myelosuppression (most serious), pruritus, erythema, alopecia, hyperglycemia
D. Protocol 3: busulfan 0.1 mg/kg/day PO until the leukocyte count is reduced to 15,000 to 20,000 cells/μL (Young and MacEwen, 1996)

III. No successful chemotherapeutic treatment for CGL in a blast crisis has been reported.

Eosinophilic Leukemia

Definition

I. Eosinophilic leukemia (EL) is a rare chronic MPD occurring primarily in cats and is characterized by peripheral eosinophilia, eosinophilic hyperplasia of the bone marrow, and eosinophilic infiltration in multiple organs.
II. EL is difficult to distinguish from the more common hypereosinophilic syndrome (HES), and some controversy exists whether EL is a distinct clinical entity or a variant of HES.
III. Support for the distinct, neoplastic nature of EL includes a more rapid disease progression, the presence of morphologically abnormal eosinophils, increased numbers of circulating and marrow eosinophilic precursors, and a more severe anemia (Huibregtse and Turner, 1994).
IV. In humans, demonstration of clonality is used to distinguish EL from the polyclonal proliferation of HES (McManus, 2005), but no such clonality studies have been performed in animals with eosinophilic proliferations.

Clinical Signs and Diagnosis

I. Older cats tend to be at greatest risk for EL, with a median age of 8 years at diagnosis.
II. EL has been reported in feline leukemia virus/feline immunodeficiency virus-infected and noninfected cats.
III. Affected animals may have vomiting, diarrhea, hepatosplenomegaly, and peripheral lymphadenopathy.
IV. Common laboratory findings include peripheral eosinophilia, hypogranular and immature eosinophils, moderate to severe anemia, and thrombocytopenia.
V. Bone marrow aspiration typically reveals eosinophilic hyperplasia with a significantly increased M:E ratio (>10:1), increased numbers of immature eosinophils, and dysmyelopoiesis.

Differential Diagnosis

I. Primary differential diagnoses for EL are HES and conditions associated with reactive eosinophilia, such as allergic bronchitis, pulmonary infiltrates with eosinophils, external and GI parasitism, heartworm disease, hypersensitivity reactions, eosinophilic enteritis, eosinophilic granuloma complex, and neoplasia (mast cell tumor, lymphoma, certain carcinomas).
II. Definitive diagnosis of EL requires a thorough clinical and diagnostic evaluation to rule out reactive eosinophilia and HES.

Treatment

I. Response to treatment in cats with EL is generally poor.
II. Average survival times of 6 months postdiagnosis have been reported with corticosteroid therapy (Goldman and Graham, 2000).
III. Give hydroxyurea initially at 40 mg/kg/day PO for 1 week, then QOD or every 3 days as needed to control the eosinophilia and prevent the development of neutropenia (Hamilton, 2002).
IV. Hydroxyurea is used in combination with prednisone 2 mg/kg PO BID initially, then reduced gradually.

Basophilic Leukemia

Definition and Classification

I. Basophilic leukemia (BL) is a chronic MPD rarely reported in dogs or cats.
II. BL is characterized by excessive marrow production of basophils, resulting in peripheral basophilia, increased circulating and marrow immature basophils, and increased numbers of marrow myeloid blast cells.

Clinical Signs and Diagnosis

I. Clinical signs of BL are nonspecific and include lethargy, inappetence, fever, lumbar pain, hepatosplenomegaly, and lymphadenopathy.
II. Clinicopathologic findings of basophilia, neutropenia, nonregenerative anemia, and thrombocytosis have been reported.
III. Bone marrow findings in one reported case of BL included 43% basophils and 29% marrow blast cells of all nucleated cells, with some blast cells exhibiting dark, basophilic-like granules (Mears et al., 1997).
IV. Cytochemical staining of marrow and blood smears with omega-exonuclease, a basophil-specific marker have been used to identify basophilic lineage of marrow blast cells and confirm the presence of immature and mature basophils (Mears et al., 1997).

Differential Diagnosis

I. BL must be differentiated from reactive basophilia associated with a hypersensitivity reaction, inflammation, or mast cell tumor/mastocytosis.
II. BL can occasionally be confused with mast cell leukemia because of the presence of dark cytoplasmic granules in both cell types.
   A. Basophils have a segmented nucleus and variable numbers of dark purple cytoplasmic granules.
   B. Mast cells are generally larger than basophils and possess a round nucleus with many small, metachromatic-

staining granules that appear pink to purple with Romanowsky-type stains.

Treatment

I. Give hydroxyurea at 20 to 25 mg/kg PO BID (Mears et al., 1997).
II. Side effects, such as severe myelosuppression, pruritus, alopecia, and diabetes mellitus, may require discontinuation of hydroxyurea in dogs with BL (Mears et al., 1997).

Chronic Myelomonocytic Leukemia/ Chronic Monocytic Leukemia

Definition and Classification

I. CMMoL and CMoL are clonal disorders with some similarity to CGL in that they present with increased granulocytic or monocytic counts, anemia, mild to moderate myelodysplasia, and <30% blast cells of all nucleated cells in the bone marrow.
II. CMMoL may occur as a form of oligoblastic or subacute leukemia, especially in cats, and may progress to acute leukemia (Raskin and Krehbiel, 1985; Hisasue et al., 2001).
III. In the human WHO classification system, CMMoL is placed in the category of myelodysplastic/myeloproliferative disease, as the disease displays both neoplastic and dysplastic features (Vardiman et al., 2002).
IV. In animals, CMMoL has been classified as a chronic myeloproliferative disorder (Jain et al., 1991) or a myelodysplastic disorder (Hisasue et al., 2000, Hisasue et al., 2001; Valli et al., 2002).

Clinical Signs and Diagnosis

I. Characteristic features of CMMoL and CMoL include an indolent clinical course with a persistent monocytosis unresponsive to antibiotic therapy.
II. Splenomegaly and hepatomegaly are common findings.
III. Bone marrow aspirates in CMoL reveal increased numbers of monoblasts and other monocytic precursors, particularly after splenectomy.
IV. The marrow contains >3% but <30% myeloblasts of all nucleated cells.
V. Peripheral blood findings include monocyte counts usually >10% (or >1,000/μL), low numbers of immature granulocytes (≤10%), some blast cells (<2%), and the presence of prominent granulocytic dysplasia.

Differential Diagnosis

I. Primary differential diagnoses for CMMoL and CMoL are inflammatory disorders, such as deep mycoses, immune-mediated diseases, and CGL.
II. Basophilia is common in CGL but not in CMMoL.
III. Demonstration of a persistent and unresponsive monocytosis, cytological and histological evidence of neoplastic cell infiltration in lymph nodes and other organs, and elimination of inflammatory causes for the leukocytosis are necessary to differentiate between CMMoL or CMoL and inflammatory disorders (Bearman et al., 1981).

Treatment

Treatment using combination chemotherapy and glucocorticoids has been attempted, but has not changed the course of disease.

Polycythemia Vera

See Chapter 64.

Essential (Primary) Thrombocythemia

Definition and Classification

I. Essential thrombocythemia (ET) is an uncommon MPD characterized by a proliferation of bone marrow megakaryocytes resulting in a significant and persistent thrombocytosis (>600,000/μL).
II. Evolution of ET to CGL has been reported in a dog (Degen et al., 1989).

Diagnosis

I. Clinical signs of ET are nonspecific and include lethargy, exercise intolerance, pallor, and hepatosplenomegaly.
II. Hemorrhage (GI or epistaxis) attributable to intrinsic platelet function defects may occur and contribute to anemia.
III. Thrombotic events (pulmonary embolism) related to the increased platelet mass, platelet hyperaggregation, or both, can arise.
IV. Splenectomy may unmask and exacerbate the disease (Degen et al., 1989).
V. Laboratory findings include a persistent thrombocytosis that may exceed 1,000,000 platelets/μL; large and hypergranular platelets (shift platelets), elevated mean platelet volume, minimally regenerative or nonregenerative anemia, neutrophilia, basophilia, and eosinophilia.
VI. Pseudohyperkalemia, most likely from release of intracellular potassium during clot formation, may be noted on the serum biochemical profile.
VII. Bone marrow aspiration reveals increased numbers of megakaryocytes, some of which may exhibit abnormal morphology, as well as erythroid hypoplasia, myeloid hyperplasia, sheets of large granular platelets, and increased numbers of free megakaryocyte nuclei.
VIII. Bone marrow histopathology often reveals increased paratrabecular reticulin fibrosis.
IX. Increased numbers of splenic megakaryocytes in the absence of extramedullary hematopoiesis are suggestive of splenic infiltration by leukemic cells (Dunn et al., 1999).

Differential Diagnosis

I. ET must be differentiated from conditions associated with reactive thrombocytosis, including iron deficiency, chronic blood loss anemia, chronic inflammation, solid tissue neoplasia, and other forms of MPD (see Chapter 67).
II. In humans, the Polycythemia Vera Study Group recommends the following criteria for diagnosis of ET (Murphy et al., 1986):
   A. Platelet count >600,000 cells/μL, with platelet counts usually >1,000,000 cells/μL

B. A normal initial hematocrit or packed-cell volume that does not increase with iron supplementation
C. Normal serum iron concentration and presence of stainable iron in the bone marrow
D. No evidence of collagen fibrosis in bone marrow
E. No identifiable cause for reactive thrombocytosis and no circulating blasts

Treatment

I. Asymptomatic animals may not require treatment.
II. In dogs, possible treatments include the following:
A. Radiolabeled phosphorus in combination with melphalan (Degen et al., 1989)
B. A combination protocol with cyclophosphamide, vincristine, cytosine arabinoside, and prednisone (Simpson et al., 1990)
C. Vincristine (0.7 mg/m^2 once IV) and hydroxyurea (500 mg/m^2 PO per day) (Favier et al., 2004).
1. The hydroxyurea dose was increased (2000 mg/m^2 PO per day) after 3 weeks in both dogs owing to insufficient response.
2. The dogs' conditions deteriorated, however, and pancytopenia was noted in the bone marrow at necropsy, most likely from the high-dose hydroxyurea therapy.
III. The following may be tried in cats:
A. Nandrolone decanoate 15 mg IM once (Evans et al., 1982)
B. Melphalan 0.5 mg PO SID for 4 days, then 0.5 mg PO QOD (Hammer et al., 1990)

Chronic Idiopathic Myelofibrosis

Definition and Classification

I. Many synonyms, such as agnogenic (idiopathic) myeloid metaplasia, osteomyelosclerosis, and chronic megakaryocytic-granulocytic myelosis, apply to this neoplastic transformation of a single hematopoietic stem cell.
II. The condition results in intramedullary and extramedullary hematopoiesis often accompanied by a nonclonal fibroblastic reaction of the bone marrow.
III. Myeloid metaplasia refers to those cases with neoplastic proliferation of predominately granulocytic and megakaryocytic precursors in organs, such as the spleen and liver, with or without marrow fibrosis.
IV. Primary myelofibrosis involves the replacement of normal hematopoietic tissue with increased fibroblasts depositing fine reticulin and thick collagen fibers (Breuer et al., 1999b).
V. Some cases of agnogenic myeloid metaplasia or idiopathic myelofibrosis were previously diagnosed as AML-M7 (Breuer et al., 1999a).

Clinical Signs and Diagnosis

I. Clinical signs include a gradual onset of lethargy, exercise intolerance, inappetence, pale mucous membranes, vomiting, diarrhea, fever, weight loss, and splenomegaly (Weiss and Smith, 2002).
II. Characteristic features include circulating immature granulocytes and erythroid cells (leukoerythroblastic reaction), splenomegaly, hepatomegaly, extramedullary hematopoiesis, and myelofibrosis.
III. Clinicopathologic abnormalities include nonregenerative anemia, poikilocytosis, dacryocytosis (teardrop-shaped erythrocytes), leukocytosis or leukopenia, thrombocytosis or thrombocytopenia (in addition to a leukoerythroblastic reaction), and pancytopenia as the disease progresses.
IV. Extramedullary hematopoiesis is often present in the spleen, liver, or both.
V. Intramedullary megakaryocytopoiesis involving variably sized or polymorphic precursors is commonly found associated with argyrophilic reticulin fibrosis.
VI. Diagnosis of myelofibrosis requires bone marrow histopathology to document replacement of normal marrow architecture by excessive amounts of collagen and reticulin fibers.
A. Evidence of marrow necrosis may be noted.
B. Aspiration for cytological examination is often unrewarding (dry tap).

Differential Diagnosis

I. The main differential diagnosis for primary myelofibrosis is secondary myelofibrosis associated with bone marrow damage and necrosis from conditions such as marrow neoplasia (lymphoproliferative, myeloproliferative, or metastatic), tumors outside the bone marrow, immune-mediated hemolytic anemia, congenital hemolytic anemia (see Chapter 64), drug-induced marrow damage, ehrlichiosis (see Chapter 115), and irradiation.
II. Other rule outs include CML, ET, and acute megakaryoblastic leukemia based on the neoplastic proliferation of granulocytic and megakaryocytic precursors.

Treatment and Monitoring

I. Immune-mediated destruction of erythroid precursors has been hypothesized to be a factor in the development of myelofibrosis in some dogs (Villiers and Dunn, 1999), so therapy is difficult.
II. Treatments that may be tried include the following (Villiers and Dunn, 1999):
A. Blood transfusions
B. Prednisolone 2 to 3 mg/kg PO SID for 3 to 4 weeks, then QOD with tapering of the dose as anemia resolves
C. Nandrolone decanoate 2 mg/kg IM weekly for 3 weeks, then once every 3 weeks
D. Azathioprine 2 mg/kg PO QOD if the anemia does not respond to initial treatments
III. In one study, four of seven dogs responded with resolution of anemia and survived for more than 2 years without continued treatment (Villiers and Dunn, 1999).

RELATED MYELOPROLIFERATIVE DISORDERS

Malignant Histiocytosis

See Chapter 77.

Mast Cell Leukemia

See Chapter 65.

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CHAPTER 67

Platelet Disorders and von Willebrand Disease

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INHERITED DISORDERS

von Willebrand Disease

Definition

von Willebrand disease (vWD) is a bleeding disorder resulting from a deficiency of functional von Willebrand factor (vWF).

Cause and Pathophysiology

I. A deficiency of vWF causes decreased platelet adhesion to the blood vessel wall and impaired formation of the primary hemostatic plug.
   A. vWF circulates in plasma as variably sized multimers of a basic glycoprotein subunit.
   B. The higher molecular weight multimers are more functional in mediating adhesion of platelets to blood vessels.
II. vWF circulates complexed to coagulation factor VIII, thereby stabilizing factor VIII.
III. It is the most common hereditary hemostatic disorder in dogs; it is occasionally identified in cats.
IV. Classification of vWD is based upon the concentration or activity of circulating vWF.
   A. Type I
      1. Concentration or activity of all multimers is reduced but measurable.
      2. The severity of the bleeding disorder is variable.
      3. It is reported in a large number of dog breeds, including Doberman pinschers.
      4. Inheritance is complex, with multiple genetic defects likely; may be an autosomal dominant with incomplete penetrance or an autosomal recessive.
   B. Type II
      1. Concentration of vWF is decreased with a disproportionately greater reduction in high-molecular-weight multimers.
      2. It usually causes a moderate to severe bleeding disorder.
      3. It occurs in German shorthaired and wirehaired pointers, and is an autosomal recessive trait.
   C. Type III
      1. Plasma concentrations of all multimers are undetectable.
      2. It causes a severe bleeding disorder.
      3. It is inherited as an autosomal recessive trait in the Chesapeake bay retriever, Dutch Kooiker, Scottish terrier, and Shetland sheepdog, and is sporadically found in other breeds.
V. Although some reports suggest that hypothyroidism and vWD are related, recent studies demonstrate no clear association between them (Stockham and Scott, 2002).

Clinical Signs

I. Affected animals may have intermittent mucosal bleeding, but petechiae are uncommon (Box 67-1).
II. Some animals do not show clinical signs until they are hemostatically challenged (e.g., surgery, trauma, estrus), become thrombocytopenic, or receive drugs that impair hemostasis.

Diagnosis

I. Platelet concentration and aggregation are usually normal (Box 67-2).
II. Buccal mucosal bleeding time (BMBT) is prolonged with vWD, thrombocytopenia, or platelet dysfunction.
III. A platelet function analyzer (PFA 100) can be used as an in-house screening assay, with prolonged times occurring with vWD, thrombocytopenia, or platelet dysfunction (Callan and Giger, 2001).
IV. Decreased concentration of plasma vWF antigen measured by immunoassay indicates that an animal has vWD or carries the vWD trait.

Box 67-1

Clinical Findings Associated with Platelet Disorders and von Willebrand Disease

Findings	Definition
Petechiae	Pinpoint hemorrhages
Ecchymoses	Bruising
Mucosal hemorrhages	Epistaxis
	Gastrointestinal bleeding
	Gingival bleeding
	Hematuria
	Vaginal bleeding
Hyphema	Ocular anterior chamber hemorrhage
Bleeding tendencies	Excess hemorrhage following trauma, surgery, venipuncture

Box 67-2

Diagnostic Tests for Suggested Platelet Disorders

Tests for Thrombocytopenia

Assay	Comments
Complete blood count	Measures platelet concentration (automated or manual) Increased mean platelet volume suggests increased thrombopoiesis Microscopic examination of blood smears to detect organisms or neoplastic cells, assess for platelet clumping, estimate platelet concentration (each platelet/100× field ≈ 15,000-20,000/μL), or evaluate for enlarged platelets (suggests increased thrombopoiesis)
Bone marrow examination	Assesses megakaryocyte density, maturation, and morphology May detect organisms or neoplastic cells May detect antibodies bound to megakaryocytes using direct immunofluorescence
Serum serology	May detect exposure or response to infectious organisms
Polymerase chain reaction assay	May detect infectious organisms
Platelet flow cytometry	Detects platelet surface-associated immunoglobulins Measures reticulated platelets—increased percentage suggests increased thrombopoiesis

Tests of Platelet Function

Assay	Comments
Buccal mucosal bleeding time	In vivo assessment of primary hemostasis—prolonged with thrombocytopenia, platelet dysfunction, vWD, vascular disorders
Platelet function analyzer (PFA 100)	Assesses primary hemostasis—prolonged times to hemostatic plug formation with thrombocytopenia, platelet dysfunction, vWD
Platelet flow cytometry	Detects platelet activation, membrane glycoproteins, fibrinogen binding, aggregation, calcium fluxes
Platelet aggregation	Assesses ability of platelets to bind to one another
Platelet secretion	Assesses release of granule contents and/or production of thromboxane A2
Platelet adhesion	Detects ability of platelets to adhere to surface

vWD, von Willebrand disease.

A. Enzyme linked immunosorbent assay (ELISA) is commonly used and is rapid and sensitive.
B. vWF concentration <50% of normal pooled plasma is generally considered abnormal.
C. Antigen concentration does not reliably identify carrier animals and may not predict the severity of clinical bleeding.
D. Immunoelectrophoresis is used to differentiate type I from type II vWD.

V. Decreased vWF activity may be measured using agglutination or collagen binding assays, or both.
VI. Rarely, activated partial thromboplastin time (aPTT) is prolonged from a secondary deficiency of factor VIII.
VII. Prothrombin time (PT) should be normal.
VIII. Molecular tests to detect the genetic defect are available in some breeds (Bernese mountain dog, Doberman pinscher, German shorthaired and wirehaired pointers, Kerry blue terrier, Manchester terrier, papillon, Pembroke Welsh corgi, poodles, Shetland sheepdog, Scottish terrier) and can identify whether dogs are normal, carriers, or affected.

Differential Diagnosis

I. Primary platelet disorders: inherited or acquired platelet dysfunction, thrombocytopenia
II. Coagulation disorders: see Chapter 68

Treatment

I. Transfusion therapy is indicated (Table 67-1) during a bleeding episode or before surgery for animals with known bleeding tendencies.
II. Desmopressin acetate (DDAVP) causes release of vWF from endothelial cells.
A. Administration to dogs with vWD (1 μg/kg SC) improves hemostatic function while minimally increasing vWF concentrations (Callan and Giger, 2002).
B. Administration to healthy donor dogs (1 μg/kg SC) 30 to 120 minutes before blood collection increases vWF concentration in plasma or cryoprecipitate.
III. Thyroid supplementation of hypothyroid dogs with vWD may increase vWF concentration in some animals, whereas administration to euthyroid dogs with vWD has no significant effect on BMBT or vWF concentration/activity (Heseltine et al., 2005).
IV. Local bleeding may be controlled with topical hemostatic agents (e.g., methacrylate), cautery, or pressure bandages.

Monitoring of Animal

I. Avoid elective surgical procedures or administration of drugs that inhibit platelet function in known affected animals whenever possible.
II. Do not breed dogs with vWD.

Intrinsic Platelet Dysfunction

Definition and Cause

I. Inherited platelet disorders that are associated with abnormal platelet function are uncommon in the dog and cat (Table 67-2).

TABLE 67-1

Transfusion Therapy for Platelet Disorders and von Willebrand Disease

PRODUCT	DOSAGE	COMMENTS
Whole blood	10-20 mL/kg IV	Supplies erythrocytes, vWF, and platelets Used in animals with severe anemia Not effective as a source of platelets in thrombocytopenic animals Volume overload may occur, so limit administration to once every 24 hours as needed
Platelet-rich plasma	6-10 mL/kg IV	Supplies vWF and platelets Prepared by centrifugation of whole blood Lower volume delivered with higher platelet concentration compared with whole blood Risks of volume overload and production of antiplatelet antibodies increase with repeated transfusions Repeat every 8-12 hours as needed
Platelet concentrate	1 unit/10 kg IV	Supplies platelets Up to 10-fold higher concentration of platelets compared to platelet-rich plasma 1 unit is amount produced from 1 unit of whole blood Risk of production of antiplatelet antibodies occurs with repeated transfusions Repeat every 8-12 hours as needed Commercial cryopreserved product is available
Fresh or fresh frozen plasma	6-12 mL/kg IV	Supplies vWF Preferred over whole blood if there is no need to replace erythrocytes Risk of volume overload occurs with repeated transfusions Repeat every 8-12 hours as needed
Cryoprecipitate	1 unit/ 10 kg IV	Contains 5 to 10 times higher concentration of vWF than plasma 1 unit is amount produced from 200 mL of plasma Causes fewer side effects than plasma Repeat every 6-12 hours as needed

vWF, von Willebrand factor.

II. Most recognized disorders are associated with hemorrhagic tendencies.

Clinical Signs

I. Petechiation, ecchymoses, or both
II. Mucosal hemorrhages
III. Prolonged bleeding after trauma or surgery

Diagnosis

I. Platelet dysfunction should be suspected when clinical signs of a bleeding disorder are present and routine hemostatic tests (platelet concentration, vWF concentration, and coagulation tests) are normal or only mildly decreased (platelet or vWF concentration) or prolonged (PT or aPTT).
II. Prolonged BMBT or PFA 100 closure times are useful screening assays but are not specific for platelet dysfunction.
III. Specific tests to assess platelet function (adhesion, aggregation, secretion; see Box 67-2) require fresh samples (within 2 hours of collection) and are available at some specialty laboratories.
IV. DNA testing is available to detect affected or carrier basset hounds with inherited thrombopathia.

Differential Diagnosis

I. vWD or other platelet disorders: thrombocytopenia, acquired platelet dysfunction
II. Hypofibrinogenemia or other coagulation disorders: see Chapter 68

Treatment

I. No specific treatment is available.
II. Local bleeding may be controlled with topical hemostatic agents, cautery, or pressure bandages.
III. Transfusion therapy is indicated (see Table 67-1) for severe anemia or life-threatening hemorrhage.
IV. Avoid elective surgeries and drugs known to impair platelet function whenever possible.

Breed-Associated Thrombocytopenia

Definition

I. Healthy greyhounds may have mildly decreased platelet concentrations.
II. Clinically normal Cavalier King Charles spaniels frequently have platelet concentrations <100,000/μL and increased numbers of large platelets (Cowan et al., 2004).

TABLE 67-2

Inherited Disorders of Platelet Function

DISORDER	SPECIES	PLATELET ABNORMALITIES AND DIAGNOSIS	CLINICAL SIGNS
Chediak Higashi syndrome	Cat	Decreased dense granules, enlarged lysosomal granules, prolonged buccal mucosal bleeding time, abnormal platelet aggregation, impaired secretion of adenosine diphosphate, triphosphate, and serotonin	Persians with partial albinism, photophobia, risk for infection, neurological defects Bleeding tendencies vary from mild to severe and include easy bruising, mucosal hemorrhages, and excess hemorrhage after trauma or surgery
Cyclic hematopoiesis	Dog	Cyclic thrombocytopenia, decreased serotonin and calcium in dense granules, abnormal platelet aggregation and secretion	Collies with stem cell defect and cyclic neutropenia Diluted hair coat color, recurrent infections, bleeding tendencies
Glanzmann's thrombasthenia	Dog	Decreased or defective membrane glycoprotein IIbIIIa complex, impaired fibrinogen binding, impaired adhesion, abnormal platelet aggregation	Otterhounds, Great Pyrenees Bleeding tendencies vary from mild to severe and include spontaneous episodes of mucosal hemorrhage
Miscellaneous signal transduction disorders	Dog, cat	Associated with postreceptor defects in production or regulation of intracellular second messengers, abnormal platelet aggregation and/or secretion	Basset hounds, spitz, domestic shorthair cats Bleeding tendencies vary from mild to severe and include spontaneous episodes of mucosal hemorrhage.
Procoagulant deficiency	Dog	Abnormal membrane phosphatidylserine exposure, abnormal platelet activity in enzyme complexes in coagulation, normal platelet aggregation and secretion	German shepherd dogs with mild to moderate bleeding tendencies that include epistaxis, hyphema, hemorrhage postsurgery
Storage pool disorders	Dog	Decreased adenosine diphosphate in dense granules, normal number of dense granules, prolonged buccal mucosal bleeding time, impaired platelet aggregation to adenosine diphosphate	American cocker spaniels with moderate to severe bleeding following trauma or surgery

Clinical Signs and Treatment

I. Dogs are asymptomatic.
II. No treatment or monitoring is required.

ACQUIRED PLATELET DYSFUNCTION

Definition

I. Platelet hyporesponsiveness or hyperresponsiveness that results from an underlying disorder.
II. Underlying pathophysiology is often unknown but may be associated with alterations in platelet membranes, receptors, or signal transduction pathways.

Causes

I. Drugs
  A. Prostaglandin inhibitors: aspirin, carprofen, ibuprofen, indomethacin, ketoprofen, naproxen, phenylbutazone
  B. Regulators of cyclic adenosine monophosphate (cAMP) or cyclic guanosine monophosphate (cGMP): dipyridamole, prostaglandin I_2, prostaglandin E_1
  C. Calcium antagonists: diltiazem, verapamil
  D. Antibiotics/antimicrobials: carbenicillin, cephalosporins, penicillin, ticarcillin
  E. Others: acepromazine, aminophylline, antihistamines, chondroitin sulfate, dextran, halothane, heparin, protamine sulfate, propanolol, ticlopidine
II. Disorders associated with decreased reactivity
  A. Disseminated intravascular coagulation (DIC)
  B. Dysproteinemia
  C. Hepatic failure
  D. Infections: rickettsial, viral
  E. Immune-mediated thrombocytopenia
  F. Neoplasia
  G. Snake venoms
  H. Uremia
III. Disorders associated with increased reactivity
  A. Canine heartworm disease
  B. Feline cardiomyopathy
  C. Infections: rickettsial, viral
  D. Neoplasia
  E. Nephrotic syndrome

Clinical Signs

I. Spontaneous hemorrhage is uncommon unless the animal is hemostatically challenged (surgery, trauma), has a concurrent coagulation disorder or thrombocytopenia, or receives drugs that inhibit hemostasis.
II. Petechiae, ecchymoses, and mucosal hemorrhages may occur if platelets are hyporesponsive.
III. Signs associated with thrombosis may develop if platelets are hyperresponsive.

Diagnosis

I. Prolonged BMBT is a useful screening assay to detect hyporesponsive platelets.
II. No readily available in-house screening assays exist to detect hyperresponsive platelets.
III. Assays to evaluate specific platelet function (adhesion, aggregation, flow cytometry; see Box 67-2) are available in specialty laboratories but require fresh samples (<2 hours old).
IV. Serum biochemistry profiles are performed to evaluate organ function and plasma protein levels.
V. A hemostatic profile is used to detect DIC (see Chapter 68).
VI. Serology and/or polymerase chain reaction (PCR) assays may be run if infection is suspected.

Differential Diagnosis

I. vWD or other platelet disorders: thrombocytopenia or inherited platelet dysfunction
II. Coagulation disorders: see Chapter 68

Treatment and Monitoring

I. Discontinue administration of drugs suspected to cause platelet dysfunction.
II. Transfusion therapy (see Table 67-1) is recommended for severe anemia or life-threatening hemorrhage.
III. Institute specific therapy for any underlying disorder.
IV. Nonsteroidal antiinflammatory drugs (aspirin 0.5 mg/kg BID) may be used in dogs to inhibit platelet function if they are at risk for thrombotic disorders.
V. Platelet function usually returns to normal when the underlying disorder is resolved.

THROMBOCYTOPENIA

Immune-Mediated Thrombocytopenia

Definition

I. Decreased platelet numbers occur from an immune response directed against platelets, megakaryocytes, or both.
II. It is a common disorder in dogs and is found only sporadically in other species.

Causes

I. With primary immune-mediated trombocytopenia (IMT), the immune response is directed against autoantigens and is not associated with an underlying disease.
   A. Possible genetic predisposition: American cocker spaniel, poodle, Old English sheepdog (Lewis and Meyers, 1996)
   B. Predilection for middle-aged, female dogs
II. With secondary IMT, the immune response is associated with an underlying disorder.
   A. Systemic immune-mediated disorders: systemic lupus erythematosus, immune-mediated hemolytic anemia (IMHA)
   B. Neoplasia: lymphoma, myeloproliferative disorders, various solid tumors
   C. Drugs: sulfonamides in dogs, methimazole or propylthiouracil in cats
   D. Infections: certain bacteria, ehrlichiosis, canine distemper virus, feline immunodeficiency virus (FIV), feline leukemia virus (FeLV), leishmaniasis, babesiosis, histoplasmosis, heartworm disease
   E. Vaccination with modified live viruses

Pathophysiology

I. Immune response causes decreased platelet lifespan because of complement-mediated intravascular platelet lysis or (more commonly) platelet removal by the mononuclear phagocytic system.
II. A secondary platelet dysfunction may also exacerbate hemorrhagic tendencies.
III. In primary IMT, the immune response is most commonly directed against membrane glycoprotein (GP) IIbIIIa.
IV. Secondary IMT can result from the following mechanisms:
   A. Cross-reactive antibodies that recognize both foreign antigens and platelet antigens
   B. Exposure of previously hidden self-antigens in platelet membranes
   C. Formation of a neoantigen from reaction between the platelet and foreign antigens
   D. Antibody reaction against foreign antigen adsorbed to platelet membrane
   E. Formation of immune complexes that subsequently bind to platelet membrane

Clinical Signs

I. Dogs with primary IMT are often asymptomatic unless there is significant associated anemia.
II. The risk for hemorrhage (see Box 67-1) depends on platelet concentrations (Box 67-3) and the presence or absence of acquired platelet dysfunction.
III. Animals with secondary IMT usually have signs associated with the underlying disease process.

Diagnosis

I. The diagnosis of primary IMT is often based upon exclusion of other causes of thrombocytopenia and the response to immunosuppressive drug therapy.
II. Complete blood count (CBC) may reveal the following (see Box 67-2):
   A. Thrombocytopenia is often severe.
   B. Anemia may be present from hemorrhage or concurrent IMHA.

Box 67-3

Risk for Hemorrhage with Thrombocytopenia

Platelet Concentration*	Risk for Spontaneous Clinical Bleeding
<50,000/μL	Microscopic hemorrhage
<20,000/μL	Mild risk
<10,000/μL	Moderate risk
<5,000/μL	Severe risk

From Abrams-Ogg ACG: Triggers for prophylactic use of platelet transfusions and optimal platelet dosing in thrombocytopenic dogs and cats. Vet Clin North Am Small Anim Pract 33:1401, 2003.
*Spontaneous clinical bleeding may occur at higher platelet concentrations in animals with concurrent platelet dysfunction, von Willebrand disease, or coagulation disorders.

C. Leukocyte values may be normal or may indicate an inflammatory or stress leukogram.

III. Mean platelet volume (MPV) may be increased, decreased, or normal.
   A. Decreased MPV occurs frequently in dogs with IMT but may be an artifact of nonplatelet debris in samples with severe thrombocytopenia.
   B. Increased MPV is suggestive of increased thrombopoiesis.
   C. Blood collected in ethylenediaminetetraacetic acid (EDTA) may have platelet swelling and an artifactual increase in MPV.

IV. Assays to detect platelet surface-associated immunoglobulin (PSAIg) may be run.
   A. Currently available assays cannot differentiate primary and secondary IMT.
   B. Flow cytometric assays have high sensitivity; however, nonspecific binding of antibodies to the platelet surface may occur.
   C. Significant increases in PSAIg occur in vitro 24 to 72 hours after sample collection (Wilkerson et al., 2001).

V. PT and APTT are normal with uncomplicated primary IMT.

VI. Activated clotting time may be prolonged with severe thrombocytopenia (<10,000/μL).

VII. Microscopic examination of the bone marrow reveals normal to an increased number of megakaryocytes if the immune response is directed against platelets, and a decreased number of megakaryocytes if the response is directed against megakaryocytes.
   A. Direct immunofluorescence is used to detect antibodies bound to megakaryocytes.
   B. Thrombocytopenia does not preclude collection of a bone marrow sample.

VIII. Serological or PCR assays are used to identify infectious agents in secondary IMT.

Differential Diagnosis

I. Nonimmune causes of increased platelet destruction, consumption, or sequestration

II. Bone marrow suppression of platelet production

Treatment

I. Institute immunosuppressive therapy with prednisone (1 to 3 mg/kg PO BID) for at least 2 weeks (Lewis and Meyers, 1996).
   A. Generally expect a response within 24 to 96 hours.
   B. Gradually taper dose over weeks to months to the minimal effective dose.
   C. Consider also using H_2 blockers (famotidine 0.5 mg/kg SID) to help prevent gastrointestinal ulceration (Couto, 2003).

II. Consider adding these other therapies to prednisone if response is unsatisfactory:
   A. Vincristine 0.02 mg/kg IV as a single dose (Rozanski et al., 2002)
   B. Danazol 5 mg/kg PO BID (Lewis and Meyers, 1996)
   C. Azathioprine 2 mg/kg PO SID initially (Lewis and Meyers, 1996; Mackin, 1995)
      1. Eventually taper to a maintenance dose of 0.5 to 1.0 mg/kg QOD
      2. More effective in maintaining than inducing remission
   D. Cyclophosphamide 50 mg/m^2 PO SID for 4 days each week until positive response (Lewis and Meyers, 1996; Mackin, 1995)

III. Splenectomy, cyclosporine, colchicine, chemotherapeutic protocols for lymphoma, or human IV immunoglobulin may be considered in refractory cases (Couto, 2003; Lewis and Meyers, 1996; Mackin, 1995).

IV. Keep the animal quiet to minimize potential trauma, and avoid elective surgeries.

V. Transfusion therapy (see Table 67-1) may be used to replace erythrocytes if there is significant anemia; however, administration of platelet concentrates is of questionable value owing to rapid removal of transfused platelets and is usually reserved for life-threatening hemorrhaging.

VI. Avoid drugs known to inhibit platelet function whenever possible.

VII. Treat underlying causes of secondary IMT.
   A. Stop administration of drugs suspected to cause thrombocytopenia.
   B. Administer appropriate antimicrobial drugs in cases of suspected infection.
   C. Initiate appropriate chemotherapy, radiotherapy, or surgery for neoplasia.

Monitoring of Animal

I. Most cases of primary IMT have increased platelet concentrations (>50,000/μL) within 1 week of initiating prednisone therapy.

II. Measure platelets every 1 to 2 days until they exceed 50,000/μL, then weekly until the concentration normalizes.

III. Approximately 40% of dogs with primary IMT have a recurrence of thrombocytopenia and some require lifelong therapy (Lewis and Meyers, 1996).

IV. Secondary IMT usually resolves following successful treatment of the underlying disorder.

Infectious Thrombocytopenia

Definition and Causes

I. Decreased circulating platelet concentrations result from infection.
II. Causes are numerous (Table 67-3).

Pathophysiology

I. Various underlying mechanisms (individually or in combination)
II. Impaired megakaryocytopoiesis from direct infection of megakaryocytes, immune responses against megakaryocytes, or inflammatory responses in bone marrow
III. Altered platelet distribution, with sequestration in spleen or other tissues
IV. Increased platelet consumption from platelet activation, vasculitis, or secondary consumptive coagulopathy
V. Direct damage to platelets causing increased destruction and removal by mononuclear phagocytic system
VI. Secondary IMT, with increased platelet destruction

Clinical Signs

I. Hemorrhages (see Box 67-1) occur with severe thrombocytopenia (see Box 67-3), or if mild to moderate thrombocytopenia is associated with acquired platelet dysfunction or vasculitis.

TABLE 67-3

Infectious Agents Associated with Thrombocytopenia in Dogs and Cats

AGENTS	CLINICAL DISEASE	SPECIES AFFECTED
Viruses	Distemper	Dog
	Feline leukemia virus	Cat
	Feline immunodeficiency virus	Cat
	Feline infectious peritonitis	Cat
	Herpesvirus	Dog
	Infectious hepatitis	Dog
	Parvovirus	Cat, dog
Bacteria	Bacteremia/endotoxemia	Cat, dog
	Bartonellosis	Dog
	Borreliosis	Dog
	Leptospirosis	Dog
	Salmonellosis	Cat, dog
Rickettsia	Ehrlichiosis	Cat, dog
	Rocky Mountain spotted fever	Dog
Protozoa	Babesiosis	Dog
	Cytauxzoonosis	Cat
	Leishmaniasis	Dog
	Toxoplasmosis	Cat
Fungi	Disseminated candidiasis	Dog
	Histoplasmosis	Cat, dog
Miscellaneous	Heartworm disease	Cat, dog
	Hemotropic *Mycoplasma* spp.	Dog

II. Usually clinical signs are associated with the underlying infectious agent.

Diagnosis

I. CBC findings are variable.
  A. Thrombocytopenia ranges from mild to severe.
  B. Concurrent leukocytosis, leukopenia, and anemia may occur, depending on the organism.
  C. Microscopic examination of a blood smear may identify infectious agents.
II. Hemostatic profile may be abnormal if a secondary coagulopathy (see Chapter 68) is present.
III. A bone marrow sample may reveal an infectious agent, and megakaryocyte production may be decreased, increased or adequate depending on the organism's effect on hematopoietic cells and/or bone marrow microenvironment.
IV. Serologic and/or PCR assays are useful to identify the infectious agent.
V. Cytology of abnormal organs (lymph nodes, liver, spleen) may also reveal organisms.

Differential Diagnosis

I. Other causes of increased platelet destruction, consumption, and sequestration
II. Primary bone marrow disorder

Treatment

I. Begin antimicrobials specific for the inciting organism.
II. Supportive care includes fluid therapy, antiinflammatory drugs, or both.
III. Transfusion therapy (see Table 67-1) is indicated for significant anemia or life-threatening hemorrhage.

Monitoring of Animal

I. Prognosis depends on the underlying etiologic agent.
II. Thrombocytopenia often resolves with resolution of the underlying infection.

Drug- or Toxin-Induced Thrombocytopenia

Definition and Causes

I. Decreased circulating platelet concentration occurs secondary to administration of some drugs or toxins.
II. See Box 67-4 for a list of causes.
III. Thrombocytopenia may be predictable and dose dependent, or it may be idiosyncratic.

Pathophysiology

I. Impaired bone marrow production from direct destruction of megakaryocytes, immune responses targeting megakaryocytes, and altered microenvironment
II. Direct activation of platelets with increased consumption
III. Direct damage to platelets leading to increased destruction and decreased lifespan
IV. Secondary IMT causing increased platelet destruction by the mononuclear phagocytic system

Box 67-4

Drugs Associated with Thrombocytopenia in Dogs and Cats

Antibiotics/Antimicrobials

Cephalosporins, chloramphenicol, dapsone, sulfonamides

Antiinflammatory Drugs

Carprofen, phenylbutazone

Chemotherapeutic Drugs

Azathioprine, cisplatin, cyclophosphamide, cytosine arabinoside, doxorubicin, 5-fluorouracil, hydroxyurea, lomustine, melphalan, mitoxantrone

Miscellaneous

Albendazole, estrogen, griseofulvin, levamisole, methimazole, phenobarbital, propylthiouracil, protamine sulfate, thiacetarsamide

Clinical Signs

I. Hemorrhages (see Box 67-1) occur with severe thrombocytopenia (see Box 67-3) or with mild to moderate thrombocytopenia associated with platelet dysfunction.
II. Signs of anemia (weakness, lethargy) or leukopenia (infection) may occur with myelosuppressive drugs.

Diagnosis

I. Thrombocytopenia ranges from mild to severe.
II. Concurrent anemia, leukopenia, or both are possible with myelosuppressive drugs.
III. A bone marrow sample may reveal a decrease in the number of megakaryocytes with myelosuppressive drugs and an adequate number to an increase in the number of megakaryocytes with drugs that cause increased extramedullary platelet destruction or consumption.
IV. Diagnosis is often based on thrombocytopenia occurring after drug administration and normalization of platelet concentration with cessation of that drug.

Differential Diagnosis

I. Other causes of increased platelet destruction, consumption, and sequestration
II. Primary bone marrow disorder

Treatment

I. Discontinue administration of suspected drug or toxin.
II. Immunosuppressive prednisone therapy is indicated if thrombocytopenia is ongoing and secondary IMT is suspected (see Diagnosis under Immune-Mediated Thrombocytopenia).
III. Transfusion therapy (see Table 67-1) is indicated for significant anemia or life-threatening hemorrhage.

Monitoring of Animal

I. Measure platelets every 1 to 2 days until platelet counts exceed 50,000/μL, then weekly until they are normal.
II. Prognosis is good if platelets increase after drug is stopped.
III. Prognosis is poor if thrombocytopenia continues after drug is stopped.

OTHER THROMBOCYTOPENIC DISORDERS

See Table 67-4.

PLATELET PRODUCTION DISORDERS

Definition

I. Decreased circulating platelets result from impaired bone marrow production.
II. Decreased production may arise from primary bone marrow disorders or from exogenous factors affecting the bone marrow.

Causes

I. Drugs: cefazedone, chemotherapeutic drugs, chloramphenicol, estrogen, griseofulvin, methimazole, phenylbutazone, sulfonamides, thiacetarsamide
II. Infections: chronic ehrlichiosis, canine distemper, parvovirus, FeLV, FIV
III. Immune reactions targeting megakaryocytes, with megakaryocyte destruction or impaired thrombopoiesis
IV. Myelophthisis from neoplasia or myelofibrosis
V. Bone marrow necrosis
VI. Irradiation

Pathophysiology

I. Megakaryocytic hypoplasia from destruction of hematopoietic precursor cells or altered microenvironment in the bone marrow
   A. Occasionally selective megakaryocytic hypoplasia
   B. Generalized bone marrow disease associated with erythroid or myeloid hypoplasia
II. Occasional dysmegakaryocytopoiesis
   A. Associated with megakaryocyte maturation and morphologic abnormalities
   B. Most commonly associated with myelodysplastic disorders or acute leukemia
III. Myelophthisis
   A. Replacement of normal hematopoietic cells by a population of abnormal cells, such as neoplastic cells or fibrous connective tissue
   B. Neoplastic cells usually of hematopoietic origin (myeloproliferative or lymphoproliferative disorders) but occasionally metastatic from other sites

Clinical Signs

I. Hemorrhage occurs with severe thrombocytopenia (see Box 67-3) or with mild to moderate thrombocytopenia associated with acquired platelet dysfunction.
II. Clinical signs of anemia, leukopenia, or both may occur with hypoplasia of other cell lines.

TABLE 67-4

Other Thrombocytopenic Disorders

DISORDER	CAUSES/PATHOPHYSIOLOGY	DIAGNOSIS	TREATMENT/PROGNOSIS
Localized or disseminated neoplasia	Impaired bone marrow production Distribution disorder DIC Secondary IMT Platelet destruction by neoplastic cells Tumor-associated hemorrhage	Mild to severe thrombocytopenia Cytology and/or biopsy of abnormal tissue to identify neoplastic cells Abnormal hemostatic profile with DIC (see Chapter 68)	Transfusion for severe anemia or life-threatening hemorrhage Treatment and prognosis specific for underlying neoplasm
Increased platelet consumption	DIC Vasculitis Hemolytic uremic syndrome Envenomation Vitamin K antagonism	Mild to severe thrombocytopenia Clinical signs associated with underlying disorder Abnormal hemostatic profile with DIC or vitamin K antagonism (see Chapter 68)	Transfusion for severe anemia or life-threatening hemorrhage Treatment and prognosis specific for underlying cause DIC or vitamin K antagonism: see Chapter 68
Distribution disorder	Organomegaly, especially splenomegaly	Mild to moderate thrombocytopenia Diagnostic imaging and/or palpation to identify organomegaly Rule out other causes of thrombocytopenia	No specific treatment for thrombocytopenia
Platelet loss	Severe hemorrhage Vitamin K antagonists	Anemia and decreased total protein concentration Mild to moderate thrombocytopenia with blood loss, occasionally severe with vitamin K antagonists Severe thrombocytopenia with hemorrhage usually suggests hemorrhage from thrombocytopenia, not thrombocytopenia from hemorrhage. Prolonged PT and APTT with vitamin K antagonism	Control hemorrhage No specific treatment for thrombocytopenia Transfusion for severe anemia or life-threatening hemorrhage Vitamin K antagonism: see Chapter 68

DIC, Disseminated intravascular coagulation; *IMT,* immune-mediated thrombocytopenia; *PT,* prothrombin time; *APTT,* activated partial thromboplastin time.

Diagnosis

I. CBC findings are variable.
   A. Thrombocytopenia varies from mild to severe.
   B. Evidence of platelet regeneration is lacking (MPV normal, no increase in large platelets) with megakaryocytic hypoplasia.
   C. Abnormal cells may be identified with leukemia or myelodysplasia.
   D. Concurrent nonregenerative anemia and leukopenia may be detected.

II. Microscopic examination of a bone marrow sample is critical for diagnosis and prognosis.
   A. Megakaryocytic hypoplasia is characterized by decreased number of megakaryocytes.
   B. Dysmegakaryocytopoiesis is characterized by maturation and morphological abnormalities (mega-megakaryocytes, dwarf megakaryocytes, nuclear hypolobulation).
   C. Neoplastic cells or infectious agents may be identified.
   D. Direct immunofluorescence detects antibodies bound to megakaryocytes in secondary IMT.

Differential Diagnosis

I. Causes of platelet destruction
II. Causes of platelet consumption and sequestration

Treatment

I. Treat the underlying cause.
   A. Chemotherapy for neoplasia
   B. Immunosuppressive therapy (see Immune-Mediated Thrombocytopenia) for suspected immune-mediated destruction
   C. Drug discontinued if suspected drug reaction
   D. Antimicrobial drugs for suspected infections

II. Recombinant human interleukin (IL) 11 increases megakaryocyte production in normal dogs and shortens recovery following irradiation (Nash et al., 1995).

A. Controlled studies are lacking on the efficacy and safety of IL11 administration in dogs or cats with spontaneous thrombocytopenia.
B. There is a risk of production of neutralizing antibodies with extended use.

III. Administer transfusion therapy (see Table 67-1) for severe anemia or life-threatening hemorrhage.

Monitoring of Animal

I. The prognosis is guarded and depends on the underlying cause.
   A. Animals with IMT and megakaryocytic hypoplasia often have a poorer prognosis and a delayed response to treatment when compared with animals with adequate to increased megakaryocyte production (Stockham and Scott, 2002).
   B. Dogs with lymphoma and bone marrow involvement have a poorer prognosis than those with no bone marrow involvement.
   C. Animals with acute myeloid leukemia have a poor prognosis.

II. Measure platelets weekly until platelet concentration normalizes.

III. Perform a bone marrow examination weekly to monitor progress if the platelet concentration does not steadily increase.

Spurious Thrombocytopenia

Definition

I. Platelet clumping artifactually lowers measured platelet concentrations.

II. It occurs from the following:
   A. Activation of platelets during venipuncture or in vitro sample handling
   B. EDTA-dependent antibody binding causing platelet agglutination
   C. Cold agglutinins causing platelet agglutination

III. Samples with large numbers of large platelets may have falsely decreased platelet counts, because large platelets are excluded by some automated hematology analyzers.

Diagnosis

I. Blood smears are microscopically evaluated for platelet clumps.

II. When clumps are present, the measured platelet concentration is considered a minimal value.

Treatment and Monitoring

I. Collection of a new sample is required to obtain an accurate platelet concentration when clumps are present.

II. Clumping can be minimized by atraumatic venipuncture, use of citrate as an anticoagulant, or addition of platelet inhibitors to the sample (Norman et al., 2001).

III. Manual platelet counts may be effective in samples with increased numbers of large platelets.

THROMBOCYTOSIS

Definition

I. Increased circulating platelet concentrations

II. Associated with a variety of disorders

Causes and Pathophysiology

I. Myeloproliferative disorders arise from clonal expansion of hematopoietic precursor cells.
   A. Thrombocytosis occurs with acute megakaryocytic leukemia or essential thrombocythemia.
   B. Platelet function may be normal, hyporesponsive, or hyperresponsive.

II. Reactive thrombocytosis occurs from increased platelet production secondary to an underlying disorder associated with increased production of leukocytes, erythrocytes, or both.
   A. It may be associated with increased production of cytokines (IL1, IL4, IL6) that stimulate megakaryocyte production or maturation in the bone marrow.
   B. Platelet function is normal and hemostatic complications are uncommon.
   C. Reported causes include iron deficiency, blood loss anemia, chronic inflammation or infection, hemolytic anemia, hyperadrenocorticism, neoplasia, trauma, drugs (vincristine) or following splenectomy.

III. Redistribution thrombocytosis develops from release of platelets from the spleen or other storage sites.
   A. Transient increases are associated with exercise, fear, stress, or acute hemorrhage.
   B. Redistribution increases circulating platelet concentration but does not alter total body platelet numbers.

Clinical Signs

I. Animals with myeloproliferative thrombocytosis are at risk for hemorrhage or thrombosis.

II. Clinical signs may be associated with the underlying disorder in reactive thrombocytosis.

Diagnosis

I. Redistribution thrombocytosis causes a transient increase in platelet concentration.

II. Reactive thrombocytosis may result in the following:
   A. CBC often reveals anemia, leukocytosis, or both, as well as normal platelet morphology.
   B. Megakaryocytic hyperplasia is expected on microscopic examination of bone marrow.
   C. Identification of an underlying inflammatory or neoplastic disorder supports the diagnosis.

III. Myeloproliferative thrombocytosis is characterized by the following:
   A. CBC may reveal abnormal platelet morphology and circulating megakaryoblasts, as well as marked thrombocytosis.
   B. Diagnosis of essential thrombocythemia is based on ruling out causes of reactive thrombocytosis in an animal with a persistent thrombocytosis (see Chapter 66).

C. Microscopic examination of a bone marrow sample is helpful.
   1. Increased number of megakaryoblasts (blasts >30% of nucleated cell population) and abnormal megakaryocytopoiesis in animals with acute megakaryocytic leukemia
   2. Increased number of megakaryocytes with or without abnormal megakaryocytopoiesis in animals with essential thrombocythemia

Treatment and Monitoring

I. No specific antiplatelet therapy is required in animals with reactive or redistribution thrombocytosis, as the thrombocytosis normalizes with resolution of underlying disorder.
II. See Chapter 66 for treatment of essential thrombocythemia.

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CHAPTER 68

Disorders of Coagulation and Fibrinolysis

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LABORATORY ASSESSMENT

I. Coagulation and fibrinolysis are intimately related, opposing processes that are often assessed together with tests of platelet function and von Willebrand disease (Chapter 67).
II. Appropriate sample collection and processing are critical for reliable results.
   A. Free-flowing blood must be collected by "clean" venipuncture.
   B. Samples should contain 1 part 3.2% or 3.8% sodium citrate anticoagulant to 9 parts blood.
   C. Blood may be collected from catheters after flushing with saline and discarding at least six times a catheter's dead space.
   D. It is best to remove plasma after centrifugation within 1 hour of collection (storage at room temperature) and to run tests within 4 hours.
   E. Plasma may be frozen and mailed on ice to arrive within 24 hours for testing.
   F. The activated coagulation time (ACT) is a cage-side test that requires specific ACT tubes.
III. Routine coagulation and fibrinolytic tests are used to recognize and characterize hemostatic disorders (Table 68-1).
   A. Prolongation of prothrombin time (PT) or activated partial thromboplastin time (aPTT) generally occurs with single-factor deficiencies ≤30% of normal and with moderate deficiencies of multiple factors.
   B. The ACT is less sensitive than the aPTT and requires single intrinsic factor deficiencies <5% to 10% of normal for prolongations.
   C. Fibrin degradation products (FDPs and D-dimers) are usually assessed for evidence of thrombosis and subsequent fibrinolysis.
   D. FDPs also increase with hyperfibrinogenolysis.
   E. Antithrombin III (ATIII) is an endogenous anticoagulant used to detect prothrombotic states that either arise from ATIII deficiency (from loss or decreased hepatic production) or cause ATIII consumption during the clotting process.
      1. ATIII inhibits all the enzymatic factors of the intrinsic and common pathway (XIIa, XIa, Xa, IXa, IIa), and its activity is greatly potentiated by heparins.

TABLE 68-1

Interpretation of Routine Tests of Coagulation and Fibrinolysis

TEST	RESULT	POTENTIAL CAUSES
ACT	Prolonged	Intrinsic and/or common pathway deficiencies, coagulation inhibitors
aPTT	Prolonged	Intrinsic and/or common pathway deficiencies, coagulation inhibitors
ATIII	Decreased	Protein-losing nephropathy/enteropathy, consumptive coagulation, decreased hepatic production, postheparin administration
D-dimers	Elevated	Fibrinolysis secondary to localized or disseminated coagulation, decreased D-dimer clearance, inflammation, trauma, surgery
FDPs	Elevated	Increased fibrin(ogen)olysis (possibly secondary to localized or disseminated coagulation), decreased FDP clearance, inflammation, trauma, surgery
PT	Prolonged	Extrinsic and/or common pathway deficiencies, coagulation inhibitors
TT*	Prolonged	Afibrinogenemia or hypofibrinogenemia from decreased hepatic production or increased consumption, dysfibrinogenemia

ACT, Activated coagulation time; *aPTT,* activated partial thromboplastin time; *ATIII,* antithrombin III; *FDPs,* fibrin(ogen) degradation products; *PT,* prothrombin time; *TT,* thrombin time.

*TT (Clauss method) is routinely used as a functional assay of fibrinogen and converted to a fibrinogen concentration (mg/dL), which is inversely related to the TT.

2. It is measured by functional assays for anti-IIa or anti-Xa activity.
3. Results are reported as the percentage of activity relative to either normal human or species-specific plasma.

IV. Additional tests are also available.
   A. For assessment of coagulation, tests include fibrinogen antigen (immunoassay), specific factor activities (II, VII, VIII, IX, X, XI, XII, prekallikrein, high-molecular-weight kininogen [HMWK]), and the Russell Viper Venom Test (RVVT) to assess the common pathway.
   B. Additional anticoagulation assays include an anti-Xa (activated Factor X) assay for animals receiving unfractionated or low-molecular-weight heparin (LMWH), and tests for protein C and lupus anticoagulants.
   C. Inhibitors of coagulation factors are assessed by functional coagulation assays and mixing studies using test plasma mixed with normal or factor-deficient plasmas.

V. Thromboelastography (TEG) is available at some institutions to analyze the entire process of clot formation and dissolution (Wiinberg et al., 2005).

INHERITED/CONGENITAL INTRINSIC PATHWAY DEFICIENCIES

Prekallikrein and Factor XII Deficiencies

Definition and Causes

I. The contact factors, Factor XII (Hageman factor), HMWK, and prekallikrein are produced by the liver; together they initiate coagulation via contact with activating surfaces (e.g., subendothelium).
II. Two of them, HMWK and prekallikrein, circulate together with Factor XI.
III. Assembly of contact factors on negatively charged endothelial cells or other activating surfaces results in the generation of Factor XIIa and subsequent cascade of the intrinsic and common pathways via Factor XIa.
IV. Decreased functional amounts of these factors in plasma are considered deficiencies.
   A. Deficiencies may occur as inherited or congenital defects.
   B. Deficiencies may also occur with hepatic failure, consumptive coagulation, or anti-factor antibodies (inhibitors).
   C. Factor XII deficiency is relatively common in cats and is an autosomal recessive trait.
      1. It may occur alone or with hemophilia A or B (Kier et al., 1980).
      2. It has been reported in a few purebred dogs, alone and combined with either von Willebrand disease (vWD) or prekallikrein deficiency.
   D. Prekallikrein deficiency has been reported in a few purebred dogs, and it may be inherited.
   E. HMWK deficiency has not been reported in dogs or cats.

Pathophysiology and Clinical Signs

I. Single contact factor deficiencies may promote hemorrhage; however, they do not *cause* hemorrhage, because the intrinsic pathway can be activated by the extrinsic and common pathways.
II. Deficiencies of these proteins may predispose to thromboembolic disease in people, but there is currently no evidence for a prothrombotic tendency in affected dogs and cats.
III. Clinical signs are not expected with single contact factor deficiencies, so recognition is incidental and occurs in animals undergoing hemostatic testing for other reasons.
IV. If hemorrhage or thrombotic disease is present, efforts are directed toward identifying other causes, although a deficiency of these factors may be contributory.

Diagnosis and Differential Diagnosis

I. Congenital contact factor deficiencies are considered when aPTT and/or ACT are prolonged, and PT and thrombin time (TT) values are normal.
II. Specific factor analyses are used to confirm a contact factor deficiency.
III. Other conditions to be considered include hemophilia A or B, Factor XI deficiency, liver disease, and intrinsic pathway factor inhibitors such as heparin, antibodies to coagulation factors (referred to as *inhibitors*), or antiphospholipid/protein antibodies.

Treatment and Monitoring

I. Treatment and monitoring are directed toward the primary problems.
II. Once other causes of aPTT prolongation have been excluded, elective surgical or other invasive procedures may proceed.
III. Fresh frozen plasma may be given before surgery for animals with prekallikrein or mixed deficiencies, or when these deficiencies may be contributing to hemorrhage.

Factor XI Deficiency (Hemophilia C)

Definition and Causes

I. Factor XI is produced in the liver and circulates with prekallikrein and HMWK.
II. Thrombin or Factor XIIa activates Factor XI to Factor XIa, which then activates Factor IX.
III. Factor XI deficiency is a decrease in functional Factor XI caused by either a dysfunctional protein or a decreased concentration of normal Factor XI.
IV. Factor XI deficiency is rare, but has been reported in Kerry blue terriers (Knowler et al., 1994), other purebred dogs, and a domestic shorthair cat.
V. It may be an autosomal trait, but heritability has been unproven in some cases.

Pathophysiology and Clinical Signs

I. Factor XI deficiency impairs the intrinsic coagulation pathway cascade.

II. Spontaneous hemorrhage is not expected, but epistaxis, menorrhagia, hematuria, bruising, hematomas, and prolonged hemorrhage after surgical or nonsurgical trauma may occur with severe deficiencies.
III. Posttraumatic hemorrhage may be delayed several days.
IV. With acute severe blood loss, clinical signs of anemia and hypovolemia may occur.

Diagnosis and Differential Diagnosis

I. Congenital or inherited Factor XI deficiency is considered along with other intrinsic pathway factor deficiencies (XII, prekallikrein, IX, and VIII) when there are unexplained prolongations of aPTT and/or ACT, and PT and TT values are normal.
II. Confirmation of a single Factor XI deficiency requires specific factor analyses.
III. Other laboratory and clinical findings help exclude secondary causes of prolonged aPTT and ACT, such as hepatic disease, vitamin K antagonism or deficiency, consumptive coagulation, Factor VIII deficiency associated with vWD, and the rare presence of coagulation factor inhibitors.

Treatment and Monitoring

I. Initial therapy is directed at expansion of circulatory volume, correction of anemia, and administration of Factor XI (Box 68-1).
II. Concurrent management of underlying or associated conditions may also be necessary.
III. With severe acute hemorrhage, initial monitoring focuses on restoration of euvolemia, a return to physiological homeostasis, and cessation of hemorrhage (Table 68-2).
IV. Avoidance of trauma, including surgical procedures, is recommended.
V. When surgical procedures are required, transfusion of plasma products is indicated.
VI. Familial genetic testing and breeding recommendations may be indicated.

Box 68-1

Initial Therapy for Acute Hemorrhage-Induced Anemia or Hypovolemia

Problem	Recommended Therapy
Hypovolemia	Expand circulatory volume with IV crystalloid or colloid fluids, and blood or blood components to normalize signs of hypovolemia (see Table 68-2). Fresh whole blood or appropriate blood components are often necessary.
Anemia	Administer 6 to 15 mL/kg packed RBCs IV. Administer 20 to 30 mL/kg fresh whole blood IV to replace RBCs and coagulation factors. Fresh whole blood and blood products may be delivered rapidly (over 5 minutes to 1 hour). Dilution of packed RBCs with 0.9% NaCl (1:1) speeds infusion by increasing the temperature of the product and decreasing viscosity. Therapeutic goals are a posttransfusion hematocrit of 20% to 25%, and resolution of signs of hypovolemia.
Coagulopathy*	Administer fresh plasma or fresh frozen plasma at 6 to 15 mL/kg IV over 30 minutes to 2 hours. Repeat as necessary until bleeding ceases. Reassessment of PT and aPTT may help guide plasma administration in certain disease processes. Fresh whole blood may be administered as outlined for anemia. Administer cryoprecipitate at 1 to 5 mL/kg IV over 1 hour for Factor VIII deficiency, fibrinogen deficiency, or von Willebrand disease. Cryosupernatant may be utilized at 10 to 15 mL/kg IV for deficiencies of Factors II, VII, IX, X, or XI when Factor VIII, fibrinogen, and von Willebrand factor are not needed. Normalize body temperature; coagulopathy is potentiated by hypothermia. Therapeutic goal is cessation of hemorrhage. Normalization of coagulation times is desirable, but may not be necessary to achieve adequate hemostasis.

RBC, Red blood cell; *aPTT,* activated partial thromboplastin time; *PT,* prothrombin time.
*Plasma, cryoprecipitate, or cryosupernatant may also be used in coagulopathic dogs that do not have hemorrhage-induced anemia or hypovolemia (e.g., before surgery).

Factor VIII and IX Deficiencies (Hemophilia A and B)

Definition and Causes

I. Factor IX is a vitamin K-dependent enzyme produced in the liver and activated by Factor XIa (intrinsic pathway) or tissue factor (TF) complexed with Factor VIIa (extrinsic pathway).
   A. Factor IXa activates Factor X at the start of the common pathway.
   B. Hemophilia B is an inherited deficiency of functional Factor IX.
      1. It has been reported in a variety of purebred and mixed breed dogs, sometimes with vWD.
      2. Affected cats include the British shorthair and Siamese-cross; some have had concurrent Factor XII deficiency.
II. Factor VIII is a nonenzymatic protein produced in the liver.
   A. It is activated to Factor VIIIa by thrombin to become a cofactor for activation of Factor X.
   B. Hemophilia A is a decrease in functional Factor VIII.
      1. It is a relatively common inherited coagulation factor deficiency in dogs.
      2. It most commonly occurs in purebred dogs, particularly in German shepherd dogs, but also in mixed-breed dogs and in cats.

TABLE 68-2

Monitoring of Animals with Acute Coagulopathy-Induced Anemia and Hypovolemia

CONCERN	PARAMETER TO MONITOR	MONITORING FREQUENCY	GOAL
Physiological homeostasis	Temperature Pulse rate Respiration rate Mucous membrane color Capillary refill time Pulse character Arterial blood pressure Arterial O_2 saturation Urine output	Every 5-15 min until normalized, then every 1-2 hr	Normalization of parameters
Blood loss	Hematocrit	Every 1 hr until Hct >20%, then every 6 hr	Hct = 20% to 25%
	Active bleeding	Every 15-30 min	Cessation of hemorrhage
	PT, aPTT, or ACT	Test coagulation times 15-30 min after transfusion	Normalization of coagulation desirable

Hct, Hematocrit; *PT,* prothrombin time*a*; a*PTT,* activated partial thromboplastin time; *ACT,* activated coagulation time.

III. Hemophilia A and B are sex-linked (X-chromosome), recessively inherited disorders.
   A. Males are either affected or clear of the defect.
   B. Females may be clear of the defect, carriers (heterozygous), or affected (homozygous).
   C. Offspring of carriers bred to unaffected males have a 50% chance of inheriting a defective X-chromosome, so 50% of males will be affected and 50% of females will be carriers.
   D. All female offspring of an affected male and a clear female are asymptomatic carriers.
   E. Female offspring from an affected male and a carrier female can be affected.

Pathophysiology

I. Mutations in the genes coding for Factor VIII or IX typically result in proportional decreases in activity and detectable antigen of these factors.
II. Several mutations have been defined for Factor IX in dogs and cats.

Clinical Signs

I. Because Factors VIII and IX are critical to normal hemostasis, severe deficiencies (<1% to 2% of normal activity) may lead to death at birth or to life-threatening spontaneous hemorrhage.
II. Milder deficiencies (3% to 30% activity) may go unnoticed in young dogs and only result in severe bleeding after surgical or nonsurgical trauma.
III. Clinical signs are related to hemorrhage and the secondary effects of acute blood loss.
   A. Hemarthrosis with lameness
   B. Spontaneous or trauma-induced hematomas
   C. Oral bleeding from tooth eruption or trauma
   D. Bleeding episodes following surgery (e.g., tail docking, dewclaw removal)
   E. Hemorrhagic effusions
   F. Hemomediastinum
   G. Hemorrhage into the central nervous system
   H. Bloody diarrhea
IV. Spontaneous hemorrhage is typically more severe in animals of greater size.
V. With acute, severe blood loss, clinical signs of anemia and hypovolemia may be present.

Diagnosis and Differential Diagnosis

I. Hemophilia A and B are considered along with other intrinsic pathway factor deficiencies (XII, prekallikrein, XI), especially in young animals, when there are unexplained prolongations of aPTT and/or ACT, and PT and TT values are normal.
II. Confirmation requires specific factor analyses.
III. Other laboratory and clinical findings help exclude secondary causes of prolonged aPTT and ACT, including hepatic disease, vitamin K antagonism or deficiency, consumptive coagulation, Factor VIII deficiency associated with vWD, factor inhibitors, or heparinization of the sample or animal.

Treatment

I. Initial therapy is directed at expansion of circulatory volume, correction of anemia, and administration of deficient coagulation factors (see Box 68-1).
II. Cryoprecipitate is preferable to plasma as a source of fibrinogen because it reduces the potential for volume overload and possibly transfusion reactions (Stokol et al., 1998).

III. Life-threatening bleeding is treated symptomatically and invasive procedures are avoided, if possible.
IV. Continued hemorrhage and prolongation of aPTT after appropriate plasma transfusion are evidence that a coagulation factor inhibitor may be contributing to the hemorrhage, especially in multiply transfused hemophiliacs.
V. Appropriate management may vary from strict rest in mild cases to euthanasia in large dogs with severe, recurrent bleeding episodes.
VI. Gene therapy for definitive treatment of Factor VIII deficiency shows promise in dogs (Jiang et al., 2006).

Monitoring of Animal

I. Affected animals are monitored as discussed under Factor XI Deficiency.
II. Carrier states cannot be reliably detected by coagulation studies, so pedigree analysis and genetic testing (in breeds with characterized mutations of Factor IX) may be required.
III. Familial genetic testing and breeding recommendations are indicated.
   A. Female carriers can be spayed without risk of bleeding from hemophilia.
   B. Males with hemophilia should not be used for breeding.

INHERITED/CONGENITAL EXTRINSIC PATHWAY DEFICIENCIES

Factor VII Deficiency

Definition and Causes

I. Factor VII is a vitamin K–dependent protein produced in the liver.
II. When activated by TF from extravascular tissues or activated monocytes, it forms Factor VIIa/TF complexes that activate the common (Factor X) and intrinsic (Factor IX) pathways.
III. Inheritance of Factor VII deficiency appears to be autosomal dominant with incomplete penetrance (Spurling et al., 1974; Spurling, 1986).
IV. Deficiency occurs in beagles and other purebred and mixed-breed dogs.

Pathophysiology and Clinical Signs

I. Mutations in the gene coding for Factor VII result in deficiencies of functional Factor VII and, typically, proportional decreases in Factor VII antigen and Factor VII activity.
II. Only low levels of Factor VII are necessary to prevent bleeding, so Factor VII–deficient dogs are often detected incidentally despite activities <10% of normal.
III. Deficient dogs may have bruising or prolonged bleeding after accidental, physiological, or surgical trauma, such as castration and parturition.

Diagnosis and Differential Diagnosis

I. Factor VII deficiency is considered when there are unexplained prolongations of PT, and aPTT, ACT, and TT are normal.
II. PT may be affected before other coagulation times in several coagulation disorders, because Factor VII has the shortest half-life of the coagulation factors.
III. Specific factor activity analysis is necessary to confirm Factor VII deficiency.
IV. Other laboratory and clinical findings help exclude secondary causes of prolonged PT, including hepatic disease, vitamin K antagonism or deficiency, consumptive coagulation, and coagulation factor inhibitors.
V. Genetic testing may identify affected beagles, including carriers not detected by PT testing.

Treatment and Monitoring

I. Because severe bleeding is rare, specific treatment often is not necessary.
II. With severe hemorrhage, initial therapy is directed at expansion of circulatory volume, correction of anemia, and administration of Factor VII (see Box 68-1).
III. Recombinant human Factor VII is immunogenic in dogs, so it is not recommended.
IV. Dogs with known factor VII deficiency are monitored for signs of bleeding during pregnancy, during and after parturition, and after invasive procedures.
V. Familial genetic testing and breeding recommendations may be indicated.

INHERITED/CONGENITAL COMMON PATHWAY DEFICIENCIES

Factor X Deficiency

Definition and Causes

I. Factor X is a vitamin K–dependent protein produced in the liver and activated by either Factor IXa (intrinsic pathway) or Factor VIIa/TF (extrinsic pathway) at the start of the common pathway.
II. It is critical to thrombin generation by either pathway.
III. Congenital or hereditary functional deficiency of Factor X has been reported in domestic shorthair cats, American cocker spaniels, and Jack Russell terriers.
IV. Inheritance of the deficiency appeared to be autosomal dominant with variable penetrance in cocker spaniels (Dodds, 1973).

Pathophysiology and Clinical Signs

I. Mutations in the gene coding for Factor X result in deficiencies of functional Factor X and hemorrhagic tendencies in homozygotes and heterozygotes.
II. Homozygous individuals typically die very young from severe hemorrhage, whereas heterozygous individuals have a mild to marked bleeding propensity.

Diagnosis and Differential Diagnosis

I. Factor X deficiency, although rare, is considered when there are unexplained prolongations of PT, aPTT, and ACT without prolonged normal TT values.
II. The RVVT time is also prolonged.
III. Specific factor analysis is necessary to confirm Factor X deficiency.
IV. Other laboratory and clinical findings help exclude secondary deficiencies, including hepatic disease, vitamin K antagonism or deficiency, and consumptive coagulation.
V. Factor X deficiency must also be differentiated from other common pathway factor deficiencies, vitamin K–dependent multifactor coagulopathy (see under Inherited/Congenital Multiple Pathway Deficiency, following), and coagulation inhibitors.

Treatment and Monitoring

I. Initial therapy is directed at expansion of circulatory volume, correction of anemia, and administration of Factor X (see Box 68-1).
II. Monitor as for Factor XI deficiency.

Factor II (Prothrombin) Deficiency

Definition and Causes

I. Factor II (prothrombin) is a vitamin K–dependent protein produced in the liver.
   A. When activated to thrombin by Factor Xa and Va, it converts fibrinogen to fibrin, which polymerizes into a clot.
   B. Thrombin also activates other coagulation factors and platelets.
II. Factor II deficiency is a quantitative or qualitative deficiency of prothrombin.
   A. It is very rare, but has been reported as a suspected autosomal hereditary disorder in an English cocker spaniel (Hill et al., 1982).
   B. It has also been reported in boxers as part of a defect in turnover of all the vitamin K–dependent factors.

Pathophysiology and Clinical Signs

I. Genetic defects responsible for Factor II deficiency in dogs have not been identified.
II. Spontaneous or traumatic mucocutaneous and cavitary hemorrhage may occur.

Diagnosis and Differential Diagnosis

I. Factor II deficiency is considered when there are unexplained prolongations of PT, aPTT, and ACT, without prolonged TT values.
II. Differential diagnoses include Factor X deficiency and its differential diagnoses.
III. Specific factor analysis is necessary to confirm Factor II deficiency.

Treatment and Monitoring

I. Treatment is the same as that for Factor XI deficiency.
II. Monitoring mirrors that of Factor XI deficiency.

Afibrinogenemia and Hypofibrinogenemia

Definition and Causes

I. Fibrinogen (Factor I) is a positive acute-phase protein produced by hepatocytes.
   A. It is the major bridging protein in platelet aggregation.
   B. It is consumed as the substrate for thrombin in the generation of a stable fibrin clot.
II. Congenital or hereditary functional fibrinogen deficiency (Factor I deficiency) is very rare and includes afibrinogenemia (absent), hypofibrinogenemia (decreased), and dysfibrinogenemia (dysfunctional protein).
   A. Afibrinogenemia reported in a bichon frise was probably congenital and possibly hereditary (Wilkerson et al., 2005).
   B. Hypofibrinogenemia and dysfibrinogenemia have been reported rarely in purebred dogs, sometimes with an apparent autosomal heritability.

Pathophysiology and Clinical Signs

I. Severe decreases in functional fibrinogen impair clot formation and result in hemorrhage.
II. Affected dogs may have mild to severe mucocutaneous or cavitary hemorrhage including epistaxis and hemarthrosis.
III. Life-threatening hemorrhage may occur after accidental or surgical trauma.

Diagnosis and Differential Diagnosis

I. Fibrinogen deficiency is considered with unexplained prolongations of all tests with fibrin clot endpoints.
   A. These include PT, aPTT, ACT, and TT.
   B. Buccal mucosal bleeding time may also be prolonged.
II. Hereditary fibrinogen deficiencies must be differentiated from fibrinogen deficiency or reduced fibrin formation from other causes.
   A. These include liver failure, consumptive coagulation, coagulation inhibitors, and hyperfibrinogenolysis from certain venoms or drugs.
   B. Clinical history, serum biochemistry, urinalysis, ATIII, FDP, and D-dimer tests may be helpful in identifying these conditions.
      1. ATIII concentration may be decreased in liver failure and consumptive coagulation.
      2. FDP and D-dimer concentrations may be increased in liver failure, consumptive coagulation, and hyperfibrinolysis.
III. In contrast to routine assessment of fibrinogen activity by the TT test, fibrinogen antigen may be assessed by immunoassay to help differentiate dysfibrinogenemia (fibrinogen antigen detected) from decreased or absent fibrinogen (little or no fibrinogen antigen detected).

Treatment and Monitoring

I. Initial therapy is directed at expansion of circulatory volume, correction of anemia, and administration of fibrinogen (see Box 68-1).
II. Cryoprecipitate is preferable to plasma as a source of fibrinogen because it reduces the potential for volume

overload and, possibly, for transfusion reactions (Stokol and Parry, 1998).
III. With severe, acute bleeding, initial monitoring focuses on restoration of euvolemia, a return to physiological homeostasis, and cessation of hemorrhage (see Table 68-2).
IV. Familial testing and breeding recommendations may be indicated.

INHERITED/CONGENITAL MULTIPLE PATHWAY DEFICIENCY

Vitamin K–Dependent Multifactor Coagulopathy

Definition and Causes

I. Vitamin K–dependent multifactor coagulopathy is a rare congenital disorder reported in Devon Rex cats and possibly a Labrador retriever (Mason et al., 2002).
II. It is caused by abnormal vitamin K–dependent gamma-glutamyl carboxylase (Soute et al., 1992).
III. Factors II, VII, IX, and X are produced in hepatocytes and require reduced vitamin K as a cofactor for posttranslational enzymatic carboxylation.
   A. Carboxylation is required for the activated factors to bind calcium and adhere to phospholipid surfaces.
   B. Defective carboxylation results in decreased plasma concentrations of carboxylated Factors II, VII, IX, and X, thus mimicking vitamin K deficiency or antagonism.

Pathophysiology and Clinical Signs

I. The responsible genetic defect has not been reported, but autosomal recessive heritability is suspected.
II. Clinical signs in affected cats vary from none to a severe bleeding diathesis manifested primarily as body cavity hemorrhage and unexplained hematomas.
III. Excessive bleeding may occur after surgical or nonsurgical trauma.

Diagnosis and Differential Diagnosis

I. The condition is considered in Devon Rex cats and other animals when there are unexplained prolongations of PT, aPTT, and ACT.
II. These prolongations occur because the factors participate in the intrinsic (IX), extrinsic (VII), and common (II, X) pathways.
III. Specific factor analyses reveal decreased activity of Factors II, VII, IX, and X.
IV. Similar and much more common conditions that must be excluded include vitamin K antagonism or deficiency (see Vitamin K Antagonism).
V. Hepatic disease and consumptive coagulopathy must also be excluded.

Treatment and Monitoring

I. Initial therapy and monitoring are the same as for Factor XI deficiency.
II. The abnormal carboxylase has decreased binding affinity for reduced vitamin K, but vitamin K supplementation results in improved carboxylation and correction of coagulation times.
   A. Give vitamin K_1 (phytonadione) at 5 mg PO SID initially.
   B. Decrease dose after signs are controlled to the minimum dose that keeps PT and aPTT within reference limits and minimizes the chance of Heinz body anemia.
III. Lifelong therapy with vitamin K_1 may be necessary.
IV. Prolongation of PT and aPTT after cessation of vitamin K supplementation supports the diagnosis.

ACQUIRED COAGULOPATHIES

Vitamin K Antagonism

Definition and Causes

I. Vitamin K antagonism is usually caused by ingestion and absorption of hydroxycoumarins and indanediones that block hepatic carboxylation of vitamin K-dependent coagulation factors (Factors II, VII, IX, and X) and vitamin K–dependent anticoagulants (protein C and protein S).
II. Sulfaquinoxaline has a similar effect.
III. Vitamin K antagonism may occur as a result of intentional therapy with warfarin for thromboprophylaxis, but it more often occurs from ingestion of vitamin K–antagonist rodenticides (see Chapter 124) or human medications.
IV. Most intoxications involve long-acting hydroxycoumarins (brodifacoum and bromodiolone) and indanediones (diphacinone).
V. It is common in dogs and less common in cats.

Pathophysiology

I. The reduced form of vitamin K is a necessary cofactor for the enzyme that carboxylates vitamin K–dependent factors in hepatocytes.
II. Carboxylation allows the factors to bind free calcium and phospholipid so they can participate in coagulation after activation.
III. Reduced vitamin K is oxidized to vitamin K epoxide during carboxylation, requiring reduction by vitamin K epoxide reductase before again functioning as a carboxylase cofactor.
IV. Vitamin K antagonists inhibit the reduction of vitamin K epoxide, thus leading to a decrease in the reduced form of vitamin K and decreased production of functional Factors II, VII, IX, and X.
V. These poorly carboxylated and poorly functional factors are still produced and transported to blood, where they are known as *proteins induced by vitamin K antagonism* (PIVKA).
VI. Hemorrhagic tendencies are most often delayed until 3 to 7 days after ingestion when circulating concentrations of functional Factors II, VII, IX, and X are depleted.
VII. These factors have half-lives of about 6 to 40 hours.

Clinical Signs

I. Clinical signs are delayed and usually occur 3 to 7 days after exposure.

II. Hemorrhage may be obvious or occult.
III. Hemorrhage occurs at any location, but is most common into potential spaces (especially the pleural space) and the lungs.
IV. Signs of hypovolemic shock (pale mucous membranes, prolonged capillary refill time, tachycardia, weak pulses) and respiratory compromise (dyspnea, increased respiratory rate and effort) are common and often accompanied by lethargy and weakness.

Diagnosis

I. The diagnosis is suspected with a history of exposure and accompanying prolonged coagulation times or evidence of hemorrhage.
II. In animals with overt bleeding, prolonged PT and aPTT or ACT are expected because vitamin K–dependent factors participate in the intrinsic (Factor IX), extrinsic (Factor VII), and common (Factors X and II) pathways.
III. PT is expected to be prolonged before aPTT because Factor VII has the shortest half-life of the vitamin K–dependent factors; however, this is not always the case.
IV. A modified PT assay (Thrombotest; Axis-Shield PoC AS, Oslo, Norway) reported to be sensitive to PIVKA is often called a *PIVKA assay,* but it is not specific for PIVKA.
    A. It is not widely available.
    B. It may detect a mild or early anticoagulant-induced coagulopathy, and may help differentiate vitamin K-antagonism from other coagulopathies (Mount et al., 2003).
V. Analysis of whole blood or postmortem liver samples for vitamin K antagonists may yield a definitive diagnosis.
VI. Factor analysis is typically unnecessary, but deficiencies of vitamin K-dependent factors would be detected.

Differential Diagnosis

I. Other conditions that can have similar presentations and hemostatic findings include liver failure (see Hepatic-Associated Coagulopathy), consumptive coagulation in the coagulopathy phase, common pathway factor deficiencies, vitamin K dependent multifactor coagulopathy, and vitamin K deficiency.
II. Response to vitamin K_1 therapy is supportive of vitamin K antagonism, vitamin K–dependent multifactor coagulopathy, or vitamin K deficiency.

Treatment

I. If ingestion occurred within the last 5 hours and earlier ingestion was not possible, induce emesis, then give activated charcoal with sorbitol (2 to 5 g/kg PO or via orogastric tube), and start vitamin K_1 (phytonadione) at 1.25 to 2.5 mg/kg PO BID.
II. Similarly, if ingestion occurred 5 to 12 hours before and earlier ingestion was not possible, give activated charcoal with sorbitol and start vitamin K_1 as previously described.
III. If ingestion occurred within the last 12 hours and earlier ingestion was possible, measure the PT.
    A. If the PT is normal and there is no bleeding, treat based on the time intervals described previously (I and II).
    B. If the PT is prolonged, do not induce emesis or orogastrically intubate the animal, but give activated charcoal with sorbitol at 2 to 5 g/kg PO and initiate vitamin K_1 therapy.
IV. If clinical hemorrhage is present, PT, aPTT, and ACT should be prolonged.
    A. The animal may need treatment for hypovolemia, anemia, and the coagulopathy (see Box 68-1).
    B. Vitamin K_1 is given at 2.5 to 5 mg/kg SC with a small-gauge needle and continued orally at the same dose, when feasible.
V. Poorly tolerated pleural or pericardial hemorrhage may require thoracocentesis or pericardiocentesis, but these procedures should follow therapy for the coagulopathy whenever possible.

Monitoring of Animal

I. Most common anticoagulant rodenticides are long-acting and necessitate treatment for 2 to 6 weeks.
    A. Ingestion of warfarin may require treatment for only 1 week.
    B. Repeated measurement of PT is unnecessary once an animal is receiving an appropriate dose of vitamin K_1, unless there are concerns about its absorption.
II. PT is measured approximately 36 hours after withdrawing vitamin K therapy to assess for residual toxicity, and therapy is reinstituted for 1 to 2 weeks if PT is prolonged.

Vitamin K Deficiency (Hypovitaminosis K)

Definition and Causes

I. Vitamin K is a fat soluble vitamin that is obtained from the diet and from production by intestinal bacteria.
II. It is absorbed with lipid through the actions of lipase and bile acids.
III. Hypovitaminosis K may develop with prolonged obstructive cholestasis, prolonged anorexia, vitamin K–deficient diets, decreased production by intestinal bacteria (e.g., after antibiotics), intestinal malabsorptive disease, or exocrine pancreatic insufficiency.
IV. Cats with hepatic lipidosis, severe inflammatory bowel disease, and cholangiohepatitis may develop laboratory evidence of impaired coagulation (usually without apparent bleeding tendencies) correctible by vitamin K administration (Center et al., 2000).

Pathophysiology and Clinical Signs

I. Hypovitaminosis K results in impaired carboxylation of vitamin K–dependent coagulation factors (II, VII, IX, and X), despite normal activity of vitamin K–reducing enzymes.
II. The effects are similar to vitamin K–antagonism, but are typically milder and often discovered only by prolonged PT, aPTT, or modified PT (Thrombotest) test results.
III. Clinical signs are related to the underlying disease and the coagulopathy.

Diagnosis and Differential Diagnosis

I. Hypovitaminosis K is considered when there is clinical hemorrhage or prolonged PT, modified PT (Thrombotest), aPTT, and ACT values in association with predisposing conditions.
II. Vitamin K antagonism and its differential diagnoses must also be considered (see Vitamin K Antagonism).
III. Appropriate diagnostic testing is done to define the underlying disease.
IV. Correction of the coagulopathy with vitamin K_1 therapy is supportive of the diagnosis.

Treatment and Monitoring

I. The underlying disease is treated.
II. Vitamin K_1 (phytonadione) is administered at 1 to 5 mg/kg SC as needed, or orally if the animal is eating and does not have a malabsorptive or maldigestive disorder.
III. Plasma may be required for severe hemorrhaging or if invasive diagnostic or therapeutic measures, such as a liver biopsy or surgery, are planned.

Hepatic-Associated Coagulopathy

Definition and Causes

I. Liver disease may result in dysregulation of hemostasis.
  A. There may be quantitative or qualitative defects in the production of procoagulants, anticoagulants, profibrinolytics, and antifibrinolytics.
  B. Thrombocytopenia or thrombopathia may occur.
  C. Clearance of coagulation and fibrinolytic factors may be decreased.
II. The net result of dysregulation is often clinically silent despite abnormalities in hemostatic laboratory tests.
III. Causative liver diseases include severe acute hepatitis, hepatic necrosis, primary or metastatic hepatic neoplasia, cirrhosis, and portosystemic shunts.

Pathophysiology and Clinical Signs

I. Markedly decreased functional hepatic mass results in multiple coagulation factor deficiencies and sometimes production of dysfunctional factors owing to abnormal cellular processes, such as carboxylation of vitamin K–dependent factors.
II. If consumptive coagulation is initiated, thrombosis may occur and contribute to a subsequent coagulopathy.
III. Clinical signs reflect the hepatic disease and the coagulopathy.
IV. Bleeding may be mild to severe and either mucocutaneous or cavitary in location.

Diagnosis and Differential Diagnosis

I. Attributing a coagulopathy to hepatic disease requires a diagnosis of hepatic failure or insufficiency, and exclusion of other causes of the coagulopathy.
II. Hemostatic test abnormalities vary, and may include prolonged PT and/or aPTT values, decreased ATIII and fibrinogen concentrations (prolonged TT), and increased FDP concentrations.
  A. Thrombocytopenia may also be present.
  B. These findings may mimic consumptive coagulation.

Treatment and Monitoring

I. Initial therapy is directed at expansion of circulatory volume, correction of anemia, and administration of deficient coagulation factors (see Box 68-1).
II. If hemorrhage is secondary to decreased functional hepatic mass, vitamin K_1 does not correct the bleeding.
III. Concurrent management of the underlying hepatic condition is necessary, if possible.
IV. With severe, acute hemorrhage, initial monitoring focuses on restoration of euvolemia, a return to physiological homeostasis, and cessation of bleeding (see Table 68-2).
V. When invasive procedures are required, transfusions of plasma products may be indicated, although prolonged PT or aPTT do not appear to be good predictors of hemorrhagic complications associated with biopsy procedures in dogs and cats (Bigge et al., 2001).

Other Acquired Coagulopathic Disorders and Factors

See Table 68-3.

CONSUMPTIVE COAGULATION AND COAGULOPATHY

Definition and Causes

I. Consumptive coagulation is a localized or disseminated increase in coagulation that results in decreased concentrations of circulating hemostatic factors.
  A. Disseminated intravascular coagulation (DIC) is always secondary to an underlying condition causing excessive or unbalanced intravascular activation of coagulation.
    1. Severe trauma, burns, tissue necrosis
    2. Disseminated neoplasia
    3. Shock, heat stroke
    4. Endotoxemia, sepsis
    5. Pancreatitis
    6. Endothelial cell injury, vasculitis
    7. Hepatic disease
    8. Some envenomations
  B. Localized consumptive coagulation may occur with activation of coagulation in a single organ or tissue.
II. Consumptive coagulopathy and clinical hemorrhage follow consumptive coagulation because of the destruction and removal of procoagulant factors and from of increased FDP concentrations.

Pathophysiology

I. Mechanisms that may contribute to excessive coagulation include excessive thrombin generation, decreased anticoagulation, impaired fibrinolysis, and inflammation.
II. Excessive coagulation leads to the following changes, which may be mild to severe.
  A. Destruction of nonenzymatic cofactors (V and VIII) by activated protein C

TABLE 68-3

Other Acquired Coagulopathic Disorders and Factors

DISORDER	CAUSES	PATHOPHYSIOLOGY	CLINICAL SIGNS	DIAGNOSIS	TREATMENT
Dilutional coagulopathy	Massive transfusion of plasma-poor packed RBCs, crystalloids, or colloids after hemorrhage	Dilution of coagulation factor concentrations Exacerbated by concurrent decrease in platelet concentration and function	Hemorrhage Signs of underlying disease	Suggested by increased hemorrhage after massive plasma-poor fluid volume replacement	Supportive Fresh frozen plasma, as needed Treat underlying disease
Hypothermia	Exposure to cold	Depression of coagulation, increased fibrinolysis, and decreased platelet concentration and function	Hemorrhage and signs related to underlying disease	Routine coagulation assays are done at 37° C and do not identify this disorder	Warming measures Fresh frozen plasma as needed Treat underlying disease
Anticoagulant Factors					
Heparin	Exogenous heparin therapy Contamination during collection Mast cell neoplasia	Increased anticoagulant activity of ATIII	Rare hemorrhage, such as hematoma formation (Mischke RH et al., 2001)	Prolonged aPTT and ACT PT and ATIII may be decreased Poor response to plasma transfusion	Protamine sulfate if hemorrhage is life-threatening
Fibrin degradation products	Fibrinolysis from consumptive coagulation, some envenomations, or administration of fibrinolytic agents	Competitive inhibition of thrombin's interaction with fibrinogen, the polymerization of fibrin, and the aggregation of platelets	Hemorrhage and signs related to underlying disease	Markedly increased fibrin degradation products and D-dimer concentration PT, aPTT, and TT may be prolonged Poor response to plasma	Monitor for bleeding when administering fibrinolytics Treat supportively
Coagulation factor inhibitors	Systemic autoimmune diseases, posttransfusion in hemophiliacs, plasma cell neoplasia	Rare allo- or autoantibodies bind to coagulation factors and decrease their activity	Hemorrhage and signs related to underlying disease	Coagulation studies Factor analysis Poor response to plasma transfusion	Supportive Fresh frozen plasma as needed Treat underlying disease
Lupus anticoagulants	Rare antibodies to phospholipids and proteins Not always associated with lupus erythematosus	Antibodies act as in vitro but not in vivo inhibitors of coagulation by binding to phospholipids Mechanism of in vivo thrombosis is unclear	Associated with thrombosis and signs related to underlying disease	Assay for lupus anticoagulants Poor response to plasma transfusion	Supportive Fresh frozen plasma as needed Treat underlying disease

RBCs, Red blood cells; *ATIII,* antithrombin III; *aPTT,* activated prothrombin time; *ACT,* activated clotting time; *PT,* prothrombin time; *TT,* thrombin time.

B. Clearance of activated coagulation enzymes by antiproteases and ATIII
C. Consumption of fibrinogen in the formation of fibrin
D. Consumption of platelets via thrombin activation
E. Impaired platelet function and fibrin formation caused by increased FDPs from fibrinolysis
F. Erythrocyte fragmentation from intravascular trauma (microangiopathic fragmentation)

Clinical Signs

I. Clinical signs vary from absent to severe, depending on the stage and underlying condition.
II. Signs usually reflect depletion of coagulation factors, and include circulatory collapse and widespread cavitary and surface bleeding.
III. Signs of thrombosis may occur in prothrombotic stages and vary with the affected organs.

Diagnosis and Differential Diagnosis

I. Definitive diagnosis is difficult to obtain and requires multiple tests.
II. Diagnosis is usually based on the presence of multiple hemostatic abnormalities in conjunction with a disorder known to be associated with consumptive coagulation.
III. Expected laboratory abnormalities include thrombocytopenia, prolonged PT and aPTT, increased D-dimer or FDP concentrations, decreased ATIII concentration and activity, or trends toward these abnormalities over serial measurements.
IV. Increased production of fibrinogen, a positive acute-phase protein, often masks its consumption.
V. It must be differentiated from liver failure, vitamin K antagonism, thrombotic thrombocytopenic purpura, afibrinogenemia, and mixed hemostatic disorders.

Treatment and Monitoring

I. The therapeutic approach varies with the underlying disorder, the severity of the hemostatic abnormalities, and the current equilibrium of prothrombotic and antithrombotic processes.
II. Treat the underlying condition and institute supportive therapies.
III. In the bleeding animal, treatment of coagulation abnormalities, hypovolemia, and anemia is indicated (see Box 68-1).
   A. Fresh frozen plasma helps to replace coagulation factors and inhibitors.
   B. Platelet concentrates may be helpful with severe thrombocytopenia (see Chapter 67).
IV. Use of heparin remains controversial, but low-dose heparin (75 U/kg SC TID) may be useful in animals with predominantly thrombotic tendencies.
V. Laboratory abnormalities in the absence of clinical signs may not necessitate treatment unless invasive diagnostic or therapeutic interventions are required.
VI. Prognosis varies from good to poor and depends on the success of treatment for the underlying disease process and on prevention of life-threatening hemorrhage.

THROMBOSIS

Definition and Causes

I. Inherited prothrombotic conditions have not been described in dogs and cats, but many acquired disorders and conditions may contribute to thrombosis.
II. Most notable of the acquired conditions is ATIII deficiency, which may occur from ATIII loss (protein-losing nephropathy/enteropathy or blood loss), consumption (consumptive coagulation or heparin therapy), or decreased production by the liver.
III. Additional acquired disorders that are associated with thrombosis include the following:
   A. Endocarditis, vasculitis
   B. Intravascular catheterization, injections of chemical irritant solutions such as hyperosmolar medications (e.g., dextrose, hypertonic saline), total parenteral nutrition
   C. Congestive heart failure, valvular insufficiency, vascular defects, feline cardiomyopathy
   D. Malignant neoplasia: some carcinomas, possibly hemangiosarcoma
   E. Surgery, trauma
   F. Immune-mediated hemolytic anemia
   G. Sepsis, parvoviral infection
   H. Hypothyroidism, hyperadrenocorticism
   I. Antiphospholipid/protein antibodies, including lupus anticoagulants (See Table 68-3)

Pathophysiology

I. Mechanisms responsible vary with the disorder and are often multifactorial or incompletely known.
II. They include vascular damage, altered blood flow, upregulated mediators of coagulation, decreased concentrations of endogenous anticoagulants, decreased fibrinolysis, platelet hyperaggregability, or a combination of these.

Clinical Signs

I. Clinical signs of thrombosis depend on the site of thrombus formation.
II. Arterial thrombus formation most commonly occurs in the terminal aorta, leading to pain, decreased pulse pressure and quality, cool extremities, decreased sensory and motor function, hyporeflexia, firm gastrocnemius muscles, and cyanotic nailbeds that may fail to bleed when cut.
III. Pulmonary arterial thrombus formation or thromboembolism most often manifests as hypoxemia that is not easily attributed to other common causes.
   A. It may be clinically silent or associated with severe dyspnea.
   B. Evidence of right-sided heart failure may be present.
IV. Signs of venous thrombosis vary with the site.
   A. Cranial vena cava: edema of the head and possibly the forelimbs
   B. Portal vein: portal hypertension, vomiting, diarrhea, peritoneal transudate

Diagnosis

I. Appropriate diagnostic tests depend on the suspected underlying disorders.
II. Common laboratory test results include decreased ATIII activity, thrombocytopenia, and increased concentrations of FDPs and D-dimers; however, increased fibrinogen production may mask its consumption (Nelson and Andreasen, 2003).
III. Other tests specific to the site of thrombus formation may be necessary for a diagnosis.
  A. Pulmonary thromboembolism (PTE)
    1. Arterial blood gas analysis frequently documents hypoxemia and hypocapnia, although findings are not specific for PTE.
    2. Thoracic radiography is useful to exclude other causes of respiratory distress, but findings are nonspecific and include truncation or pruning of lobar pulmonary arteries, oligemia, low volumes of pleural effusion, and variable pulmonary infiltrates.
    3. Selective pulmonary arterial angiography or helical computed tomographic (CT) angiography are currently the most sensitive and specific diagnostic methods for PTE in dogs and cats.
  B. Aortic thromboembolism or systemic arterial thromboembolism
    1. Diagnosis is most often based on physical examination findings, but additional findings may be supportive or confirmatory.
    2. Ultrasonic Doppler may be used to confirm absence of blood flow through an affected artery, using the contralateral limb for comparison if a single limb is affected.
    3. Color flow Doppler is useful to visualize the length and location of thrombi, with more mature thrombi appearing more hyperechoic.
    4. In limbs with decreased blood flow, blood lactate concentrations may be increased and blood glucose concentrations may be decreased compared with values for glucose and lactate in the systemic circulation.
    5. Selective angiography or helical CT angiography can be used to detect the presence or absence of blood flow in systemic arteries.
    6. Thrombosis of specific organs may result in specific laboratory abnormalities, such as azotemia with bilateral renal thrombosis.
  C. Cranial vena cava and portal vein thrombosis
    1. Ultrasonography may be used to visualize flow or the presence of a filling defect in the cranial vena cava or portal vein.
    2. Selective angiography or helical CT angiography may provide a definitive diagnosis of thrombosis of the cranial vena cava or portal vein.
    3. Animals with portal vein thrombosis and secondary portal hypertension are commonly critically ill, with ascites (transudate) and signs of gastrointestinal compromise (vomiting, diarrhea).

Differential Diagnosis

I. PTE
  A. Other causes of respiratory distress: pneumonia, congestive heart failure
  B. Pleural cavity diseases: pneumothorax, pleural effusion
II. Aortic or systemic arterial thromboembolism
  A. Any generalized compromise of perfusion or mechanical/extravascular vessel compression of the vessel
  B. Neurological and musculoskeletal conditions of the extremities
III. Cranial vena cava thrombosis
  A. Intravascular or extravascular mediastinal neoplasia
  B. Decreased oncotic pressure, retention of sodium and water
IV. Portal vein thrombosis
  A. Extravascular or intravascular neoplastic obstruction of the portal vein
  B. Various protein-losing enteropathies, gastrointestinal lymphoma, lymphangiectasia

Treatment

I. Institute treatment for the underlying disease process.
II. Heparin potentiates the activity of ATIII and is the most common thromboprophylactic agent used for non–life-threatening arterial and venous thrombosis/thromboembolism.
  A. Do not administer heparin to animals that already have evidence of spontaneous hemorrhage or are scheduled to undergo invasive diagnostic or therapeutic procedures.
  B. Heparin may result in hemorrhage, so monitor animals receiving heparin for clinical and laboratory evidence of bleeding.
  C. Many dosing regimens have been reported, but the following are recommended:
    1. Cats require lower heparin dosages than dogs.
    2. Use continuous rate infusion (50 to 200 U/kg IV bolus followed by 10 to 50 U/kg/hr IV) for sustained anticoagulation in animals with known thrombosis or at very high risk of thrombosis.
    3. To prevent thrombosis and enlargement of current thrombi, give heparin at 100 to 200 U/kg SC QID or 200 to 300 U/kg SC TID.
  D. Unfractionated heparin and LMWH have decreased anticoagulant effects during ATIII deficiency, but may still provide desirable effects with little toxicity.
  E. LMWH may allow less frequent dosing and a more predictable effect than unfractionated heparin once dosing and monitoring protocols become established.
    1. In dogs, give dalteparin at 150 U/kg SC BID.
    2. In cats, give dalteparin at 100 to 150 U/kg SC BID, but note there is a significant interindividual variation in anti-Xa Factor activity in cats receiving LMWH.
III. Coumadin has a delayed onset of action and is difficult to titrate to effect, so it is rarely used in dogs and cats.

IV. Platelet inhibitors may be useful to control thrombosis, particularly arterial thrombosis.
   A. Aspirin may be used at 0.5 mg/kg PO BID in dogs and 6 to 10 mg/kg PO every 2 to 3 days in cats.
   B. Clopidogrel, a platelet ADP receptor inhibitor that inhibits platelet aggregation, is well tolerated in cats at 18.75 mg PO SID, but its efficacy is unknown.
V. Fibrinolytic (thrombolytic) agents, such as streptokinase and tissue plasminogen activator, are reserved for acute life-threatening thrombosis/thromboembolic disease, because they are very expensive and require intensive monitoring.
VI. With ATIII deficiency, ATIII may be partially replaced via fresh frozen plasma transfusions at 10 to 15 mL/kg IV BID (Rozanski et al., 2001).

Monitoring of Animal

I. Goals of therapy vary with the situation.
   A. For animals that are at risk of thrombosis or thromboembolism, the goal is to prevent thrombus formation and thromboemboli.
   B. For animals with non–life-threatening thrombosis, the goal is to prevent enlargement of thrombi while allowing the normal fibrinolytic pathways to gradually break down the thrombi.
   C. The primary goal for animals with life-threatening thrombosis/thromboembolism is to restore blood flow via thrombolysis with thrombolytic agents.
II. Monitor animals receiving heparin with aPTT testing.
   A. The target aPTT is 1.5 to 2.5 times healthy control or baseline values.
   B. Assess aPTT 6 to 8 hours after initiating therapy and SID thereafter.
III. Animals receiving antiplatelet drugs or LMWH are often not monitored.
IV. Long-term prognosis is related to the underlying disease process, and short-term prognosis is related to the location and duration of thrombosis.
   A. With aortic and systemic arterial thromboembolism, the prognosis is fair to good for restoration of blood flow to affected organs.
   B. The prognosis is poor if PTE is extensive enough to cause severe dyspnea.
   C. With cranial vena cava thrombosis, prognosis is good for restoration of blood flow and resolution of clinical signs, with successful thrombolytic therapy.
   D. Prognosis is poor for portal vein thrombosis because of prolonged venous congestion of the splanchnic circulation, secondary bacterial translocation, and sepsis.
   E. Prognosis is good for partial thrombosis if only partial thrombosis is present and thrombolysis is successful.

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CHAPTER 69

Diseases of Lymph Nodes and Lymphatics

Jennifer S. Thomas

CONGENITAL DISORDERS

Primary Lymphedema

Definition and Causes

I. Accumulation of interstitial fluid secondary to developmental abnormalities of the lymphatic system
II. Cause often idiopathic but congenital forms suspected in some dog breeds

Pathophysiology

I. Morphological and functional abnormalities
  A. Aplasia or hypoplasia of the lymphatic vessels or valvular incompetence
  B. Lymph node fibrosis or decreased lymph node size and number
II. Superficial lymphatics more commonly affected than deep or muscular lymphatics

Clinical Signs

I. Pitting edema is usually present at birth or within the first few months of life.
  A. Transient or permanent
  B. Pelvic limbs most commonly affected, often bilateral
  C. Generalized form less common and may involve limbs, trunk, head, and tail
II. Severity of edema varies from mild to severe.
  A. Pitting edema
    1. Edema is painless, not cool or warm to touch, and not affected by rest or massage.
    2. Animal is usually not lame unless there is severe enlargement of a limb.
    3. Activity and growth are normal.
    4. Affected area is at risk for trauma, infection, secondary inflammation, pain, ulceration, or drainage.
  B. Induration and fibrosis with long-standing edema
III. Regional lymph nodes may be normal, small, or absent.

Diagnosis

I. Often young animal with no history of trauma, surgery, neoplasia, or infection
II. Tests for underlying cause of edema (either lymphatic or venous in origin)
  A. Results of complete blood count (CBC), biochemical profile, and urinalysis are usually normal unless edema is complicated by secondary infection or inflammation.
  B. Diagnostic imaging (radiography, ultrasonography) of abdominal and thoracic cavities may be performed to rule out secondary causes of edema.
III. Fine-needle aspirate (FNA) of edematous swelling for cytological examination
  A. Poorly cellular transudate if uncomplicated
  B. Increased numbers of neutrophils, macrophages, or both if secondary inflammation or infection present
IV. Radiographic lymphangiography often diagnostic (Fossum et al., 1992)
  A. May demonstrate lymph node aplasia
  B. May show lymphatics that end blindly or do not empty into lymph node
V. Surgical biopsy and histological examination of tissue to rule out secondary causes of edema

Differential Diagnosis

I. Secondary lymphedema
II. Other causes of edema
  A. Vascular disorders: obstruction, arteriovenous fistula, vasculitis, thrombosis
  B. Hypoproteinemia
  C. Impaired venous return from congestive heart failure or portal hypertension

Treatment

I. Mild cases require no treatment.
II. Conservative management is tried initially.
  A. Pressure bandages or splints to limit fluid accumulation and encourage lymphatic flow
  B. Topical skin care as needed
  C. Long-term diuretic therapy contraindicated
III. Surgical management can be undertaken if conservative management is ineffective.
  A. Enhance lymphatic drainage: lymphangioplasty, bridging procedures, lymphatic to vein (lymphaticovenous) shunts, superficial to deep lymphatic anastomosis
  B. Excision of affected tissue

Monitoring of Animal

I. Prognosis is guarded for resolution of edema, although some cases spontaneously regress.

II. Severe generalized forms are usually lethal within the first few weeks of life.
III. The condition is not usually life-threatening if animals survive the neonatal period.

ACQUIRED DISORDERS

Lymph Node Atrophy

Definition and Causes

I. Lymph node atrophy is the loss of lymphoreticular cells in lymph nodes.
II. Acquired forms are more common than hereditary forms.
  A. Viral infections: feline immunodeficiency virus (FIV), feline leukemia virus (FeLV), parvovirus, canine distemper virus
  B. Advanced age and/or senility
  C. Severe malnutrition or cachexia
  D. Immunosuppressive or cytotoxic drugs: corticosteroids, chemotherapeutic agents
  E. Environmental toxins or radiation
III. Immunocompromise, with increased susceptibility to infections, is a common sequela.

Clinical Signs

I. Often associated with secondary chronic or recurrent infections
II. Systemic signs: weight loss, poor development, fever, lethargy, anorexia

Diagnosis

I. History of recurrent or unresponsive infections
II. Microbial culture to identify infectious agents
III. CBC and biochemical profile
  A. Possible lymphopenia
  B. Possible hypoglobulinemia
IV. FeLV and FIV testing in cats
V. Surgical biopsy and histological examination of lymphoid tissue to confirm atrophy

Treatment and Monitoring

I. Identify and treat underlying cause of acquired immunocompromise.
II. Administer appropriate antimicrobial therapy for secondary infections.
III. Provide supportive care and proper nutrition to support regeneration of lymphoid tissue.
IV. The efficacy of immunostimulants has not been proven in dogs and cats.
V. Prognosis depends on the degree of immunocompromise and the underlying cause.

Secondary Lymphedema

Definition and Causes

I. Secondary lymphedema is accumulation of interstitial fluid from acquired abnormalities of lymphatic system.
II. It is caused by destruction or occlusion of lymphatic vessels, lymph nodes, or both.
  A. Surgical excision or trauma
  B. Lymphangitis/lymphadenitis
  C. Compression or invasion by space-occupying mass (e.g., neoplasm)
  D. Radiation

Pathophysiology

I. The severity of lymphedema is determined by collateral circulation, interlymphatic and lymphaticovenous anastomoses, perilymphatic drainage of fluid, and venous fluid uptake.
II. Affected animals are at risk for infections, abrasions, and fibrosis.

Clinical Signs

I. Pitting edema of tissue, with extent depending on location and severity of lymphatic damage
  A. Edema is often localized to the periphery of the limb.
  B. Intrapelvic or sublumbar lesions cause edema of external genitalia and hind limbs.
  C. Mediastinal lesions cause edema of forelimbs, ventral thorax, neck, and head.
II. Clinical signs related to underlying disorder: weight loss, fever, anorexia

Diagnosis

I. Note history of previous surgery, trauma, infection, or neoplasia.
II. Search for underlying inflammatory, infectious, or neoplastic processes.
  A. CBC, biochemical profile, and urinalysis
  B. Radiography and/or ultrasonography of affected region for masses or destructive lesions
  C. Regional lymph node palpation, including rectal examination if pelvic limbs affected
  D. FNA of edematous tissue, enlarged lymph nodes, or masses for cytological evaluation
    1. Microscopically evaluate for inflammatory cells, organisms, or neoplastic cells.
    2. Fluid is a poorly cellular transudate unless complicated by infection or inflammation.
  E. Surgical biopsy of any affected tissue for histologic examination and microbial culture
III. Consider lymphangiography.
  A. Lymphatics are often enlarged and tortuous.
  B. Lymph nodes with inflammatory or neoplastic foci are often enlarged with filling defects.

Differential Diagnosis

I. Primary lymphedema
II. Nonlymphatic causes of edema, as listed under Primary Lymphedema

Treatment

I. Identify and treat underlying disorder.
  A. Long-term, antimicrobial therapy if secondary to infection

B. Surgical excision, chemotherapy, and radiation therapy if associated with neoplasia

II. Postsurgical or posttraumatic lymphedema may respond to short-term, antiinflammatory drugs (e.g., prednisone), diuretics, bandaging, or physical therapy.

III. If the underlying disorder cannot be resolved, treatment options include conservative medical and surgical management, as discussed under Primary Lymphedema.

Monitoring of Animal

I. Prognosis depends on the underlying disorder.

II. No treatment is required if lymphedema is mild, self-limiting, or localized.

Lymphangitis

Definition and Causes

I. Inflammation of lymphatic vessels

II. Usually secondary to drainage of inflammatory agents and by-products from an underlying inflammatory disorder (often involving skin, mucous membranes, or subcutaneous tissues)
   A. Infection: bacteria, fungi
   B. Neoplasia
   C. Trauma, chronic irritation or foreign body
   D. Immune-mediated disorder

III. May result in secondary lymphedema

Clinical Signs

I. Systemic clinical signs associated with underlying disorder: fever, depression, anorexia

II. Affected area swollen, warm, painful
   A. Lameness if involving a limb
   B. May ulcerate through overlying skin

III. Possible enlargement of regional lymph nodes from hyperplasia or lymphadenitis

Diagnosis

I. Clinical signs and history inconsistent with primary lymphedema

II. Cytological and histological examination: neoplastic cells, inflammatory cells, or infectious agents

III. Microbial culture for identification of infectious agent

IV. Contrast radiographs and surgical exploration for foreign body, abscesses, or fistulous tracts

Differential Diagnosis

I. Primary or secondary lymphedema

II. Nonlymphatic causes of edema

Treatment

I. Treat the underlying cause.
   A. Local and systemic antimicrobial therapy for infection
   B. Surgical exploration for foreign bodies, fistulous tracts, or abscesses
   C. Immunosuppressive therapy if immune-mediated disease detected
   D. Surgical excision, chemotherapy, and radiation therapy if neoplasia diagnosed

II. Apply warm, moist compresses or soaks to promote drainage.

Monitoring of Animal

I. Prognosis depends on the underlying disorder and is generally good for infections if appropriate antimicrobial therapy is instituted.

II. Fibroplasia and irreversible thickening of tissue may occur if chronic lymphedema develops.

Nonneoplastic Lymph Node Enlargement

Definition

I. Lymphadenopathy commonly refers to lymph node enlargement for any reason (hyperplasia, inflammation, primary or secondary neoplasia).

II. Lymphadenitis refers to an influx of inflammatory cells (neutrophils, eosinophils, or macrophages) into lymph nodes, often secondary to the drainage of by-products or infectious agents from a distant site of inflammation.

III. *Hyperplasia* (also called *reactive hyperplasia*) refers to increased numbers of lymphocytes, plasma cells, or macrophages in lymph nodes in response to antigenic stimulation.

Causes

I. Suppurative lymphadenitis
   A. Localized or systemic infections: bacteria, fungi
   B. Rapidly enlarging neoplasm
   C. Infarction
   D. Immune-mediated disorder

II. Pyogranulomatous or granulomatous lymphadenitis
   A. Fungal infection: histoplasmosis, blastomycosis, cryptococcosis, coccidioidomycosis
   B. Chronic or complex bacterial infection
   C. Chronic immune-mediated disorder
   D. Foreign body reaction
   E. Protozoal infection: toxoplasmosis, leishmaniasis
   F. Algal infection: protothecosis

III. Eosinophilic lymphadenitis
   A. Parasitism
   B. Allergic disorders
   C. Eosinophilic granuloma complex
   D. Some types of neoplasia: mast cell tumor, lymphoma
   E. Other infections: pythiosis

IV. Hyperplasia
   A. Systemic or localized infection
      1. Rickettsial infection: ehrlichiosis
      2. Viral infection: FIV, FeLV
      3. Bacterial infection
      4. Fungal infection
   B. Immune-mediated disorders or postvaccination
   C. Any source of chronic antigenic stimulation: neoplastic or inflammatory disorders

V. Idiopathic syndromes in cats (Couto et al., 2000)
   A. Generalized lymphadenopathy in young cats (1 to 4 years)

1. Some features of lymphoma were present on histological examination.
2. Lymphadenopathy spontaneously regressed in 5 to 120 days.
3. Cats were negative for FeLV antigen.

B. Distinctive peripheral lymph node hyperplasia in young cats (5 months to 2 years)
1. Generalized lymphadenopathy regressed in some cats.
2. Some cats were asymptomatic; others had fever, lethargy, anorexia.
3. Many cats were FeLV positive.
4. Histological findings resembled experimental FeLV infection in cats.

C. Plexiform vascularization of lymph nodes of unknown cause
1. Solitary cervical or inguinal lymphadenopathy in adult cats (most asymptomatic)
2. Histological findings: tissue replaced by plexiform proliferation of vascular channels
3. Surgical excision: curative, although lymphedema a possible sequela

Clinical Signs

I. Lymph node enlargement
A. Hyperplasia: usually nonpainful, firm, not warm, no adhesion to surrounding tissue
B. Lymphadenitis: often painful, soft, warm, ± adhesion to surrounding tissue
C. May cause obstruction or compression of adjacent tissues
1. Mandibular or retropharyngeal lymph nodes: dysphagia
2. Mediastinal or cervical lymph nodes: precaval syndrome or dyspnea
3. Thoracic lymph nodes: respiratory difficulties or pleural effusion
4. Sublumbar lymph nodes: tenesmus

II. Clinical signs associated with underlying diseases

Diagnosis

I. Look for an underlying disorder.
A. CBC: inflammatory leukogram (neutrophilia, left shift, monocytosis)
B. Biochemical profile: hyperglobulinemia, hypercalcemia rarely with granulomatous disease
C. Bone marrow examination: organisms with some systemic infections

II. Perform diagnostic imaging (radiography, ultrasonography) to identify involvement of thoracic and abdominal lymph nodes, liver, or spleen.

III. Lymph node cytology of FNA is often diagnostic.
A. Hyperplasia
1. Heterogeneous cell population with small lymphocytes predominating
2. ± Relative increase in medium and large lymphocytes, plasma cells, and macrophages
3. Few neutrophils, eosinophils, or mast cells

B. Lymphadenitis
1. Increased neutrophils (>5% of nucleated cells), eosinophils (>3% of nucleated cells), or macrophages (>2% of nucleated cells) (Duncan, 1999)
2. Often concurrent hyperplasia
3. May identify etiologic agent

IV. Lymph node biopsy with histologic examination is recommended if results of FNA are equivocal.
A. Core biopsy: sample size often too small for adequate assessment of architecture
B. Wedge biopsy: used if unable to remove entire node
C. Excisional biopsy: best sample to assess architecture
D. Special stains to identify organisms: fungi, bacteria, parasites, protozoa

V. Identify underlying infections.
A. Serological testing for certain infectious agents
B. Microbial culture of tissue sample

Differential Diagnosis

I. Lymphoma
II. Metastatic neoplasia

Treatment

I. Treat underlying disorder.
II. Surgical excision or drainage may be helpful for abscessed or fistulated lymph nodes.

Monitoring of Animal

I. Prognosis depends on the underlying disorder.
II. Resolution is expected with removal of antigenic or inflammatory stimuli.
III. Repeat surgical biopsy or FNA of lymph nodes if lymphadenopathy persists, because it may be difficult to differentiate severe hyperplasia from lymphoma, especially in cats.

NEOPLASTIC DISORDERS

Lymphangioma

Definition and Cause

I. Rare benign proliferation of lymphatic vessels
II. Cause unknown

Clinical Signs

I. Reported sites: subcutaneous tissue (most common), mediastinum, retroperitoneal space, mesentery, urinary bladder, liver, kidney, tongue, spleen, oral cavity, and nasopharynx
II. Poorly circumscribed, fluctuant masses with fluid-filled spaces lined by endothelial cells
III. Often incidental finding but may compress surrounding structures and alter function
IV. Possible leakage of lymphatic fluid onto skin through draining tracts

Diagnosis

I. Definitive diagnosis requires surgical excision and histological examination of tissue.

II. Cytological examination often reveals a poorly cellular transudate with variable protein concentration.

Differential Diagnosis

I. Lymphangiosarcoma or other neoplasm
II. Space-occupying, nonneoplastic masses: abscess or cysts
III. Lymphatic disorders: lymphedema, lymphangitis

Treatment and Monitoring

I. Surgical excision is the treatment of choice if complete removal is possible.
II. Recurrence is common because of difficulty in identifying tumor boundaries.

Lymphangiosarcoma

Definition and Cause

I. Rare malignant proliferation of endothelial cells lining lymphatic vessels
II. Cause unknown but medium- to large-breed dogs at greater risk

Clinical Signs

I. Primary site often subcutaneous tissue on extremities or ventral abdomen
II. Depends on site of primary tumor or metastases
   A. Pitting edema of affected region
   B. Chylous effusions (pleural, peritoneal, or subcutaneous spaces) in some cases
III. Poorly circumscribed, soft, fluctuant mass on palpation

Diagnosis

I. Cytological examination of FNA shows pleomorphic mesenchymal cells suggestive of sarcoma.
II. Surgical biopsy and histological examination of tissue are required for definitive diagnosis.
III. Look for evidence of metastasis.
   A. Examination of draining lymph nodes
   B. Diagnostic imaging (radiography, ultrasonography) of thoracic and abdominal cavities

Differential Diagnosis

I. Other soft-tissue sarcomas: hemangiosarcoma, fibrosarcoma, hemangiopericytoma
II. Lymphangioma

Treatment

I. Surgical excision if possible
II. Efficacy of radiation therapy and chemotherapy not determined in cats and dogs

Monitoring of Animal

I. Complete surgical excision of the neoplasm is difficult and the local recurrence rate is high.
II. The neoplasm tends to exhibit rapid local invasion, with frequent distant metastasis.

Lymphoma

Definition

I. Proliferation of malignant lymphoid cells originating outside of bone marrow and primarily affecting lymph nodes or visceral organs (e.g., liver, spleen, kidney)
II. Most common hematopoietic tumor in dogs and cats
III. Also known as *malignant lymphoma* or *lymphosarcoma*

Causes

I. Associated directly with FeLV or indirectly with FIV infection in cats (Louwerens et al., 2005)
II. No clear association with viral infection in dogs (Vail and Thamm, 2005)
III. Possible association with exposure to tobacco smoke in cats (Louwerens et al., 2005)
IV. Possible association with herbicides, magnetic fields, or environmental pollutants in dogs (Vail and Thamm, 2005)
V. Possible genetic predisposition (Louwerens et al., 2005; Modiano et al., 2005)

Classification

I. Anatomic site
   A. Distribution in dogs (Vail and Thamm, 2005)
      1. Most common: multicentric (80% to 85% of all cases)
      2. Less common: alimentary (7%), cutaneous (6%), mediastinal (3%), and other extranodal sites (<1%)
   B. Distribution in cats
      1. Distribution changing as prevalence of FeLV infection decreases; currently <15% of cats with lymphoma are FeLV positive (Louwerens et al., 2005)
      2. Distribution and FeLV association (Vail and Thamm, 2005)
         a. Multicentric: 10% to 25% of cases (approximately one third FeLV positive)
         b. Mediastinal/thymic: 10% to 20% of cases (majority FeLV positive)
         c. Alimentary: 50% to 70% of cases (few FeLV positive)
         d. Nasal: 10% of cases (few FeLV positive)
         e. Renal: 5% to 10% of cases (few to moderate FeLV positive)
         f. Other: 5% to 25% of cases (variable FeLV status)
      3. Feline Hodgkin's-like lymphoma (Walton and Hendrick, 2001)
         a. Majority of cats present with unilateral mandibular or cervical lymphadenomegaly.
         b. Preliminary study suggests it may be less aggressive than non-Hodgkin's lymphoma.
II. World Health Organization (WHO) clinical stage (Box 69-1)
III. Histological and cytological appearance (e.g., Kiel, National Cancer Institute Working Formulation)
   A. Lymphomas are graded based on architecture (diffuse, follicular), mitotic index, and cellular morphology (size, nuclear shape, chromatin density, nucleolar features).

Box 69-1

World Health Organization Clinical Stages for Lymphoma

Stage*	Clinical Findings
I	Involvement of single lymph node or lymphoid tissue in single organ (except bone marrow)
II	Involvement of multiple, regional lymph nodes
III	Generalized lymph node involvement
IV	Liver and/or spleen involvement, with or without lymph node involvement
V	Bone marrow or blood involvement and/or other organ systems

*Each stage is subdivided into (a) no systemic signs of disease and (b) systemic signs of disease.

B. They are divided into low, intermediate, and high grades.
   1. In dogs, approximately 75% of lymphomas are considered high grade (Fournel-Fleury et al.,1997).
   2. In cats, 54% of lymphomas are considered high grade, 35% medium grade, and 11% low grade (Valli et al., 2000).

IV. Immunophenotype
   A. Dogs (Modiano et al., 2005)
      1. Majority B cell: range 55% to 82%, average 67%
      2. Fewer T cell: range 18% to 42%, average 27%
      3. Occasional (4%) null cell or biphenotypic
   B. Cats (Valli and Thamm, 2005)
      1. Majority are B-cell tumors.
      2. Prevalence of T-cell lymphomas varies according to anatomical location (common in alimentary and mediastinal/thymic sites) and FeLV status (majority of lymphomas in FeLV-positive cats are T cell).

Clinical Signs

I. Signalment is as follows:
   A. Dogs (Modiano et al., 2005)
      1. Usually middle-aged to older: >90% are >5 years old, range <1 to >15 years old
      2. Numerous breeds affected
   B. Cats (Louwerens et al., 2005)
      1. Median age 11 years: range <1 to >20 years old
      2. Occurs in young cats if associated with FeLV infection
      3. Occurs in middle-aged to older cats if FeLV negative
      4. Numerous breeds affected
      5. High incidence of mediastinal lymphoma in Siamese-type breeds

II. Clinical signs depend on site(s) affected.
   A. Clinically ill (WHO substage b) (MacDonald et al., 2005; Rassnick et al., 2002; Vail and Thamm, 2005)
      1. Dogs: 10% to 44%
      2. Cats: >75%
   B. Multicentric
      1. Lymphadenopathy (WHO stage II or III) ± hepatosplenomegaly (WHO stage IV)
      2. Nonspecific findings: lethargy, inappetence, weight loss
      3. Polyuria/polydipsia if hypercalcemic
   C. Bone marrow involvement (WHO stage V)
      1. Cytopenia in blood if significant involvement
      2. Nonregenerative anemia, hemorrhagic diathesis from thrombocytopenia, or sepsis from neutropenia
   D. Alimentary
      1. Gastrointestinal involvement, with or without intra-abdominal lymphadenopathy
      2. Vomiting, diarrhea, or both (± melena)
      3. Inappetence, weight loss, depression
   E. Mediastinal
      1. Includes mediastinal lymph nodes, sternal lymph nodes, or thymus
      2. Dyspnea or coughing; muffled heart sounds from pleural effusion
      3. Pitting edema of thoracic limbs, face, and neck if invasion or compression of vena cava
      4. Polyuria/polydipsia if hypercalcemic
   F. Cutaneous
      1. Single to multiple lesions anywhere on skin or in oral cavity with possible pruritus
      2. Vary from erythematous scales, plaques, nodules, or serpiginous branching tracts
   G. Miscellaneous extranodal: variable presentation
      1. Spinal cord: limb paresis, ataxia
      2. Intracranial: ataxia, circling, blindness, seizures
      3. Renal: polyuria/polydipsia, weight loss, large irregular kidneys
      4. Nasal: sneezing, nasal discharge, exophthalmos, facial deformity
      5. Ocular: uveitis, hyphema, hypopyon, epiphora, blepharospasm, third eyelid infiltration

Diagnosis

I. Physical examination
   A. Palpate all accessible lymph nodes (including rectal and abdominal palpation).
   B. Palpate the liver, spleen, kidneys, mesentery, and intestines for enlargement or thickening.
   C. Auscultate the thorax in dogs and cats and perform thoracic compression in cats.
   D. Check the mucous membranes for anemia and petechiae.
   E. Perform an ocular (including funduscopic) examination.

II. CBC
   A. Anemia
      1. Nonregenerative anemia of chronic disease (most common) or if bone marrow infiltration by neoplastic cells
      2. Regenerative if blood loss or hemolysis
   B. Thrombocytopenia if bone marrow infiltration by neoplastic cells, immune-mediated destruction, splenic sequestration, or disseminated intravascular coagulation

C. Neutropenia from bone marrow infiltration or neutrophilia from inflammation
D. Lymphopenia or lymphocytosis: circulating atypical lymphocytes suggestive of bone marrow involvement (WHO stage V)

III. Bone marrow aspirate or core biopsy
A. Important for clinical staging: presence of neoplastic lymphocytes
B. Useful if lymphoma suspected but not identified elsewhere

IV. Biochemistry abnormalities
A. Hypercalcemia (Baskin et al., 2000; Vail and Thamm 2005)
1. Identified in 10% to 20% of all dogs with lymphoma.
2. Identified in approximately 40% of dogs with mediastinal involvement.
B. Azotemia (increased blood urea nitrogen or creatinine concentrations): renal infiltration, hypercalcemic nephropathy or dehydration
C. Increased liver enzyme activity and bilirubin concentration: hepatic infiltration
D. Hypoproteinemia secondary to alimentary lymphoma and protein-losing enteropathy
E. Monoclonal gammopathy occasionally with B-cell lymphoma

V. FeLV and FIV testing in cats

VI. Diagnostic imaging important for diagnosis and clinical staging
A. Options: radiography, ultrasonography, computed tomography, spinal myelography
B. Thoracic abnormalities: pulmonary infiltrates, thoracic or mediastinal lymphadenopathy, pleural effusion
C. Abdominal abnormalities: enlargement of sublumbar or mesenteric lymph nodes, organomegaly (e.g., liver, spleen, kidney), intestinal infiltration, abdominal effusion

VII. Cytological examination of FNA
A. Lymph nodes
1. There is usually a predominance of a homogeneous population of immature lymphocytes (Duncan, 1999).
a. Presence of >50% immature cells (medium and large lymphocytes) is suggestive of lymphoma.
b. Increased number of mitotic figures, tingible-body macrophages, cytoplasmic fragments, or cellular pleomorphism may also be found.
c. Lymphomas with mixed cellularity are easily missed.
2. Small-cell lymphomas are difficult to diagnose using cytology.
a. Absence of medium and large lymphocytes and plasma cells is suggestive.
b. Often surgical biopsy and histological examination is required for diagnosis.
3. Severe reactive hyperplasia may be confused with neoplasia (particularly in cats).
4. Cytological examination is diagnostic in a majority of lymphomas.
B. Fluid cytology: pleural, peritoneal, cerebrospinal fluid
C. Other organs if affected: liver, spleen, kidney, nasal mass, eye, dermal mass
D. Immunocytochemistry to phenotype cells: prognostic significance in dogs

VIII. Histological examination of tissue required if cytological findings equivocal
A. Excisional biopsy preferred: allows thorough evaluation of architecture and invasiveness
B. Various histochemical and immunohistochemical stains to characterize cells
1. Immunophenotyping: B cell, T cell, null (non-B, non-T cell), biphenotypic (coexpression of B- and T-cell markers)
2. Assessment of tumor proliferation rates, multidrug resistance expression, and apoptosis (Lee et al., 1996; Kiupel et al., 1999; Rassnick et al., 1999; Vail and Thamm, 2005)

IX. Additional diagnostic assays
A. Flow cytometry to phenotype cells (Wilkerson et al., 2005)
B. Detection of clonal rearrangement of immunoglobulin and T-cell receptor genes (Burnett et al., 2003)

Differential Diagnosis

I. Generalized lymphadenopathy
A. Hyperplasia, lymphadenitis, or both
B. Other hematopoietic (e.g., leukemia, histiocytic sarcoma) or metastatic neoplasms

II. Alimentary
A. Lymphoplasmacytic enteritis or other inflammatory bowel disorders
B. Nonlymphoid intestinal neoplasms

III. Cutaneous
A. Dermatitis: infectious or immune-mediated disorders
B. Other cutaneous neoplasms

IV. Mediastinal
A. Other neoplasms: thymoma, chemodectoma, ectopic thyroid tumor
B. Granulomatous/pyogranulomatous inflammatory disorders (e.g., systemic fungi)

Treatment and Monitoring

I. Options
A. Systemic chemotherapy is recommended in most cases.
B. Local surgery or radiation therapy may be used for solitary or extranodal lymphoma.
1. Systemic lymphoma is likely to develop months to years later at which time systemic chemotherapy is required.
2. Radiation therapy is most effective for nasal lymphoma.

II. Systemic chemotherapy in dogs
A. Combination chemotherapy usually results in longer disease-free intervals and survival periods than with single-agent protocols.

TABLE 69-1

Examples of Chemotherapeutic Induction Protocols for Dogs with Lymphoma

REFERENCE	DRUG PROTOCOL*	REMISSION RATE (CR/PR)	MEDIAN DURATION OF FIRST CR	MEDIAN SURVIVAL PERIOD
Khanna et al., 1998	PRED 40 mg/m^2 PO SID DOX 30 mg/m^2 IV: wk 3, 6, 9 VCR 0.65 mg/m^2/wk IV: wk 2, 4, 5, 8, 10, 11, 12 CTX 50 mg/m^2 PO (days 4-7): wk 2, 5, 8, 11, 12 L-ASP 20,000 IU/m^2 SC: wk 1	79%/8%	309 days	519 days
Boyce et al., 2000	PRED 20 mg/m^2 PO SID for 1 wk then QOD for 7 wk DOX 30 mg/m^2 IV: wk 6, 9, 12 VCR 0.5 mg/m^2 IV: wk 1, 2, 3, 4, 5, 7, 8, 10, 11, 12 CTX 50 mg/m^2 PO QOD for 8 wk L-ASP 10,000 IU/m^2 SC: wk 1, 2	80%/12%	36 wk CR, 4 wk PR	40 wk CR, 12 wk PR
Jeffreys at al., 2005	PRED 20 mg/m^2 PO BID; repeat for 6 wk VCR 0.7 mg/m^2 IV day 1; repeat for 6 wk CTX 50 mg/m^2 PO days 4, 5, 6, 7; repeat for 6 wk L-ASP 10,000 IU/m^2 SC day 2; wk 1, 2	79%/2%	25 weeks	NR
MacDonald et al., 2005	PRED 2 mg/kg PO SID for 1 wk, then 1.5 mg/kg PO SID for 1 wk, then 1.0 mg/kg PO SID for 1 wk, then 0.5 mg/kg PO QOD for 1 wk L-ASP 400 U/kg SC: wk 1 VCR 0.5-0.7 mg/m^2 IV: wk 1, 3, 6, 8, 11, 13, 16, 18 CTX 250 mg/m^2 IV: wk 2, 7, 12, 17 DOX 30 mg/m^2 IV: wk 4, 9, 14, 19	83%/6%	206 days	310 days
Carter et al., 1987	DOX 30 mg/m^2/wk IV every 3 wk for total of 5-8 treatments	76%/NR	206 days	270 days

CR, Complete remission; *PR,* partial remission; *PRED,* prednisone; *DOX,* doxorubicin; *VCR,* vincristine; *CTX,* cyclophosphamide; *L-ASP,* L-asparaginase; *NR,* not reported.

*Unless stated otherwise, drug given on day 1 of indicated week.

1. A number of protocols are available, with no clear optimal protocol (Table 69-1).
2. Complex protocols tend to provide the longest remission and survival times but are more expensive, require greater owner commitment, and have more toxic side effects.
3. Most complex protocols are modified protocols that include cyclophosphamide (C), doxorubicin (hydroxydaunorubicin [H]), vincristine (Oncovin [O]), and prednisone (P), (i.e., CHOP protocols).
4. L-asparaginase is frequently added but its effect on outcome is debated (Jeffreys et al., 2005; MacDonald et al., 2005).
5. Treatment generally starts with an induction phase (drugs administered weekly) followed by maintenance phases (drugs given less frequently, longer drug-free intervals).
6. Remission rates, duration of remission, and long-term survival rates depend on the presence or absence of factors known to affect prognosis (see Box 69-2).

B. Single-drug protocols are not ideal.
   1. Doxorubicin is the most effective single chemotherapeutic agent (see Table 69-1).
   2. Prednisone (2 mg/kg/day PO) alone often extends life 1 to 2 months; however, remission and survival times are shorter if additional chemotherapy is subsequently initiated.

III. Systemic chemotherapy in cats
   A. It generally induces lower remission rates, remission durations, and survival times than in dogs, but a significant percentage (30% to 40%) of cats that go into complete remission live longer lives (Vail and Thamm, 2005).
   B. Combination protocols are more effective than single-agent chemotherapy (Table 69-2).
   C. Doxorubicin is not effective as a single chemotherapeutic drug (see Table 69-2) but, when following a combination protocol, may prolong remission and survival rates (Kristal et al., 2001; Vail and Thamm, 2005).

IV. Monitoring during chemotherapy
   A. Frequency and severity of side effects depend on the protocol used.

Box 69-2

Factors Reported to Affect Prognosis in Dogs and Cats with Lymphoma

Factor	Effect
WHO clinical stage	Poorer prognosis for stage V with significant bone marrow involvement in dogs
WHO substage	Substage b associated with poorer prognosis in dogs and cats
Immunophenotype	T-cell origin: shorter remission and survival times in dogs; not shown to be predictive of outcome in cats
Histologic grade	Study results variable: not predictive of outcome in some studies, significant prognostic differences between subtypes in other studies Animals with low-grade tumors may live longer
Proliferation activity markers	Study results variable AgNORs assessment in tissue predictive of survival time in dogs in some but not all studies PCNA and AgNORs not predictive of outcome in cats
P-glycoprotein expression	Expression negative predictor of overall survival in dogs
FeLV positive	Shorter remission and survival times in cats
History of chronic inflammatory disorders	Shorter remission times in dogs
Hypercalcemia	Shorter survival times in dogs, possibly from T-cell association
Initial response to chemotherapy	Positive prognostic indicator in dogs and cats

WHO, World Health Organization; *AgNORs,* argyrophilic nucleolar organizer regions; *PCNA,* proliferation cell nuclear antigen; *FeLV, feline* leukemia virus.

1. Quality of life is considered acceptable in most animals.
2. Side effects include the following:
   a. Gastrointestinal disorders: vomiting, diarrhea, anorexia
   b. Leukopenia, thrombocytopenia, or both
   c. Cardiotoxicity: associated with doxorubicin
   d. Renal toxicity: associated with doxorubicin in cats
   e. Miscellaneous: hemorrhagic cystitis (associated with cyclophosphamide), fever, neurologic signs (e.g., psychosis, pelvic weakness), allergic reactions, alopecia

B. Perform a CBC before administering chemotherapeutic drugs, and alter protocol if significant thrombocytopenia or neutropenia is detected.
   1. For drugs that alter hematopoiesis, discontinue use for 5 to 7 days.
   2. After blood cell counts increase, give drugs at a decreased dose or frequency.

C. Monitor for organ damage associated with specific chemotherapeutic drugs.

D. Recheck monthly to detect recurrence.

E. Cytological examination of FNA is more effective than physical examination alone to determine remission status (Williams et al., 2005).

V. Rescue chemotherapy

A. Initiate once lymphoma recurs after remission or if initial chemotherapeutic protocol fails.
   1. Often more drug-resistant lymphoma
   2. Remission rates of 25% to 50%, with median remission periods of 1.5 to 2 months (Vail and Thamm, 2005)

B. First administer the chemotherapeutic protocol that caused the initial remission.

C. If there is no response, then initiate rescue protocols that use drugs not included in the initial induction protocol.
   1. Dogs: actinomycin D; mitoxantrone; doxorubicin with dacarbazine; combined mechlorethamine, vincristine, procarbazine, and prednisone (MOPP); cisplatin with cytosine arabinoside; lomustine (CCNU); dexamethasone, melphalan, actinomycin D, and cytosine arabinoside (D-MAC) (Kitchell and Dhaliwal, 2000; Rassnick et al., 2002; Vail and Thamm, 2005)
   2. Cats: mitoxantrone, doxorubicin, MOPP (Vail and Thamm, 2005)

VI. Extranodal lymphoma

A. Central nervous system involvement
   1. Add cytosine arabinoside (penetrates blood-brain barrier) to standard protocols.
   2. Consider radiation therapy.

B. Cutaneous forms
   1. Surgical excision or radiation therapy if solitary
   2. Systemic chemotherapy if multifocal
      a. Generally poorer response to chemotherapy than multicentric lymphoma
      b. Appropriate chemotherapeutic drugs (singly or in combination): vitamin A analogs (e.g., cis-retinoic acid), L-asparaginase, dacarbazine, CCNU, CHOP protocols (Vail and Thamm, 2005; Williams et al., 2006)

VII. Adjunctive or experimental therapies

A. Total-body or half-body radiotherapy (Williams et al., 2004)

B. Dietary modification: n-3 fatty acid supplementation (Ogilvie et al., 2000)

C. Experimental techniques: immunomodulation (e.g., tumor specific antibodies), stimulation of apoptosis, and limitation of development of multidrug resistance

VIII. Prognosis dependent on a number of factors (Box 69-2)

TABLE 69-2

Examples of Chemotherapeutic Induction Protocols for Cats with Lymphoma

REFERENCE	DRUG PROTOCOL*	REMISSION RATE (CR/PR)	MEDIAN REMISSION DURATION (CR/PR)	MEDIAN SURVIVAL PERIOD (CR/PR)
Mooney et al., 1989	PRED 2 mg/kg PO SID VCR 0.025 mg/ kg IV: wk 1, 3, 5, 7 CTX 10 mg/kg IV: wk 2, 6 L-ASP 400 IU/kg IP: wk 1 MTX 0.8 mg/kg IV: wk 4, 8	62%/20%	NR/NR	7 mo/2.5 mo
Kristal et al., 2001	DOX 25 mg/m^2 or 1 mg/kg IV every 3 wk for total of five treatments	26%/16%	92 days/NR	NR
Teske et al., 2002	PRED 50 mg/m^2 PO SID for 1 year or until relapse VCR 0.75 mg/m^2 IV: wk 1, 2, 3, 4, then every 3 wk for 1 year or until relapse CTX 300 mg/m^2 PO: wk 1,4, then every 3 wk (1 day after VCR) for 1 year or until relapse	75%/14%	251 days/NR	266 days
Milner et al., 2005	PRED 2 mg/kg PO SID for 2 wk, then 1 mg/kg PO SID for 1 wk, then 1 mg/kg PO QOD for remaining weeks DOX 25 mg/m^2 or 1 mg/kg IV: wk 4, 9, 25 VCR 0.5-0.7 mg/m^2 IV: wk 1, 3, 6, 8, 11, 15, 19, 23 CTX 200 mg/m^2 IV: wks 2, 7 L-ASP 400 U/kg SC: wk 1 MTX 0.5-0.8 mg/kg IV: wk 17 Chlorambucil 1.4 mg/kg PO: wks 13, 21	47%/37%	654 days/114 days	654 days/122 days

CR, Complete remission; *PR,* partial remission; *PRED,* prednisone; *VCR,* vincristine; *CTX,* cyclophosphamide; *L-ASP,* L-asparaginase; *IP,* intraperitoneally; *MTX,* methotrexate; *NR,* not reported; *DOX,* doxorubicin.

*Unless otherwise stated, drug given on day 1 of indicated week.

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CHAPTER 70

Disorders of the Spleen

William L. Spangler

SPLENOMEGALY

Definition

I. Splenomegaly describes any enlargement of the spleen.
II. With uniform or symmetrical splenomegaly, the basic shape of the enlarged spleen is retained.
III. In nodular or mixed splenomegaly, one or more distinct nodules occurs within normal or congested splenic parenchyma, or in a background of generally expanded reticular tissue.

Causes and Pathophysiology

I. Uniform and/or symmetrical splenomegaly
  A. Congestive splenomegaly occurs when the flow of blood through the red pulp and vessels is impeded.
    1. Anesthetic agents or tranquilizers cause increased pooling of blood in the red pulp via relaxation of smooth muscle.
    2. Splenic torsion can occur alone or in association with gastric dilation-volvulus.
    3. Splenic arterial thrombosis from torsion of the splenic pedicle occurs spontaneously and results in focal areas of infarction or larger areas of ischemia in the spleen.
    4. Congestion may arise secondary to portal hypertension from right-sided congestive heart failure, obstruction of the caudal vena cava or portal vein, and increased intrahepatic vascular resistance (cirrhosis, hepatitis, lipidosis).
  B. Hyperplastic (reactive) splenomegaly results from the following:
    1. Immunological stimulation: increased volume and accumulation of lymphocytes, plasma cells, and macrophages
    2. Associated with certain diseases
      a. Systemic immune-mediated diseases: systemic lupus erythematosus
      b. Bacterial infections: canine brucellosis, bacterial endocarditis, mycobacterial infections, Lyme borreliosis
      c. Hemolytic anemias: immune-mediated, Heinz body, hemobartonellosis, pyruvate kinase deficiency
      d. Rickettsial infections: canine ehrlichiosis, Rocky Mountain spotted fever
      e. Protozoal infections: babesiosis, leishmaniasis, trypanosomiasis, cytauxzoonosis, toxoplasmosis
      f. Other infections: histoplasmosis, feline infectious peritonitis
      g. Myeloid metaplasia or hypersplenism
  C. Extramedullary hematopoiesis, although common in aging dogs, is seldom responsible for splenomegaly.
II. Nodular and/or mixed splenomegaly: nonneoplastic causes
  A. Nodular hyperplasia and hematoma formation
    1. Self-limiting nodular hyperplasia and hematoma formation are the most common causes in dogs.
      a. They account for 53% of canine splenectomies (Table 70-1).
      b. Similar lesions occur in cats but are less prevalent (see Table 70-1).
    2. Nodular hyperplasia (single or multiple nodules) consists of lymphoid cells, hematopoietic cells, and plasma cells.
    3. Disruption of the microvascular circulation in the marginal zone of lymphoid follicles results in hematoma formation.
    4. Nodular hyperplasia is usually self-limiting, but progressive enlargement of nodules results from sporadic bleeding episodes.
    5. Rupture of a large hematoma may account for significant blood loss.
    6. The mean age for dogs with hyperplastic nodule-related splenectomy is 11 years (Spangler and Kass, 1997).
  B. Splenic abscess
    1. Rare in dogs; not reported in cats
    2. Common isolate: *Staphylococcus* spp. (Spangler and Kass, 1997)
III. Nodular and/or mixed splenomegaly: neoplastic causes
  A. Benign neoplasms of dogs and cats (see Table 70-1)
    1. Lipoma and myelolipoma
    2. Hemangioma, leiomyoma, or both
    3. Plasmacytosis
  B. Malignant neoplasms of dogs: 31% of splenomegaly cases (see Table 70-1)
    1. Hemangiosarcoma (HSA)
      a. It is the most common splenic malignancy in dogs (18%) (Spangler and Kass, 1997).
      b. Mean age is 11 years.

TABLE 70-1

Relative Prevalence of Splenic Diseases in Dogs and Cats

SPLENIC DISORDER	PREVALENCE IN DOGS*	PREVALENCE IN CATS†
Nodular hyperplasia, hematoma	53%	9%
Hemangiosarcoma	18%	6%
Splenic sarcomas (fibrosarcoma, osteosarcoma, myxosarcoma, leiomyosarcoma, liposarcoma, undifferentiated sarcoma)	8%	4%
Splenic torsion, arterial thrombosis	5%	—
Splenic infarction alone	—	2%
Lymphosarcoma	4%	18%
Mastocytosis	<1%	30%
Myeloid, lymphoid, and/or reticuloendothelial hyperplasia	3%	1%
Myeloproliferative disease	<1%	13%
Miscellaneous benign neoplasms (e.g., fibroma, leiomyoma, lipoma)	3%	2%
Metastatic neoplasms	1%	4%
Malignant histiocytosis	1%	—
Plasma cell myeloma	<1%	2%
Splenic abscess	<1%	—
Nonspecific splenitis	—	4%
Mycobacterial splenitis	<1%	—
Amyloidosis	<1%	<1%
Accessory spleen‡	—	3%

*Combined and edited data from 1,429 splenectomies (Spangler WL, Culbertson MR: The prevalence, type and importance of canine splenic diseases [a diagnostic survey]. J Am Vet Med Assoc 200:829, 1992; Spangler WL, Kass PH: Pathologic factors affecting postsplenectomy survival in dogs. J Vet Intern Med 11:166, 1997).

†Combined and edited data from 217 splenectomies (Spangler WL, Culbertson MR: The prevalence and type of splenic diseases in cats: 455 cases [1985-1991]. J Am Vet Med Assoc 201:773, 1992).

‡Not associated with splenomegaly; an incidental surgical finding of dark, red islands of splenic tissue in the parenchyma of the pancreas or adjacent omentum.

   c. Neoplastic proliferation often activates coagulation and fibrinolysis sequence, resulting in systemic disseminated intravascular coagulation (DIC), and liquid blood-filled spaces within the spleen.
   d. Sometimes, vascular spaces filled with clotted blood cannot be distinguished (grossly) from a hematoma of nodular hyperplasia.
2. Lymphosarcoma (LSA): 4.9% of splenomegaly cases (Spangler and Kass, 1997)
3. Primary mesenchymal (nonangiomatous/nonlymphomatous) tumors of the dog
   a. Fibrosarcoma
   b. Undifferentiated sarcoma
   c. Leiomyosarcoma
   d. Osteosarcoma
   e. Myxosarcoma
   f. Histiocytic sarcoma
   g. Liposarcoma
   h. Malignant fibrous histiocytoma.
4. Fibrohistiocytic nodules (malignant fibrous histiocytoma): transitional nodular splenomegaly ranging from benign to malignant in behavior
5. Mast cell tumor, mastocytosis
   a. Most dogs with systemic mastocytosis and splenic involvement also have primary cutaneous mast cell tumors, of which 77% are grade III (O'Keefe et al., 1987).
   b. There is no breed or gender predilection; the mean age is 9.5 years.
6. Myeloproliferative diseases (see Chapter 66): splenomegaly and proliferation of neoplastic myeloid cells common

C. Malignant neoplasms of cats: 75% of splenomegaly cases (Spangler and Culbertson, 1992a)
1. Mastocytosis
   a. The most common cause of splenomegaly (30%), also reflects systemic mast cell disease
   b. Uniformly symmetric enlargement of the spleen with characteristic speckled, orange color
2. LSA (see Chapter 69)
   a. LSA is a major cause, accounting for 18% of splenic enlargement in cats and 5% in dogs (Spangler and Culbertson, 1992a, b).
   b. Splenomegaly is part of a multiorgan systemic disease.
3. Myeloproliferative disorders (see Chapter 66): splenomegaly common component
4. Hemangiosarcoma
   a. Minor cause of splenomegaly (8%)
   b. Usually life-threatening

D. Myeloid metaplasia, hypersplenism, histiocytosis of dogs
1. These are histologically distinctive causes of splenomegaly.

2. Changes range from reactive splenitis associated with immunological damage of red blood cells (RBCs) (hypersplenism) to neoplastic proliferation of histiocytic components (hemophagocytic histiocytic sarcoma).

Clinical Signs

I. Signalment
   A. Clinical signs are not generally helpful in differentiating splenic hematoma or hyperplastic nodules from neoplasms.
   B. Dogs in both groups have a mean age of 9 to 10 years, are medium- to large-breed dogs (e.g., German Shepherds, Labrador and golden retrievers), and are evenly distributed relative to gender.
   C. Dogs with myeloid metaplasia, splenic torsion, or splenic abscess are younger (6 to 7 years), and show no breed or gender predilection.

II. Nonspecific signs attributable to splenomegaly
   A. Abdominal distention, ± discomfort
   B. Malaise, lethargy, depression
   C. Decreased appetite, weight loss
   D. Polyuria, polydipsia
   E. Cardiac arrhythmias in approximately 30% of cases of nodular splenomegaly (Keyes et al., 1993)

III. Signs associated with splenic torsion and HSA
   A. Collapse, shock, ± vomiting, abdominal pain, pale mucous membranes, ± tense painful abdomen
   B. Splenic torsions: rapid onset and progression, massively enlarged spleen
   C. HSA: episodic weakness and collapse, sometimes with apparent recovery, hemoabdomen

IV. Clinical signs associated with systemic mastocytosis
   A. Affected cats often have gastrointestinal signs (e.g., vomiting, diarrhea, and bleeding) caused by histamine release.
   B. Although this type of mastocytoma is rare in dogs, signs are similar.

V. Signs associated with myeloid metaplasia, hypersplenism, malignant histiocytosis, and LSA
   A. Fever, lethargy, and anorexia
   B. Lymphadenopathy and hepatomegaly

VI. Signs suggestive of histiocytosis in Bernese mountain dogs
   A. Respiratory signs: cough, dyspnea, and abnormal lung sounds
   B. Weakness, pallor from anemia, thrombocytopenia

Diagnosis

I. History
   A. No specific historical attributes
   B. Nonspecific historical signs: lethargy, abdominal discomfort, decrease in stamina, malaise

II. Physical examination
   A. Splenomegaly is detected by palpation of a mass in the cranial abdomen.
   B. Free blood may be detected in the abdomen.
   C. Pallor from anemia or shock may be noted.

III. Hematology and serum biochemistry results
   A. Biochemistry profiles and complete blood counts are essential.
   B. Anemia, thrombocytopenia, leukopenia, reticulocytosis, and any combination of cytopenias are nonspecific findings in animals with splenic disease.
   C. Erythrocyte morphological abnormalities that reflect blood flow through an abnormal spleen include acanthocytes, nucleated or fragmented RBCs, normocytic target cells, increased numbers of Howell-Jolly bodies, schistocytes, and keratocytes.
   D. Spherocytes, Heinz bodies, and erythroparasites, as well as positive direct Coombs' test, antinuclear antibody, and rheumatoid factor assays are associated with hemolysis and splenic hyperplasia resulting from systemic disease.
   E. Circulating neoplastic leukocytes suggest secondary or primary splenic involvement in such diseases as LSA, acute leukemia, chronic leukemia, and systemic mastocytosis (see Chapters 66 and 69).
   F. Hypercalcemia suggests LSA or multiple myeloma.
   G. Hyperglobulinemia is associated with chronic inflammatory disease or lymphoid (myeloma) neoplasia (see Chapter 77).
   H. Hypoproteinemia and hypoalbuminemia may be noted in dogs with malignant histiocytosis.

IV. Bone marrow evaluation
   A. Examination of marrow aspirates is indicated in refractory anemia with splenomegaly.
   B. Potential findings include the following:
      1. Hemolymphatic neoplasms
      2. Excess macrophages and RBC phagocytosis in marrow that is inactive or depleted
         a. Myeloid metaplasia
         b. Hemophagocytic syndrome or hemophagocytic histiocytic sarcoma
         c. Immune-mediated hemolytic anemia
      3. Erythroid hyperplasia with hemolytic anemias
      4. Granulocytic hyperplasia possible with inflammatory disorders

V. Radiography and ultrasonography
   A. The size and location of the spleen are assessed by plain radiography unless abdominal effusion obscures detail.
   B. Congestive enlargement is expected in anesthetized or sedated animals.
   C. Patterns suggestive of splenic torsion include the following:
      1. Identification of the spleen in an abnormal location
      2. Displacement of other organs
      3. C-shaped spleen folded over on itself
      4. Gas bubbles in the spleen from gas-forming bacteria multiplying in ischemic areas
   D. Three views of the thorax are indicated to look for possible metastases and pleural effusion.
   E. Ultrasonography of the abdomen is essential.
      1. Ultrasonography is more sensitive in the diagnosis of LSA and HSA than plain radiography because it identifies masses and patterns compatible with neoplasia.

2. HSA produces a nonhomogeneous echogenic pattern with hypoechoic blood-filled spaces and hyperechoic solid tissue.
3. Ultrasonography provides a method for guiding fine-needle aspirates of the spleen.
4. An abdominal ultrasound in any aging dog should include detailed evaluation of the spleen.

VI. Cytology of fine-needle aspirates
- A. Cytology is most useful when a diagnosis or additional information is sought before abdominal surgery, when the spleen is diffusely affected, or in animals in which the spleen is only marginally enlarged.
- B. It is contraindicated if HSA is suspected, if coagulation abnormalities exist, or if the spleen cannot be immobilized.

VII. Exploratory laparotomy
- A. Indicated when less invasive procedures are nondiagnostic.
- B. First correct severe anemia or any existing coagulopathy.
- C. It allows assessment and biopsy of other organs for evidence of involvement.
- D. It permits intraoperative cytological evaluation of splenic tissue or splenectomy.

Treatment

I. Medical therapy of the underlying disease
- A. Chemotherapy for hemolymphatic neoplasms
- B. Appropriate antimicrobial therapy for infectious diseases
- C. Immunosuppressive therapy for immune-mediated diseases

II. Indications for splenectomy
- A. Splenomegaly
  1. Abdominal exploration and splenectomy are often the primary diagnostic and treatment methods when splenomegaly is discovered.
  2. Splenectomy is the treatment of choice for splenomegaly in many dogs and cats, especially if the underlying cause is refractory to medical therapy.
- B. Splenic torsion
- C. Splenic masses
  1. Gross appearance does not reliably distinguish hematoma or a hyperplastic nodule from HSA.
  2. Cytological evaluation of tissue imprints, histologic evaluation of splenic tissue, or both are needed to reliably distinguish benign versus malignant disease.
  3. Perform total splenectomy, unless an intraoperative diagnosis of benign disease is assured.
  4. Submit the entire spleen for pathologic evaluation.
- D. Mastocytoma
  1. Splenectomy significantly extends life expectancy in cats with mastocytosis.
  2. Splenectomy is beneficial in removing a large portion of the tumor cell burden.
- E. Splenic rupture regardless of the underlying disease
- F. Immune-mediated hemolytic anemia or thrombocytopenia that is recurrent or refractory to drug therapy
- G. Adjunctive procedure to chemotherapy for LSA
  1. Alleviation of signs of massive splenomegaly (if present) before chemotherapy
  2. Progressive splenomegaly despite chemotherapy

III. Preoperative care
- A. Stabilize animals in shock with IV fluids (for correction of acid-base balance), corticosteroids, antibiotics, whole-blood transfusions or packed RBCs, and treatment for DIC.
- B. With mastocytosis, minimize the effects of mast cell degranulation with preoperative antihistamines and histamine$_2$ receptor antagonists.

IV. Consequences of splenomegaly
- A. No higher incidence of infectious disease occurs in splenectomized dogs, except when they are exposed to erythroparasites.
- B. Splenectomized animals are more susceptible to infection when immunosuppressed and are more easily immunosuppressed.

Monitoring of Animal

I. Effective medical therapy of the underlying disorder results in reduction of splenic size, and resolution of clinical signs and laboratory abnormalities.

II. Following splenectomy, animals must be monitored carefully for several days.
- A. Monitor for recurrent abdominal hemorrhage or effusion, and coagulation abnormalities.
- B. Monitor electrocardiogram for ventricular arrhythmias.

III. Prognosis for specific splenic disorders is as follows:
- A. Splenic torsion
  1. The prognosis depends heavily on elapsed time between torsion and splenectomy.
  2. Expected mortality in the postsplenectomy interval is up to 50% (Stevenson et al., 1981).
- B. Hyperplastic nodule/hematoma (Spangler and Kass, 1997)
  1. The prognosis is good.
  2. Eighty-five percent of animals survive splenectomy, 65% are alive at the end of the first year, and 70% of those dying in the first year do so from unrelated causes.
- C. HSA (Spangler and Kass, 1997)
  1. The prognosis for splenic HSA is guarded.
  2. Expect 90% mortality in the 7 months after splenectomy.
  3. Early detection and splenectomy provide the longest survival times.
  4. Survival time in dogs is significantly improved (12 to 35 months) when a single nodule (rather than multiple nodules) of HSA is present.
- D. LSA (Spangler and Kass, 1997)
  1. Splenomegaly arising solely from nodular enlargements of neoplastic lymphoid tissue
     a. The prognosis is favorable.
     b. Expect 28% to 30% mortality within 6 months and mean survival of 8.4 months postsplenectomy.

2. Uniformly enlarged spleen from lymphocyte infiltration with regional nodular formations
   a. The prognosis is poor.
   b. Expect up to 90% mortality in the 6 months after splenectomy and mean survival of 2.8 months.

E. Nonangiomatous/nonlymphomatous sarcomas (Spangler et al., 1994)
1. With the exception of splenic mesenchymoma (median survival 12 months), dogs with all other types of sarcomas have a median survival time of 4 months, with 80% to 100% mortality in 12 months.
2. Prognosis for this class of splenic neoplasms is most closely correlated with the mitotic index (Spangler et al., 1994).

F. Myeloid metaplasia, hypersplenism, histiocytosis (Spangler and Kass, 1999)
1. Postoperative 12-month survival in dogs is 30%.
2. About 50% have multiorgan involvement at time of splenectomy or develop it shortly thereafter.
3. Hemophagocytic histiocytic sarcoma, as a distinct neoplastic entity within the broad category of splenic myeloid metaplasia, is a major cause of mortality for this category of splenic disease (Moore et al., in press).

G. Benign neoplasms (lipoma, myelolipoma, hemangioma): good prognosis

H. Fibrohistiocytic nodules, malignant fibrous histiocytoma
1. The prognosis is dependent on histological grading of the nodule (Spangler and Kass, 1998).
2. Grade I and II nodules have a 12-month survival of 87% (good prognosis).
3. Grade III nodules have a 12-month survival of 45% (guarded prognosis).

I. Mastocytosis (O'Keefe et al., 1987)
1. The prognosis is guarded because 88% of dogs die as a direct result of the neoplasm.
2. Mean survival time is 3 months.

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CHAPTER 71

Transfusion Medicine

K. Jane Wardrop

GENERAL CONSIDERATIONS

Definition

I. Transfusion medicine is a multidisciplinary science concerned with the proper use of blood or blood products in the treatment or prevention of disease.

II. Optimal transfusion therapy requires knowledge of blood types and crossmatching procedures, blood sources and donor selection, blood collection and administration techniques, component therapy, transfusion reactions, and red blood cell (RBC) substitutes.

Canine and Feline Blood Types

I. Erythrocytes possess characteristic cell-surface glycolipid or glycoprotein antigens.
   A. A blood group system is a group of antigens produced by allelic genes located at a single locus and inherited independently of any other genes. Blood group systems are species specific.
   B. Animals commonly make antibodies against foreign blood group antigens. Naturally occurring alloantibodies may be a result of exposure to common environmental antigens that are similar or identical to foreign blood group antigens.
   C. The importance of any particular blood group system depends on both the frequency with which alloantibodies of the system occur and the characteristics of the alloantibody, such as titer, class, temperature-dependent activity, and ability to activate complement or agglutinate RBCs.

II. Canine blood groups have the following characteristics:
   A. Current nomenclature uses the prefix dog erythrocyte antigen (DEA) to describe canine blood types.
      1. Antibodies or typing sera for some of the originally identified canine blood groups are no longer available, and commercial typing sera currently test for six blood types in dogs (DEA 1.1, 1.2, 3, 4, 5, and 7).
      2. Several of these blood types can occur together on the erythrocyte and may vary in frequency with breed, geographic location, and antisera used (Table 71-1) (Bull, 1976; Giger et al., 1995; Hale, 1995).
   B. DEA 1 is a four-allele system.
      1. Dogs can be DEA 1 negative, DEA 1.1 positive or DEA 1.2 positive.
      2. DEA 1.3 also has been described in Australia (Symons and Bell, 1991).
      3. Naturally occurring antibody to DEA 1 is not present.
         a. Transfusion of DEA 1-positive blood into a DEA 1-negative recipient will result in anti-DEA 1 alloantibody synthesis and shortened lifespan of the transfused erythrocytes.
         b. Subsequent transfusions mismatched at that allele will result in an acute hemolytic transfusion reaction.
   C. DEA 3 and 5 are present in low incidence, and naturally occurring antibody to these antigens can occur (Swisher et al., 1962; Hale, 1995).
   D. DEA 4 is a high-incidence antigen with no naturally occurring antibody. A hemolytic transfusion reaction has been described in a DEA 4-negative dog given repeated transfusions of DEA 4-positive blood (Melzer et al., 2003).
   E. DEA 7 is a soluble nonerythroid antigen that is adsorbed onto the RBC surface (Bull et al., 1975), and dogs that are negative for DEA 7 may have naturally occurring anti-DEA 7 alloantibodies (Bull, 1990; Hale, 1995).

TABLE 71-1

Canine Blood Type Frequencies

DEA	FREQUENCY (%)
1.1	33 to 45
1.2	7 to 20
3	6 to 10
4	87 to 98
5	12 to 23
7	8 to 45

From Bull RW: Canine immunohematology. In Animal Models of Thrombosis and Hemorrhagic Diseases. Washington, DC, US Dept. of Health, Education, and Welfare Publication No. 76-982, 1976; Giger U, Gelens CJ, Callan MB et al: An acute hemolytic transfusion reaction caused by dog erythrocyte antigen 1.1 incompatibility in a previously sensitized dog. J Am Vet Med Assoc 206:1358, 1995.

DEA, Dog erythrocyte antigen.

F. Canine blood donors should be DEA 1.1 and 1.2 negative if their blood is to be used with type-unmatched recipients. Dogs that are 1.1 positive can be used with DEA 1.1-positive recipients.
G. Dogs that are negative for DEA 1.1, 1.2, 3, 5, and 7 and are positive for DEA 4 are considered to be universal donors.
H. Other RBC antigens may be present. The newly described Dal RBC antigen is capable of producing a hemolytic transfusion reaction in sensitized dogs (Blais et al., 2005).

III. The major blood group system recognized in cats is the AB system; cats can have blood types A, B, or AB.
A. Types A and B are allelic at the same gene locus, and the A allele (A) is dominant over the B allele (a).
B. The rare blood type AB is thought to be the result of a third allele; however, the exact mode of inheritance is unclear (Griot-Wenk et al., 1996).
C. The frequencies of feline blood types vary geographically and within breeds.
1. Type A is most common, with more than 95% of domestic shorthair (DSH) and domestic longhair (DLH) cats being typed as blood type A (Giger et al., 1989).
2. Type B is seen in a variety of cat breeds (Table 71-2) and is seen with higher frequency in DSH and DLH cats on the west coast of the United States (Giger et al., 1991).
D. Cats with type B erythrocytes have strong, naturally occurring anti-A hemagglutinins and hemolysins, consisting primarily of immunoglobulin (Ig) M and a lesser amount of IgG (Bucheler and Giger, 1993). Transfusion of type A blood into a type B recipient will result in an acute hemolytic transfusion reaction following the first transfusion.
E. Cats with type A erythrocytes have a low titer of naturally occurring anti-B alloantibodies, consisting of IgM hemagglutinins and IgG and IgM hemolysins (Wilkerson et al., 1991).
1. A transfusion of type B RBCs into a type A cat may induce only a minor transfusion reaction in the presence of alloantibodies.
2. However, rapid destruction of the donor RBCs will render the transfusion ineffective.
F. Type AB cats have neither anti-A nor anti-B alloantibodies.
G. Feline blood type A donors are essential, and ideally blood type B cats are also available.
H. Neonatal isoerythrolysis (hemolytic disease of the newborn) may be seen in kittens with type A blood born to type B queens (Bucheler and Giger, 1993).
I. An additional blood group antigen, the Mik RBC antigen, recently has been described . Cats that lack this antigen can form naturally occurring alloantibodies and may experience a hemolytic transfusion reaction if transfused with the Mik antigen (Weinstein et al., 2005).

TABLE 71-2

Rights were not granted to include this table in electronic media.
Please refer to the printed publication.

From Giger U, Griot-Wenk M, Bucheler J et al: Geographical variation of the feline blood type frequencies in the United States. Fel Pract 19:21, 1991.

DSH, Domestic shorthair cat; *DLH,* domestic longhair cat.

TECHNICAL PREPARATIONS

Blood Typing and Crossmatching

I. Blood typing refers to identifying RBC blood group antigens by reacting RBCs with antibodies or other reagents in an agglutination or hemolytic assay.
II. Crossmatching refers to detecting the presence of anti-erythrocyte antibodies occurring between the donor and the recipient.
III. The rationale for blood typing and crossmatching is as follows:
A. Avoid an immediate hemolytic transfusion reaction.
B. Provide maximum survival of transfused cells by avoiding a delayed hemolytic transfusion reaction.
C. Prevent sensitization of the recipient to future incompatible transfusions.
D. Avoid sensitization of breeding females and subsequent hemolytic disease of neonates.
IV. Blood typing is performed in both dogs and cats.
A. Dogs
1. Canine donors are ideally DEA 1.1 and 1.2 negative.
2. If donors are typed as DEA 1.1 positive, blood is transfused only into recipients typed DEA 1.1 positive.
3. Antisera for typing is available from Midwest Animal Blood Services (517-851-8244; Stockbridge, Mich.), but the techniques involved require laboratory skills and experience.
4. Blood typing is also performed by some commercial veterinary laboratories or veterinary blood banks (send 2 to 7 mL of ethylenediamine tetraacetic acid [EDTA] or acid-citrate-dextrose [ACD] anticoagulated blood via overnight mail).
5. Cards for the typing of DEA 1.1 are available from DMS Laboratories, Inc., 2 Darts Mill Road, Flemington, NJ 08822, (800-567-4367).

6. Gel testing for DEA 1.1 (Giger et al., 2005) is available from Diamed North America, Inc. (305-558-0161; Miami, Fla.).

B. Cats
1. Blood type A and B donors are needed, but the majority of feline recipients are blood type A.
2. Blood typing can be performed by some commercial veterinary laboratories or veterinary blood banks (send 2 to 3 mL of EDTA or ACD anticoagulated blood via overnight mail).
3. Cards for the typing of A and B are available from DMS Laboratories, Inc. .
4. Gel testing for A and B typing (Stieger et al., 2005) is available from Diamed North America, Inc.

V. Crossmatching is very important.
A. Crossmatching in dogs is advised, even at first transfusion, to detect the presence of antibodies to blood groups.
B. Crossmatching is imperative in dogs that have been transfused previously.
C. Crossmatching in dogs does not indicate that the donor and recipient are the same blood type, and thus does not prevent sensitization.
D. Crossmatching does not guarantee that a transfusion reaction from white blood cell, protein, or platelet incompatibility will not occur.
E. Crossmatching is crucial in cats because of the high prevalence of naturally occurring alloantibodies.
F. Crossmatching is divided into two parts (Box 71-1).
1. In the major crossmatch, the recipient's plasma is mixed with the donor's RBCs.
2. In the minor crossmatch, the donor's plasma is mixed with the recipient's RBCs.
G. A major crossmatch kit that uses gel tubes to detect a positive/incompatible response is commercially available (Midwest Animal Blood Services, Inc.).
H. The major crossmatch is the most important for a safe transfusion.
1. The minor crossmatch is of less clinical significance because donor antibodies administered intravenously are rapidly diluted within the recipient.
2. Nonetheless, blood resulting in an incompatible minor crossmatch is best avoided for transfusion.

Box 71-1

Crossmatching Procedure

1. Obtain an anticoagulated (EDTA) and nonanticoagulated specimen of blood from animal and donor.
2. Centrifuge at 1000 × *g* (2500 to 3500 rpm) for 10 minutes and separate serum from RBCs.
3. Wash RBCs by adding 2 to 4 drops of EDTA blood to three quarters of a tube (12 × 75-mm size) of saline or phosphate-buffered saline, mixing and centrifuging for 1 minute at 1000 × *g*. Decant the saline and repeat three times.
4. After last wash, decant supernatant and resuspend cells with saline to give a 2% to 4% suspension (0.1 mL of RBCs in 2.4 mL saline gives a 4% suspension).
5. Make the following mixtures by adding the indicated amount of the well-mixed RBC suspension and serum to 12 × 75-mm tubes and mixing gently:
   a. *Major crossmatch:* 2 drops patient sera, 1 drop donor 2% to 4% RBC suspension
   b. *Minor crossmatch:* 2 drops donor sera, 1 drop patient 2% to 4% RBC suspension
   c. *Include controls:* 2 drops patient sera, 1 drop patient 2% to 4% RBC suspension and 2 drops donor sera, 1 drop donor 2% to 4% RBC suspension
6. Incubate tubes 15 to 30 minutes at 37° C.
7. Centrifuge for 15 seconds (1000 × *g*).
8. Examine tubes for hemolysis and agglutination.
   a. Rotate gently to observe cells coming off the red cell "button" in the bottom of the tube.
   b. In a compatible reaction, there is no hemolysis and the cells should float off freely, with no macroscopic or microscopic clumping/hemagglutination (compare to the control tubes).
9. Rouleaux formation can be falsely interpreted as agglutination. If rouleaux is suspected, a saline replacement technique can be used (replace serum with saline, mix, recentrifuge, and re-evaluate).

Blood Sources

I. Commercial sources
A. Several commercial veterinary blood banks exist in the United States.
B. These blood banks can supply canine and/or feline whole blood, plasma, and packed RBCs.

II. Blood donors
A. Inpatient donors are those that are kept on the premises, usually for emergency situations.
B. Outpatient donors, also known as *volunteer donors,* are generally client-owned animals brought in for emergency or regularly scheduled blood donations.
C. Selection and maintenance of canine donors is as follows:
1. Use large dogs (>30 kg), 1 to 7 years old, with a packed cell volume (PCV) >40% and in good physical condition.
2. Use DEA 1.1- and 1.2-negative donors if possible.
   a. DEA 1.1 negative status is a must unless recipients are type matched.
   b. Avoid donors with a history of previous transfusions or pregnancy, as they may have developed antierythrocyte antibodies.
3. Dogs should have normal von Willebrand factor (vWf) concentrations (if their plasma is to be used to provide this factor) and be negative for *Babesia canis*, *Babesia gibsoni, Leishmania donovani, Ehrlichia canis*, and *Brucella canis*.
4. Screening for other infectious organisms may be necessary, depending on the geographic region (Wardrop, 2005).

5. Keep canine donors current on routine immunizations (distemper, adenovirus, parvovirus, coronavirus, rabies, leptospirosis, parainfluenza).
6. Donor dogs should test negative for *Dirofilaria immitis,* and dogs in endemic areas should be on preventative therapy.
7. Fecal flotation, hemograms, and chemistry profiles should also be performed to ensure the health of the donor.
8. Iron supplementation is advisable with frequent donation.

D. Selection and maintenance of feline donors is as follows:
1. Use feline donors in good physical condition, >3.5 kg, 1 to 7 years old, and having a PCV >35%.
2. Blood type A donors are essential, and ideally blood type B cats are also available for use.
3. Cats must be negative for feline leukemia virus (FeLV), feline immunodeficiency virus, and *Mycoplasma* spp.
4. Screening for *Bartonella* spp. should also be considered (Wardrop, 2005).
5. Keep feline donors current on routine immunizations (feline parvovirus, viral rhinotracheitis, calicivirus, rabies, FeLV).
6. Annual fecal flotation, hemograms, and chemistry profiles are performed.
7. Consider iron supplementation with frequent donation.

Blood Collection and Storage

I. Canine blood collection
A. Jugular venipuncture is performed with the dog sitting, or in lateral or sternal recumbency.
B. Blood is collected by gravity or with the aid of a vacuum system into anticoagulant, such as ACD, citrate-phosphate-dextrose (CPD) or derivatives.
C. For whole blood, a single ACD, CPD or citrate-phosphate-dextrose-adenine (CPDA-1) plastic bag is used.
D. For components, a CPD or CPDA-1 bag is used with sterilely attached satellite bags or an additive solution (e.g., *Adsol, Optisol*) system.
E. If sedation is required, butorphanol (0.1 mg/kg IV) may be administered 15 minutes before collection (Hohenhaus, 2000).

II. Feline blood collection
A. Blood collection in cats generally requires sedation, and a combination of ketamine (1 to 2 mg/kg), diazepam (0.1 mg/kg) and atropine (0.01 mg/kg) can be administered IV (Griot-Wenk and Giger, 1995).
B. Inhalant anesthesia with sevoflurane has also been described (Troyer et al., 2005).
C. With the cat in sternal, lateral, or dorsal recumbency, blood is collected from the jugular vein into a syringe containing ACD, CPD, or CPDA-1 solutions (1 mL/9 mL blood), or heparin (5 units/mL blood).
D. Feline blood cannot be stored in a syringe.
1. If blood is to be stored, blood obtained via syringe can be sterilely transferred to a small collection bag.
2. Systems consisting of a syringe attached directly to a blood bag are available from commercial veterinary blood banks.

III. Frequency and volume of donation for canine and feline donors
A. Amount drawn from dogs
1. A total of 15 mL/kg or 450 mL can be safely taken from a 30-kg dog, with ideal frequency no more than every 6 weeks.
2. Reduce the frequency of donation if the PCV or total protein fails to return to baseline values.
B. Amounts drawn from cats
1. A total of 10 to 15 mL/kg or 60 mL total can be taken every 6 weeks in cats.
2. Reduce the frequency of donation if the PCV or total protein fails to return to baseline values.

THERAPEUTIC CONSIDERATIONS

Component Therapy

I. Whole blood is often centrifuged and processed into blood components, such as packed RBCs, plasma, platelets, and cryoprecipitate, by using multiple, sterilely connected plastic bags.

II. Advantages to blood component therapy include better conservation of blood resources, longer storage of components, more specific therapy, and fewer complications from circulatory overload because of the minimal volume administered.

III. Component types and indications are as follows:
A. RBCs
1. Fresh whole blood provides coagulation factors, other proteins (albumin and globulins), RBCs, and platelets.
a. It is used where multiple components are needed.
b. Stored whole blood does not provide viable platelets or sufficient labile coagulation factors.
2. Packed RBCs are the best product for most RBC needs and can be supplemented with plasma or platelets if needed.
3. The shelf life or expiration date of RBCs may vary with the anticoagulant-preservative used.
4. Whole blood can generally be stored for 3 to 4 weeks at 1° to 6° C, whereas packed RBCs in additive can be stored for 5 weeks (Wardrop, 1995).
B. Plasma
1. Fresh frozen plasma (FFP) is plasma that has been frozen within 6 hours of collection and stored at −18° C or colder.
a. It contains labile (V and VIII) and stable (II, VII, IX, and X) coagulation proteins.
b. It is used to treat hemophilia A, hemophilia B, von Willebrand disease, warfarin toxicity, or other factor deficiencies.

c. It can be stored for 1 year from the collection date (Brooks, 2000).

2. Cryoprecipitate-poor plasma is plasma with cryoprecipitate removed.
   a. This plasma contains the more stable clotting factors and can be used in cases of warfarin toxicity or hemophilia B.
   b. Cryoprecipitate-poor plasma and frozen plasma can be stored for up to 5 years.
3. Frozen plasma is plasma that has been frozen >6 hours after blood collection (e.g., removed from expired whole blood units), or FFP that has been stored >1 year.
4. Either FFP, cryoprecipitate-poor plasma, or frozen plasma may be used in cases of hypoproteinemia; however, synthetic colloids such as hetastarch are probably more effective in severe hypoproteinemias resulting from renal or intestinal protein loss.

C. Platelets
1. Platelet-rich plasma or platelet concentrates may be used to stop or prevent hemorrhage in animals with thrombocytopenia or platelet function disorders.
2. Fresh whole blood may be substituted as a source of platelets when components are unavailable.
3. Platelet products must be stored at room temperature (no refrigeration) and their storage time is short—3 to 5 days with continuous agitation.

D. Cryoprecipitate
1. Prepared from FFP as a concentrated form of factor VIII:C, vWf, and fibrinogen
2. Preferred component for treatment or prevention of hemorrhage resulting from hemophilia A or von Willebrand disease
3. Stored at −18° C or colder for up to 1 year from collection date

Administration

I. General guidelines
A. Use blood or component administration sets with filters (150 to 170 μm) to administer all blood or blood products.
B. Only normal saline (0.9%) may be mixed with blood components.
C. Monitor temperature, pulse and heart rate, and respiratory rate and sounds before, during, and after transfusion.
D. Volume overload can occur if too much of a blood product is given or if the product is given too quickly, especially if the animal has cardiac or renal disease.
E. Complete the transfusion within 4 hours.
F. Use the intravenous route; the osseous intramedullary route may be used if necessary.

II. Rate and volume
A. The desirable rate of infusion varies with the patient's blood volume, hemodynamic condition, and cardiac, renal and hepatic status of the animal.
1. Give slowly (<5 mL/kg/hr IV) for the first 15 minutes, then increase rate.
2. Give more rapidly in hypovolemic animals.
3. Give more slowly in animals with cardiac, hepatic, or renal failure (approximately 1 mL/kg/hr IV).

B. Volume of whole blood or packed RBC to administer is calculated as follows:
1. Determine the PCV of the animal.
2. Volume (mL) of donor blood in anticoagulant to administer is calculated as follows:

$$\text{Animal weight (kg)} \times \text{blood volume} \times \frac{\text{(desired PCV} - \text{present PCV)}}{\text{PCV of donor blood in anticoagulant}}$$

NOTE: The blood volume in the dog is approximately 90 mL/kg; the volume in the cat is approximately 70 mL/kg.

3. Transfusion of 20 mL/kg of whole blood or 10 to 15 mL/kg of packed RBC raises the PCV of the recipient by 10%.

C. FFP, frozen plasma or cryoprecipitate-poor plasma are given as follows:
1. To thaw, place in a waterproof plastic bag and thaw at 37° C.
2. Thawing at room temperature or in a refrigerator is avoided because cryoprecipitate will form.
3. Administer immediately on thawing, or store between 1° and 6° C.
4. Administer FFP within 24 hours of thawing if used as a source of labile coagulation factors.
5. Give at the rate of 5 to 10 mL/kg/hr IV.
6. Use 10 to 20 mL/kg of plasma to treat coagulation deficiencies or hypoalbuminemia (NOTE: Synthetic colloids may be preferred for increasing oncotic pressure in hypoalbuminemic cases).

D. Administer platelet-rich plasma or platelet concentrate as follows:
1. Give at 5 to 10 mL/kg/hr IV.
2. Dosage is 1 unit (from 450 mL of blood)/10 kg to increase the platelet count by 20,000 to 40,000/μL.
3. Frozen canine platelets are available commercially.
   a. One unit of frozen platelets/10 kg increases the platelet count by approximately 20,000 platelets/μL.
   b. The product expires 6 months from the time of collection.

E. Cryoprecipitate requires special handling.
1. Thaw in a waterproof plastic bag at 37° C; do not thaw in a refrigerator or at room temperature.
2. A bag of cryoprecipitate prepared from 200 mL of plasma contains approximately 100 to 150 units of vWf and factor VIII:C.
3. The product is administered at a dosage of 10 to 20 U/kg IV.

Transfusion Reactions

I. Immediate, immune-mediated reactions
A. Hemolytic transfusion reaction
1. Caused by antibodies in recipient plasma that destroy donor RBCs

2. Can occur as early as 5 minutes after initiating transfusion
3. Clinical signs: fever, tachycardia or bradycardia, hypotension, dyspnea, cyanosis, emesis, defecation, collapse, opisthotonus, cardiac arrest, hemoglobinemia, or hemoglobinuria (Giger and Akol, 1990; Giger et al., 1995)
4. Treatment
   a. Stop the transfusion and treat for shock, with maintenance of cardiac, respiratory, and renal function.
   b. Avoid this reaction through appropriate typing and crossmatching before transfusion.

B. Nonhemolytic febrile reaction
1. Characterized by temperature rise of 1° C (2° F) occurring within 1 to 2 hours of transfusion without hemolysis or another explanation.
2. The reaction arises from recipient antibodies directed against donor leukocyte antigens.
3. Rule out early hemolytic or septic reaction.
4. Stop transfusion; use antipyretics if necessary.

C. Urticarial reaction
1. Recipient antibodies directed against donor plasma proteins
2. A relatively common but mild complication of transfusions
3. Treatment: stop or slow transfusion, diphenhydramine 2 mg/kg IM

II. Immediate, nonimmune-mediated reactions

A. Sepsis
1. Usually not a problem if care has been taken to properly prepare donor phlebotomy site, a closed system is used, and the blood product is appropriately stored
2. Reactions generally from endotoxins
3. Signs of endotoxic shock: fever, hypotension, disseminated intravascular coagulation, renal failure
4. Treatment: for shock, antibiotics
5. Culturing of blood bag indicated

B. Circulatory overload
1. Seen more commonly with compromised cardiac, pulmonary or renal function, especially in cats and miniature or toy breeds of dogs
2. Signs: coughing, cyanosis, and dyspnea (pulmonary edema)
3. Treatment: stop transfusion, institute diuretics and cardiorespiratory support

C. Citrate toxicity
1. Hypocalcemia from rapid infusion of citrated products (whole blood, plasma)
2. Signs: vomiting, tremors, tetany
3. Treatment: stop transfusion, resume at slower rate, and administer calcium gluconate if reaction severe

D. Hemolysis
1. From improper blood handling (e.g., freezing or overheating of blood or mixing with nonisotonic solutions)
2. Causes hemoglobinemia/hemoglobinuria and must be differentiated from an immune-mediated hemolytic transfusion reaction

III. Delayed reactions

A. Immune-mediated: delayed hemolytic transfusion reaction
1. Within 3 days (anamnestic response) or several weeks (primary response) after transfusion
2. Not detected by crossmatching
   a. An unexplained decline in PCV and positive direct antiglobulin test
   b. Possibly asymptomatic or presence of fever and icterus
   c. Treatment: not generally required

B. Nonimmune-mediated
1. Reactions arise from infectious diseases.
2. All donors must be carefully selected and screened to avoid transmittance of disease.

Red Blood Cell Substitute

I. A hemoglobin-based oxygen-carrying solution (Oxyglobin, Biopure Corp., Cambridge, Mass.) has been approved by the Food and Drug Administration (FDA) for use in dogs with anemia (Rentko and Sharpe, 2000).

II. Oxyglobin is purified bovine hemoglobin in a modified lactated Ringer's solution.
   A. It is isosmotic, with a pH of 7.8, and half-life of 18 to 43 hours, depending on dosage.
   B. The product comes in 125 mL bags and can be stored for 3 years at room temperature.

III. The recommended dosage in dogs is 10 to 30 mL/kg IV at a maximal rate of 10 mL/kg/hr.

IV. A standard IV infusion set can be used, and crossmatching is not required.

V. Overdose or rapid administration can cause circulatory overload.
   A. Monitor using hemoglobin, not PCV.
   B. It is contraindicated in dogs with advanced cardiac disease or with acute renal failure, because of the potential for circulatory overload.

VI. Side effects include skin and mucous membrane discoloration, vomiting and diarrhea, alterations in serum chemistries from discoloration of serum, and transient hemoglobinuria.

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CHAPTER 72

Principles of Oncology

Philip J. Bergman

GENERAL CONSIDERATIONS

Definition

I. Many resources attempt to define *tumor* (neoplasm); the simplest definition is that a tumor is an abnormal group of cells.
II. Older definitions commonly stated that tumors arose from uncontrolled cell division, but it is now known that they occur from increased cell division and/or decreased cell death.
III. Neoplasms can be categorized into benign and malignant forms.
  A. Benign neoplasms
    1. Benign tumors do not typically invade adjacent normal tissues, though exceptions exist.
    2. They do not have the capability to spread (metastasize).
    3. For most benign tumors, the tumor name ends in "oma," without "carc" or "sarc" as a prefix.
    4. Some exceptions exist (e.g., lymphoma, glioblastoma).
  B. Malignant neoplasms
    1. Cells may invade adjacent tissues.
    2. The ability to invade adjacent tissues provides potential for secondary tumors to form at distant sites (metastasize).
    3. Metastasis may occur through the bloodstream and/or through the lymphatics.
    4. The term *cancer* refers to a malignant tumor.
IV. Tumors are further classified according to their tissue of origin.
  A. Epithelial
    1. Adenomas are benign tumors of epithelial origin.
    2. Carcinomas are malignant tumors of epithelial origin.
    3. Adenocarcinomas are malignant tumors of epithelial glandular origin.
  B. Mesenchymal
    1. They are composed of connective tissue, such as bone, muscle, or vessels (blood, lymphatics).
    2. Leiomyomas are benign tumors of smooth muscle origin.
    3. Chondromas are benign tumors of cartilage origin.
    4. Sarcomas are malignant tumors of mesenchymal origin.
    5. Osteosarcomas are malignant tumors of bony origin.
    6. Leiomyosarcomas are malignant tumors of smooth muscle origin.
  C. Discrete cell tumors
    1. These tumors have a variety of origins and malignant potentials, but cytologically they look like separate cells that do not cluster together.
    2. They were previously called *round cell tumors.*
    3. They include lymphoma, mast cell tumor, transmissible venereal tumor (TVT), plasma cell tumor, and histiocytoma.

Differential Diagnosis

I. The list is extremely lengthy and includes autoimmune disorders, trauma, and infectious diseases.
II. Differential diagnosis for a given tumor is dependent on size, invasiveness, anatomical location, presence or absence of paraneoplastic syndromes (see Chapter 73), and the presence or absence of metastasis.
III. Tumors may generate secondary conditions that may mask the primary disorder (e.g., clotting abnormalities, renal failure, autoimmune hemolytic anemia).

Staging

I. The stage of the tumor is determined by a systematic evaluation of the extent of disease.
II. Staging is imperative for most tumors.
  A. This process allows for the most precise delineation of the prognosis.
  B. Correct staging also helps determine the most appropriate treatment.
III. The tumor-node-metastasis (TNM) scheme from the World Health Organization is the most commonly used staging system.
  A. T0 denotes no evidence of primary tumor, and T1 through T4 indicate increasing size of the primary tumor.
  B. N0 denotes no evidence of lymph node metastasis, and N1 through N3 indicate increasing size, firmness, or decreasing movability of the lymph node.
  C. M0 denotes no evidence of distant metastatic disease and M1 indicates distant metastasis.
  D. The designation *X* generally means it is impossible to assess the extent of disease in a particular area, which is not the same as finding no lesion in the area.

E. Some systems further define whether the outcomes were determined through pathologic or clinical means (e.g., pT2, cN0, cM0).

IV. Staging systems vary depending on the tumor but follow a general pattern of more extensive disease correlating with increased stage and decreased prognosis.

V. Subclassifications within a stage (e.g., a, b, c) are used to signify differences within that stage (e.g., IIa = no clinical signs, IIb = with clinical signs).

VI. *Stage 0* generally denotes intraepithelial (newer term for in situ) disease.
   A. This was previously called *tumor in situ* (Tis).
   B. This term is only appropriate for carcinomas as it refers to no invasion through the basement membrane, and nonepithelial tumors (sarcomas) do not have this characteristic.

VII. Additional descriptors used in conjunction with the TNM system include the following:
   A. R classification = presence of residual tumor after treatment
   B. G classification = inclusion of histological grading
   C. C factor = certainty of diagnosis
   D. L = lymphatic invasion
   E. V = vascular invasion

GENERAL THERAPEUTIC CONSIDERATIONS

I. It is imperative to determine a histopathologic diagnosis and stage (extent of disease) to be able to appropriately select a treatment course.

II. An understanding of the biological behavior of the tumor is also critical.
   A. The biological behavior of a tumor is related to two primary features.
      1. Local invasiveness
      2. Metastatic propensity
   B. Tumors are generally treated with one or more of three modalities, namely surgery, radiation, or chemotherapy (immunotherapy may become a fourth routine modality in the future).
      1. Locally invasive tumors are treated with local modalities (e.g., surgery, radiation).
      2. Tumors with a high propensity for metastasis are treated with systemic therapies (e.g., chemotherapy).
      3. Tumors that are locally invasive and have a high metastatic propensity are treated with surgery, radiation or both, in addition to chemotherapy.
   C. The goal of treatment (palliative versus curative intent) must be decided.
      1. Curative intent is ideal but may not be realistic in some cases (e.g., metastatic hemangiosarcoma).
      2. The most aggressive modalities with proven benefit are used first when there is curative intent.
      3. The initial use of less aggressive options, followed by more aggressive therapies, generally leads to treatment failure.
      4. The primary goal of palliation is an improved quality of life.

III. The animal must be evaluated for any concurrent medical problems that may impact the prognosis or treatment options.

IV. Tumors are evaluated before starting treatment and then serially at each recheck (in addition to a full physical examination).
   A. Single tumors are measured in three dimensions (with calipers when possible), and the results recorded.
   B. When multiple tumors are present, a minimum of two to three are measured in three dimensions; the remaining tumors are mapped and the single largest dimension is recorded.

V. Terms for response to treatment include the following:
   A. Complete remission (CR): complete disappearance of all clinically detectable tumor
   B. Partial response (PR): >50% decrease in tumor volume; no new tumors
   C. Stable disease (SD): <50% decrease or <10% increase in tumor volume
   D. Progressive disease (PD): >10% increase in tumor volume or appearance of new tumors
   E. Variations
      1. Percentages used for PR, SD, PD can vary across studies, but the above percentages are good starting guidelines.
      2. Volume (triaxial measurements) may not always be used.
         a. Single largest measurement systems or response evaluation criteria in solid tumors (RECIST) exist.
         b. Area-based systems (two largest measurements used) are commonly used when a third measurement is not possible.
      3. Lymphoma: CR, out of remission (OR)

VI. Combinations of modalities are commonly utilized for a wide variety of cancers, because therapies have differing mechanisms of action that increase efficacy without increasing toxicity.

SPECIFIC THERAPIES

Surgery

Definition

I. Surgery is the ideal treatment for localized tumors.

II. When indicated, surgery is the treatment modality that is most likely to provide a cure.

Applications and Goals

I. Cure
   A. A cure is possible with localized tumors with low metastatic propensity in an animal without distant disease on staging.
   B. Benign tumors and well-localized nonmetastatic malignancies are often cured with appropriate surgical

extirpation (e.g., benign and low-grade canine mammary gland tumors).

II. Debulking or cytoreductive surgery is commonly used to reduce a tumor to microscopic disease so it is more susceptible to other treatment modalities (e.g., soft-tissue sarcomas debulked followed by radiation therapy).

III. Animals with highly metastatic but slow-growing tumors may benefit from local control surgery (e.g., anal sac apocrine adenocarcinoma).

IV. Metastasectomy is rarely used.
   A. It may be useful in dogs with metastatic osteosarcoma, under stringent criteria.
   B. The procedure may be useful where lymph node metastasis does not automatically signal widespread metastasis (e.g., mast cell tumor with metastasis only to a lymph node).
   C. It may be useful when the metastatic lesion is significantly reducing quality of life, or is the cause of a paraneoplastic syndrome (e.g., hypertrophic osteopathy).

Principles

I. Knowing the tumor type via cytological examination and/or incisional biopsy is imperative.

II. The aggressiveness of surgery is extremely variable and dependent on the tumor type and its expected degree of invasiveness locally.

III. A minimum preoperative work-up includes complete staging, with a complete blood count (CBC), biochemistry profile, urinalysis, and three radiographic views of the thorax.

IV. The best chance for cure is obtained at the first surgery.
   A. Wide excision typically includes 2- to 3-cm lateral margins and one fascial plane deep.
      1. The definition of wide excision varies among tumor types, which reinforces the need to know the tumor type before surgery.
      2. Wide excision of a mammary tumor is typically 1 to 2 cm around it, and one fascial plane deep.
      3. Wide excision of a feline vaccine-associated sarcoma is typically 3 to 5 cm margins in all planes.
      4. Wide excision for a sebaceous adenoma is typically 0.5 to 1.0 cm.
   B. Previous needle aspiration or biopsy tracts are included in the resection to remove tumor cells that may have seeded these areas.
   C. Early vascular ligation may be important to reduce the chance of tumor embolization, especially from malignancies in retained testicles, the spleen, and the lungs.
   D. Avoid incising the tumor during removal.
   E. Handle tumors gently to reduce the risk of cells exfoliating into the operative field.
   F. Tumors commonly have a pseudocapsule that is composed of compressed tumor cells, so shelling out a tumor may lead to recurrence from incomplete margins.
   G. Hemostatic surgical clips (hemoclips) are useful to delineate the extent of surgery, especially if radiation therapy is planned in the future.
   H. Lasers may provide an easier and less bloody removal of a tumor, but coagulative necrosis induced at the edge of the resection can complicate histopathologic evaluation of margins, so their routine use is not recommended.

V. After the tumor has been removed, use clean instruments for closure to reduce the chances of tumor seeding of the surgical site, and when more than one mass is being removed, use different surgical packs.

VI. Every mass removed is submitted for histopathologic evaluation.
   A. Submit the entire mass, if possible.
   B. Partial submissions do not allow delineation of margins, which may require additional local therapy in the future (whether it is truly needed or not).
   C. Inking of surgical margins with yellow or black ink is commonly used to help delineate completeness of resection (www.bradleyproducts.com).
   D. Sutures, hemoclips, or both may also be used to mark edges and aid in orientation of the tissues (dorsal, lateral, ventral, medial).

VII. Fixation is important.
   A. A 10:1 ratio of formalin to tissue is needed to properly fix the tumor.
   B. Tumors >3 to 4 cm may be partially incised to allow increased penetration of the fixative.
   C. If the volume of formalin and tissue is so large as to prevent transport to the laboratory, the tissues can be fixed for 24 hours, removed from the formalin, and wrapped in formalin-soaked paper towels for submission.

Cryotherapy

Definition

I. The induction of a controlled rapid freeze and slow thaw of tissues via liquid nitrogen or nitrous oxide

II. Cell death mechanisms
   A. Direct cell death is from ice crystal formation and secondary damage of cell membranes.
   B. Indirect cell death arises from vascular damage to blood vessels.

Applications and Goals

I. Indications are primarily for small, benign tumors (recurrence rates increase with lesions >0.5 cm).

II. It is not often used because of the need for histopathologic evaluation of the extirpated tissue.

III. It is used for susceptible tumors (e.g., discreet cell tumors, melanomas) in areas where excision is difficult or disfiguring (e.g., periocular, oral, on the digits).

IV. Advantages are as follows:
   A. Short procedure
   B. Easy to perform
   C. Anesthesia not always necessary
   D. Possible multiple treatments over time

V. Disadvantages include the following:
   A. Expense of equipment

B. Need for postoperative cleaning or debridement of necrotic tissue
C. No ability for histopathologic determination of status of margins

Radiation Therapy

Definition

I. Radiation therapy (RT) uses high energy, penetrating waves or particles (x-rays, gamma rays, proton or neutron rays) to destroy cancer cells or sterilize them.
II. Radiation therapy is sometimes called *radiotherapy, x-ray therapy, cobalt therapy, electron beam therapy,* or *irradiation.*
III. The goal of RT is to kill or at least damage cancer cells.
  A. RT itself is painless.
  B. Radiation only acts on the area of the body exposed to it.
IV. High-energy radiation kills cells by damaging DNA.
  A. This damage blocks the ability of tumor cells to divide and inhibits tumor growth.
  B. Cancer cells generally grow and divide quickly, which makes them particularly vulnerable to radiation.
  C. Radiation also damages normal cells, but they are usually growing more slowly and are better able to repair radiation damage.

Types

I. Teletherapy
  A. Delivery of a beam of RT from outside the body
  B. Megavoltage radiation: ≥1 million electron volts (MeV)
    1. Cobalt-60 source machine or linear accelerator is the most common.
    2. Cobalt-60 machines are relatively inexpensive but require source changes intermittently because cobalt-60 has a 5-year half-life.
    3. Linear accelerators are relatively expensive but do not require source changes.
    4. Megavoltage radiation has good penetration of tissues.
    5. More even and predictable deposition in tissues allows for increased use of computer-based treatment planning.
    6. Some linear accelerators produce photons and electrons of varying energies, which allows greater treatment flexibility.
    7. The energy from cobalt-60 and linear accelerator-derived photons does not build to a therapeutic level until it has passed through 1 cm of tissue, so it is partially skin sparing.
    8. The use of tissue-equivalent material can increase energy deposition at the skin surface.
  C. Orthovoltage radiation
    1. Relatively low energy source of x-rays
      a. It is typically operated at 250 kV.
      b. Maximum dose is deposited at the skin surface.
      c. Acute skin effects are severe.
      d. Dose falls to 90% at approximately 2 cm depth.
      e. It is difficult to treat deep-seated tumors with this source.
    2. Differential absorption of dose in bone versus soft tissue
    3. Not commonly used in animals owing to its various limitations and rare indications
    4. Primarily for superficial tumors that do not involve adjacent bone
      a. Skin tumors
      b. Nasal cavity tumors after cytoreductive surgery
    5. Advantages
      a. Relatively inexpensive
      b. Equipment relatively easy to repair and maintain
      c. Less shielding and space required
II. Brachytherapy
  A. It is the implantation or application of a radioactive source to tissue.
  B. *Brachy* signifies the radiation source is close to the tumor.
  C. It is not routinely used in small animals.
  D. Iridium-192 is the most commonly used source.
  E. Use of iridium-192 requires quarantine of the animal.
III. Plesiotherapy
  A. It is the topical application of a radiation source.
  B. *Plesios* is Greek for *close* or *near*.
  C. Strontium-90 is the most common source.
    1. Beta-radiation is often applied via an ophthalmic applicator.
    2. Source is attached to a handle protected with Plexiglas.
    3. Dose falls off rapidly in tissues.
      a. Delivered to the surface: 100%
      b. Depth of 1 mm: 50%
      c. Depth of 2 mm: approximately 25%
    4. Potential indications include the following:
      a. Nasal planum squamous cell carcinoma in cats
      b. Squamous cell carcinoma in situ in cats
      c. Cutaneous mast cell tumors of cats
IV. Systemic therapy
  A. It is the systemic administration of a radioactive source.
  B. Iodine-131 is commonly used for feline hyperthyroidism.
  C. It routinely requires quarantine of the animal.

Applications

I. Useful in diseases that are not systemic or metastatic
II. ± Useful for palliation in the face of metastases
III. Most effective when used with other modalities
  A. Sequential combinations
    1. Postoperative RT may be used to eradicate residual tumor when complete surgical excision is not possible.
    2. When a tumor is not resectable, preoperative RT may be used to shrink it and make it more operable.
    3. RT followed by surgery and chemotherapy may be used for vaccine-associated sarcoma in cats and for other tumors.

B. Concurrent combinations
   1. Intraoperative RT delivers radiation to an open surgical tumor bed.
   2. Some chemotherapeutics can sensitize tumors cells to radiation therapy (chemoradiotherapy).

IV. The primary treatment modality for radiation-sensitive tumors and small superficial tumors
   A. Facial squamous cell carcinoma in cats
   B. Nasal lymphoma in cats
   C. Oral acanthomatous epulis, dental tumors
   D. Plasma cell tumors

V. Palliative intent RT
   A. It may not shrink the tumor or extend survival, but it may improve quality of life.
   B. Fractions (dose per treatment) are infrequent and typically larger than with curative intent (full course) RT.
      1. Minimizes numbers of treatments and visits
      2. Minimizes stress of animal and time commitment of owner
   C. Indications include relief of pain associated with bone tumors (osteosarcoma), rapid shrinkage of tumors (some lymphomas), and relief of dyspnea, pain, and dysphagia from oral tumors.

Chemotherapy

Definition

I. Chemotherapy is a systemic treatment and is the primary treatment for systemic malignancies (e.g., lymphomas, leukemias) and metastatic tumors.

II. It is most effective against small tumors and least effective against large tumors, unless they are extremely sensitive (e.g., lymphoma, TVT).
   A. Most effective against rapidly dividing cells
   B. Most effective against cells near a vascular supply
   C. Less effective against quiescent and hypoxic cells (e.g., large tumors)

III. Chemotherapy can be used in conjunction with other treatment modalities.

IV. The safety range for chemotherapeutic agents is narrow (i.e., therapeutic and toxic doses are similar).
   A. Dose response curves for most cytotoxic chemotherapy agents are sigmoidal and not linear.
      1. A 5% to 10% decrease in dose often translates into a ≥10% to 20% decrease in efficacy.
      2. A 5% increase in dose often leads to significant toxicity.
   B. It is imperative that doses be accurately calculated.
      1. Rounding down the dose to decrease toxicity leads to decreased efficacy and is not advisable.
      2. Many chemotherapeutic agents are dosed are based on body surface area (BSA), as shown in Tables 72-1 and 72-2.
      3. Because of the potential for mistakes, use BSA charts that provide doses in either kilograms or pounds of body weight (not both).

TABLE 72-1

Canine Body Surface Area Conversion Chart

BODY WEIGHT (kg)	SURFACE AREA (m^2)	BODY WEIGHT (kg)	SURFACE AREA (m^2)
0.5	0.064	25.0	0.864
1.0	0.101	26.0	0.886
2.0	0.160	27.0	0.909
3.0	0.210	28.0	0.931
4.0	0.255	29.0	0.953
5.0	0.295	30.0	0.975
6.0	0.333	31.0	0.997
7.0	0.370	32.0	1.018
8.0	0.404	33.0	1.029
9.0	0.437	34.0	1.060
10.0	0.469	35.0	1.081
11.0	0.500	36.0	1.101
12.0	0.529	37.0	1.121
13.0	0.553	38.0	1.142
14.0	0.581	39.0	1.162
15.0	0.608	40.0	1.181
16.0	0.641	41.0	1.201
17.0	0.668	42.0	1.220
18.0	0.694	43.0	1.240
19.0	0.719	44.0	1.259
20.0	0.744	45.0	1.278
21.0	0.769	46.0	1.297
22.0	0.785	47.0	1.302
23.0	0.817	48.0	1.334
24.0	0.840	49.0	1.352

V. Historically, emphasis was placed on a drug's effect within the cell cycle to delineate chemotherapy protocols; however, the use of standardized protocols and accurate dosages are likely more important in the clinical setting.

Types

I. There are six major categories of chemotherapeutic agents (Table 72-3).

II. Most cause bone marrow, alopecia, or gastrointestinal (BAG) side effects.
   A. Many agents cause bone marrow suppression; however, when used at normal doses, corticosteroids, vincristine, L-asparaginase, and bleomycin do not.
   B. Alopecia occurs primarily in breeds that continuously grow hair.
      1. Hair begins to regrow weeks to months after termination of chemotherapy and typically has a slightly different color.
      2. Shaved sites do not regrow while on chemotherapy.
      3. Cats typically do not experience chemotherapy-associated alopecia, but lose their whiskers instead.

TABLE 72-2

Feline Body Surface Area Conversion Chart

BODY WEIGHT (kg)	SURFACE AREA (m^2)	BODY WEIGHT (kg)	SURFACE AREA (m^2)
1.0	1.100	5.6	0.315
1.2	0.113	5.8	0.323
1.4	0.125	6.0	0.330
1.6	0.137	6.2	0.337
1.8	0.148	6.4	0.345
2.0	0.159	6.6	0.352
2.2	0.169	6.8	0.360
2.4	0.179	7.0	0.366
2.6	0.189	7.2	0.373
2.8	0.199	7.4	0.380
3.0	0.208	7.6	0.387
3.2	0.217	7.8	0.393
3.4	0.226	8.0	0.400
3.6	0.235	8.2	0.407
3.8	0.244	8.4	0.413
4.0	0.252	8.6	0.420
4.2	0.260	8.8	0.426
4.4	0.269	9.0	0.433
4.6	0.277	9.2	0.439
4.8	0.285	9.4	0.445
5.0	0.292	9.6	0.452
5.2	0.300	9.8	0.458
5.4	0.307	10.0	0.464

Biological Response Modifiers (Immunotherapy)

Definition

I. These are natural or synthetic compounds that alter the host's response to a tumor.
II. Relatively few biological response modifiers (BRM) are available for clinical use in animals.
III. The availability of animal-specific BRMs is eagerly anticipated and likely in the next 5 to 10 years.

Types

I. Nonspecific immunomodulators
  A. Cytokines and hematopoietic growth factors are glycoproteins that stimulate differentiation, growth, and effector functions of hematopoietic or bone marrow-derived cells.
    1. Interferons
      a. Produced in response to viral infections and various mitogens
      b. Cytostatic, cytotoxic, and immunomodulatory properties
      c. No experience with cancers of small animals to date
      d. May be useful for feline leukemia virus infections in cats
    2. Interleukins
      a. Pleiotropic cytokines that activate lymphocytes and natural killer cells
      b. Initially promising results in vitro against cancer but toxicities have prevented widespread use
    3. Granulocyte and granulocyte-monocyte colony-stimulating factors
      a. Stimulate proliferation and maturation of neutrophils and monocytes (macrophages in circulation) in the bone marrow
      b. Used for chemotherapy-associated neutropenia
  B. Bacterial agents
    1. Bacillus Calmette-Guérin (BCG)
      a. Attenuated mycobacterium with activity against some human and equine tumors
      b. No uses to date in small animals
    2. Liposome encapsulated muramyl tripeptide-phosphatidylethanolamine (L-MTP-PE)
      a. Mycobacterial cell-wall fragment with macrophage activation properties
      b. Useful in canine osteosarcoma and hemangiosarcoma, but not mammary carcinoma
      c. Not commercially available at present but expected soon (*Junovan;* IDM Pharma, Irvine, Calif.)
  C. Miscellaneous agents
    1. Imiquimod (*Aldara)*
      a. Topical cream that activates toll-like receptor 7
      b. Potent immunomodulator with antiviral and anticancer properties
      c. May be useful for feline Bowen's disease, although no published studies to date
    2. Isotretinoin (*Accutane)*
      a. Oral vitamin A derivative with differentiation properties
      b. Used in mycosis fungoides and other epitheliotropic T-cell lymphomas
    3. Piroxicam (*Feldene)*
      a. Potent nonsteroidal antiinflammatory drug (NSAID) with anticancer and antimetastatic properties
      b. Used with mitoxantrone in dogs for urinary bladder transitional carcinoma
      c. Possibly useful in dogs with osteosarcoma
      d. May be useful in squamous cell carcinoma and other tumors that overexpress cyclooxygenase-2
    4. Cimetidine
      a. Histamine-2 receptor antagonist
      b. May be of use in recalcitrant canine papillomatosis
      c. True efficacy unproven
II. Specific immunomodulators
  A. Tumor cells frequently produce unique, abnormal, and embryonic proteins that can be targeted by the immune system.

Text continued on p. 724.

TABLE 72-3

Chemotherapeutic Agents and Their Applications in Dogs and Cats

DRUG NAME *(BRAND NAME)*	DRUG CLASS	PRIMARY INDICATIONS	DOSAGE	TOXICITIES AND PRECAUTIONS	GENERICS AVAILABLE	RELATIVE COST
Actinomycin-D *(Cosmegen)*	Antitumor antibiotic	Alternative for canine lymphoma	0.5-0.9 mg/m^2 IV slowly every 3 weeks	Myelosuppression, vomiting, diarrhea, and extravasation reaction	No	++
L-Asparaginase *(Elspar)*	Enzyme	Lymphoma	10,000 IU/m^2 or 400 IU/kg IM, SC	Anaphylaxis (treat for shock and never give again) Rarely pancreatitis, and coagulopathy can decrease clearance	No	++
Carboplatin *(Paraplatin)*	Platinum	Canine osteosarcoma, carcinomatosis, sarcomatosis malignant effusions Mild efficacy in canine melanoma Safe in cats	*Large dogs:* 300 mg/m^2 IV every 3 weeks *Small dogs:* 250 mg/m^2 or 10 mg/kg IV every 3 weeks *Cats:* 180 mg/m^2 IV every 4 weeks	Myelosuppression, mild vomiting or diarrhea, and mild nephrotoxicity Do not use in animals with renal compromise	Yes	+++
Chlorambucil *(Leukeran)*	Alkylating agent	Chronic lymphocytic leukemia and feline small-cell gastrointestinal lymphoma Used as substitute when cyclophosphamide not tolerated	Dosage varies greatly between protocols Continuous: 4-6 mg/m^2 PO SID Intermittent: 15 mg/m^2 PO SID for 4 days every 3 weeks	Myelosuppression Perform serial CBCs and platelet counts every 4-6 weeks Reduce dose or discontinue if neutropenia or thrombocytopenia occur	Yes	+
Cisplatin *(Platinol)*	Platinum	Canine osteosarcoma, malignant effusions, and some carcinomas Contraindicated in cats	*Dogs only:* 50-70 mg/m^2 IV every 3 weeks Saline diuresis required Prevent vomiting with butorphanol, dexamethasone, ondansetron, or dolasetron	Contraindicated in cats Severe nephrotoxin Myelosuppression, vomiting, and diarrhea	Yes	+++
Cyclophosphamide *(Cytoxan)*	Alkylating agent	Lymphoma, lymphoid leukemias, some carcinomas and sarcomas	200-250 mg/m^2 IV every 3 weeks or 200 mg/m^2 PO divided over 3-5 days every 3 weeks	Myelosuppression, mild vomiting, diarrhea, and sterile hemorrhagic cystitis Reduce chance of cystitis with injectable furosemide or corticosteroids	Yes	++
Cytosine Arabinoside *(Cytosar)*	Antimetabolite	Rarely used Renal and central nervous system lymphoma	200-300 mg/m^2 SC BID for 2 days or 100 mg/m^2/day constant rate infusion IV over 3-4 days	Myelosuppression, mild vomiting, diarrhea, and anorexia	Yes	++

+, Low relative expense; ++, moderate relative expense; +++, high relative expense; *CBC*, complete blood cell count.

TABLE 72-3

Chemotherapeutic Agents and Their Applications in Dogs and Cats—*cont'd*

DRUG NAME *(BRAND NAME)*	DRUG CLASS	PRIMARY INDICATIONS	DOSAGE	TOXICITIES AND PRECAUTIONS	GENERICS AVAILABLE	RELATIVE COST
Dacarbazine *(DTIC)*	Alkylating agent	Rarely used Rescue protocols for lymphoma Possible mild efficacy in melanoma	*Dogs:* 200 mg/m^2 IV slowly SID for 5 days every 3 weeks	Myelosuppression, vomiting, diarrhea, and extravasation reaction Should not be used in cats	No	++
Doxorubicin *(Adriamycin)*	Antitumor antibiotic	Lymphoma, lymphoid leukemias, canine osteosarcoma, and various solid tumors	*Medium to large dogs:* 30 mg/m^2 IV over 20 minutes every 3 weeks *Small dogs, cats:* 1 mg/kg to 25 mg/m^2 IV every 3 weeks	Myelosuppression, vomiting, diarrhea, serious extravasation reaction Cumulative doses >180 mg/m^2 increase risk of dilated cardiomyopathy in dogs Colitis and cardiotoxicity in dogs Possible nephrotoxin or hepatotoxin in cats Allergic reactions possible if given too quickly	Yes	+
Gemcitabine *(Gemzar)*	Antimetabolite	Poor efficacy to date May have a role as radiosensitizer	Not well delineated Bolus dosing not recommended owing to mechanism of action	Relatively few when given by bolus May cause myelosuppression, vomiting, and diarrhea when given at lower doses over longer periods Local tissue reactions when used with radiation	No	+++
Hydroxyurea *(Hydrea)*	Antimetabolite	Polycythemia vera, chronic myelogenous leukemia Used rarely for other diseases	*Dogs:* 80 mg/kg PO every 3 days *Cats:* 25 mg/kg PO three times per week	Myelosuppression and anemia Monitor serial CBCs and platelet counts and reduce dosage if neutropenia, thrombocytopenia and anemia occur	Yes	+
Ifosfamide *(Ifex)*	Alkylating agent	Canine lymphoma rescue protocols Some efficacy in feline vaccine-associated sarcomas or other solid tumors	*Dogs:* 350 mg/m^2 IV every 2-3 weeks *Cats:* 900 mg/m^2 IV every 3 weeks	Myelosuppression Urotoxicity prevented with diuresis and mesna administration	No	++
Lomustine *(CCNU; CeeNu)*	Nitrosourea	Lymphoma rescue protocols Mast cell tumors and central nervous system tumors	*Medium to large dogs:* 70-80 mg/m^2 PO every 4-6 weeks *Small dogs, cats:* 50-60 mg/m^2 PO every 4-6 weeks	Myelosuppression, vomiting, and diarrhea Thrombocytopenia with cumulative doses Hepatotoxicity in dogs Pulmonary toxicity in cats	No	+
Melphalan *(Alkeran)*	Alkylating agent	Multiple myeloma	*Dogs:* 0.1 mg/kg PO SID for 10 days, then 0.05 mg/kg PO SID for maintenance	Myelosuppression Monitor serial CBCs and platelet counts every 4-6 weeks Reduce dosage or discontinue if neutropenia or thrombocytopenia occur	Yes	+

Continued

TABLE 72-3

Chemotherapeutic Agents and Their Applications in Dogs and Cats—*cont'd*

DRUG NAME *(BRAND NAME)*	DRUG CLASS	PRIMARY INDICATIONS	DOSAGE	TOXICITIES AND PRECAUTIONS	GENERICS AVAILABLE	RELATIVE COST
Methotrexate *(Trexall, Rheumatrex)*	Antimetabolite	Very few indications May or may not be useful in multiagent lymphoma protocols	*Dogs:* 0.6-0.8 mg/kg IV every 3 weeks or as protocol dictates *Cats:* 0.8 mg/kg IV every 4 weeks or as protocol dictates	Myelosuppression, vomiting, and diarrhea	Yes	++
Mitotane *(Lysodren)*	Unclassified	Adrenocortical tumors	Induction: 25 mg/kg PO BID Maintenance (once ACTH stimulation test results have normalized): 50 mg/kg PO per week divided into two or three doses	Iatrogenic hypoadrenocorticism: adjust dose and give corticosteroids as needed Vomiting, diarrhea, and neurological signs	Yes	+
Mitoxantrone *(Novantrone)*	Antitumor antibiotic	Canine transitional cell carcinoma, anal sac apocrine adenocarcinoma, carcinomatosis/ sarcomatosis, malignant effusions Mild activity in rescue protocols for lymphoma Some efficacy for various other solid tumors	*Dogs:* 5.5-6.0 mg/m^2 IV every 3 weeks *Cats:* 5.0-6.5 mg/m^2 IV every 3 weeks	Myelosuppression, vomiting, diarrhea Possible mild cardiotoxin in dog Mild to moderate irritant with extravasation	No	+++
Mechlorethamine *(Mustargen)*	Alkylating agent	Rescue protocols for lymphoma and other lymphoid leukemias	*Dogs, cats:* 3.0 mg/m^2 IV on weeks 1 and 2 or 3 of the 4-week MOPP protocol	Myelosuppression, vomiting, diarrhea Serious extravasation reaction	Yes	++
Piroxicam *(Feldene)*	Nonsteroidal antiinflam-matory drug	Canine transitional cell carcinoma and osteosarcoma May have activity against squamous cell carcinoma and other tumors Good palliative agent	*Dogs:* 0.3 mg/kg PO SID *Cats:* 0.3 mg/kg PO SID-QOD	May cause nausea, vomiting, diarrhea, or melena Use gastrointestinal protectants concurrently Can also cause nephrotoxicity or hepatotoxicity	Yes	+
Prednisone	Corticosteroid	Lymphoma, mast cell tumor, other lymphoid leukemias, central nervous system tumors Palliative agent	Dosage extremely variable across protocols Follow specific protocol guidelines General dose: 1 mg/kg PO SID for 30 days, then QOD	Iatrogenic hyperadrenocorticism, gastrointestinal upset Do not give if diagnosis of lymphoma has not been confirmed Do not give alone if multiagent chemotherapy protocol for lymphoma is being considered	Yes	+

ACTH, Adrenocorticotropic hormone; *MOPP,* mustargen, oncovin, procarbazine, and prednisone.

TABLE 72-3

Chemotherapeutic Agents and Their Applications in Dogs and Cats—*cont'd*

DRUG NAME *(BRAND NAME)*	DRUG CLASS	PRIMARY INDICATIONS	DOSAGE	TOXICITIES AND PRECAUTIONS	GENERICS AVAILABLE	RELATIVE COST
Procarbazine *(Matulane)*	Alkylating agent	Lymphoma rescue as part of MOPP protocol Other lymphoid leukemias	*Dogs:* 50 mg/m^2 PO SID for 14 days every 4 weeks on MOPP protocol Use compounded formulations to increase dosing precision	Myelosuppression, vomiting, and diarrhea	Yes	+++
Vinblastine *(Velban)*	Mitotic inhibitor	Mast cell tumor, rescue protocol for lymphoma, or as substitute when vincristine not tolerated well	*Dogs, cats:* 2.0-3.0 mg/m^2 IV every 1 to 3 weeks	Myelosuppression, mild vomiting, diarrhea Extravasation reaction	Yes	+
Vincristine *(Oncovin)*	Mitotic inhibitor	Lymphoma, transmissible venereal tumor	*Dogs with lymphoma:* 0.5-0.75 mg/m^2 IV, as per protocol *Cats with lymphoma:* 0.025 mg/kg IV, as per protocol *Dogs with TVT:* 0.5 mg/m^2 IV weekly until resolution (typically ≤6 weeks)	Extravasation reaction Rarely ileus, peripheral neuropathy Rarely vomiting on administration to cats	Yes	+
Vinorelbine *(Navelbine)*	Mitotic inhibitor	Rescue protocols for lymphoma and lung tumor New agent, so more indications may be identified over time	*Dogs:* 15-18 mg/m^2 IV every 1-2 weeks	Myelosuppression and extravasation	No	++

B. Targeting approaches are numerous.
   1. Monoclonal antibodies (MAb)
      a. These are single antibodies that recognize tumor-specific antigens.
      b. Their use has not been reported in companion animals.
      c. MAb 231 (Synbiotics, Inc., Lyon, France) recognizes canine lymphoma cells and may be useful for this disease in the future.
   2. Vaccines and dendritic cell approaches are also used.
      a. Genetically engineered sources of antigens are used to generate an antitumor immune response.
      b. A xenogenic DNA vaccine was approved in 2007 for the treatment of canine malignant melanoma.
      c. Studies are ongoing for the use of DNA vaccines and dendritic cell approaches in canine lymphoma and other tumors.

Photodynamic Therapy

Definition

I. Photodynamic therapy (PDT) is a local anticancer treatment that uses a photosensitizer that interacts with a light source.
   A. The photosensitizer is generally administered systemically but is thought to preferentially accumulate in the tumor.
   B. Most photosensitizers are inert and only become activated upon interaction with a specific wavelength of light.
   C. When activated, the drug interacts with molecular oxygen to create oxygen radicals.
   D. Oxygen radicals then cause local tumor cell death, local vasculature cell death, and possibly death of nearby normal cells.
II. Materials needed include a photosensitizer (most are porphyrin derivatives) and a light source.
   A. Lasers are preferred but not absolutely necessary for PDT.
   B. The light source is applied a variety of ways.
   C. Fiberoptics are most consistently used because of their compatibility with lasers.

Applications

I. PDT has been used for a wide variety of tumors in small animals, including soft-tissue sarcomas, transitional cell carcinomas, mast cell tumors, and nasal squamous cell carcinomas in cats.
II. Advantages include the following:
   A. May only require a single treatment
   B. Typically well tolerated
   C. Easy to administer multiple treatments over time
III. Disadvantages are as follows:
   A. Expense of equipment and photosensitizers
   B. Can be toxic and large clinical studies not available to date
   C. Only useful for superficial tumors because of poor penetration of most light wavelengths (≤5 to 10 mm)
   D. Hypersensitivity reactions possible

Hyperthermia

Definition

I. Heating of tissues to ≥42° C to cause cell death
II. Most efficacious when used in conjunction with other modalities

Applications

I. Whole body by radiant heat
   A. Limited to institutional research settings
   B. Can be efficacious but also causes significant side effects
II. Regional hyperthermia
   A. Feasible in practice owing to less equipment needs
   B. Radiofrequency, ultrasonic, or microwave techniques
   C. Limited benefit or no benefit over surgery

Palliation

Definition

I. The goal of palliation is increased quality of life independent of changes in the course of the disease.
II. It is traditionally used in animals with poor to grave prognoses, and cancer-associated pain.
III. It often includes administration of analgesics or palliative RT.

Types of Analgesics

I. General aspects
   A. Analgesia is most effective if instituted before onset of pain.
   B. Give postoperative analgesics prophylactically instead of waiting for signs of pain.
II. NSAIDs
   A. Mild to moderate efficacy as analgesics
   B. Can be toxic to the gastrointestinal tract, kidneys, and liver
   C. Must not be used concurrently with corticosteroids (increased toxicity)
   D. Give with food whenever possible (unless not recommended)
III. Corticosteroids
   A. Mild to moderate efficacy as an analgesic
   B. May stimulate appetite
   C. May provide mild to moderate antiemetic activity during chemotherapy
   D. Must not be used concurrently with NSAIDs
IV. Nonnarcotic analgesics
   A. Tramadol
      1. It is useful for moderate to severe pain.
      2. Side effects include constipation, weakness, dizziness, sedation, and nausea; reduce dose if sedation is significant.

3. It should not be used with selective serotonin reuptake inhibitors (e.g., fluoxetine) or monoamine oxidase inhibitors (e.g., selegiline).
4. Dose is 2 to 4 mg/kg BID to QID in dogs.
5. Dose is 12.5 mg PO BID in cats.

B. Amantadine
1. It is an N-methyl-D-aspartate receptor antagonist.
2. It is useful for mild to moderate chronic pain when administered with NSAIDs or corticosteroids.
3. Reduce dosage if significant agitation or gastrointestinal toxicity occur.
4. Dose is 3 to 4 mg/kg PO BID in dogs.
5. Dose is 3 mg/kg PO SID in cats.

V. Narcotics
A. Greater efficacy with injectables
B. Butorphanol
1. It is a partial opiate agonist/antagonist.
2. It should not be used concurrently with opiate agonists owing to its partial antagonist properties.
3. It is generally well tolerated but may cause sedation without significant analgesia.
4. Dose is 0.2 to 0.6 mg/kg IV, IM, SC, PO every 1 to 4 hours in dogs.
5. Dose is 0.005 to 0.01 mg/kg IV, IM, SC, PO every 4 to 12 hours in cats

C. Buprenorphine
1. It is a partial opiate agonist.
2. It generally provides more analgesia than butorphanol.
3. Dose is 0.005 to 0.02 mg/kg IM, IV, SC, PO BID to QID in dogs.
4. Dose is 0.005 to 0.01 mg/kg IM, IV, SC, PO BID to QID in cats.

D. Oral sustained-release morphine
1. It is an opiate agonist.
2. Oral bioavailability in dogs is erratic, so it is not routinely recommended.
3. Dose is 1.5 to 3 mg/kg PO BID in dogs.

E. Fentanyl transdermal patches
1. Fentanyl is an opiate agonist.
2. Each patch delivers approximately 72 hours of steady-state blood levels of fentanyl.
3. It takes about 12 hours to reach steady state, so apply the patch before anticipated onset of pain, or use concurrently with other analgesics in the first 12 hours.

VI. Palliative RT: See Radiation Therapy earlier in this chapter.

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CHAPTER 73

Paraneoplastic Diseases

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CANCER-ASSOCIATED HYPERCALCEMIA

Definition

I. Hypercalcemia is defined as a value greater than the upper limit of the reference interval (generally ≥12.0 mg/dL) (Bergman, 2002).
II. It is the most common cause of persistent hypercalcemia in animals (Capen, 2002).

Causes

I. It is described most often in the dog and less frequently in the cat (Morrison, 2002).
II. In dogs, the tumors most often responsible include lymphoma, anal sac apocrine gland adenocarcinoma, and myeloma (Capen, 2002; Morrison, 2002).
III. In cats, the tumors most often responsible include lymphoma, squamous cell carcinoma, and some hematological malignancies (Capen, 2002; Morrison, 2002).
IV. Lymphoma is the leading cause in both dogs and cats (Capen, 2002).

Pathophysiology

I. Endocrine-mediated hypercalcemia (humoral) arises when tumor-derived products reach the bloodstream and have a systemic effect (uncontrolled hypercalcemia).
   A. Parathyroid hormone (PTH) is produced by a functional parathyroid tumor.
   B. Products of tumors mimic the effects of PTH or other hormones.
      1. PTH-like product called *parathyroid hormone-related protein* (PTHrP): most common mechanism
      2. Possible inappropriately increased circulating concentrations of $1,25(OH)_2$–vitamin D
      3. Transforming growth factor (TGF), tumor necrosis factor (TNF), and interleukin (IL)-1 possibly act with PTHrP (Sellers et al., 2002)
II. Paracrine-mediated hypercalcemia is associated with bone marrow neoplasms, such as myeloma.
   A. Tumors of the bone marrow may secrete products that act locally to cause resorption of calcium from bone and result in hypercalcemia (Teske, 2004; Capen, 2002).
   B. Implicated products include PTHrP, TGF, TNF, IL-1, and IL-6.
III. Mechanisms of hypercalcemia secondary to tumor metastases to bone are unknown, but a variety of cytokines, tumor products, and inflammatory mediators are implicated.
IV. Hypercalcemia has deleterious effects on multiple organs.
   A. Kidneys
      1. Decreased urine concentrating ability
      2. Interference with the effects of antidiuretic hormone (ADH)
      3. Secondary to renal tubular injury, mineralization, and ischemia
   B. Muscles of the skeleton and gastrointestinal (GI) tract: interference with muscle contractility
   C. Cardiovascular system
      1. Vasoconstriction
      2. Interference with contractility, rhythm and excitability of the myocardium
   D. Nervous system
      1. Interference with normal brain function
      2. Polydipsia from stimulation of the central nervous system (CNS) thirst center
   E. Metastatic mineralization in various organs

Clinical Signs

I. Clinical signs related to the primary neoplastic process
II. Clinical signs associated with hypercalcemia
   A. Most severe: calcium >16 mg/dL
   B. Polyuria, polydipsia
   C. Renal failure
   D. Vomiting, constipation, and anorexia
   E. Muscle weakness and twitching
   F. Bone pain, lameness
   G. Seizures, coma, stupor and/or depression, changes in behavior
   H. Cardiac arrhythmias and abnormalities in the electrocardiogram (e.g., shortened Q-T interval, prolongation of P-R interval, arrhythmias)

Diagnosis

I. Persistently increased ionized calcium or total calcium concentrations
   A. Because most calcium in blood is bound to albumin/proteins, correction formulas may be used in dogs to obtain an estimated total calcium concentration

to compensate for the effects of hyperproteinemia (Stockham and Scott, 2002a).
1. Adjusted total calcium concentration (estimated) = measured total calcium concentration − measured albumin concentration + 3.5
2. Adjusted, estimated total calcium concentration = measured total calcium concentration − (measured total protein concentration × 0.4) + 3.3

B. In a hyperproteinemic and hypercalcemic animal, a corrected total calcium concentration or an ionized calcium concentration that is normal supports the conclusion that hypercalcemia is secondary to changes in protein concentrations.
C. The acid-base status must also be considered, as acidemia increases the concentration of ionized calcium in the blood.
D. Inorganic phosphorus concentration is normal to decreased unless complicated by renal failure and inappropriately increased concentration of $1,25(OH)_2$–vitamin D.

II. Increased serum PTHrP concentration
A. Assays are available in commercial and university diagnostic laboratories
B. PTHrP concentration in normal dogs is low (<0.2 pmol/L) (Foley et al., 2000).

III. Serum PTH concentration: decreased to normal, unless hypercalcemia is secondary to parathyroid adenoma
IV. Azotemia and renal failure possible with extensive renal injury
V. Diagnostic tests for underlying neoplasia
A. Diagnostic imaging
B. Laboratory testing: complete blood count (CBC), serum biochemical profile, protein electrophoresis
C. Fine-needle aspirates, biopsy, and histopathology

Differential Diagnosis

I. Primary hyperparathyroidism
II. Intoxication from ingestion of vitamin D_3 or vitamin D_3 analogues, rodenticides, or nutritional supplements
III. Granulomatous inflammation (Stockham and Scott, 2002a): blastomycosis, cryptococcosis, histoplasmosis
IV. Adrenocortical insufficiency
V. Thiazide diuretics
VI. Iatrogenic hypercalcemia: administration of calcium-containing intravenous products.
VII. Urine acidifying diets in cats (McClain et al., 1999)
VIII. Primary renal failure

Treatment

I. The primary goal is treatment or elimination of the associated neoplasm; however, hypercalcemia must be controlled promptly to avoid detrimental effects on other organs.
II. Fluid therapy is used to induce diuresis and correct electrolyte abnormalities (Bergman, 2002).
A. NaCl 0.9% supplemented with potassium chloride if animal is hypokalemic
B. Dose: 50 to 70 mL/kg/day IV for mild (12 to 14 mg/dL) to moderate (14 to 16 mg/dL) hypercalcemia
C. ≥80 mL/kg/day IV for severe hypercalcemia (>16 mg/dL calcium concentration)

III. Correct acid-base disturbances.
IV. Diuretics such as furosemide at 1 to 2 mg/kg IV SID to BID, may be useful in well-hydrated animals (Bergman, 2002).
V. Prednisone 1 to 2 mg/kg PO SID to BID may be given after a diagnosis is reached in cases of moderate hypercalcemia (14 to 16 mg/dL [Bergman, 2002]) or when other therapies fail (Kirby et al., 2000).
VI. Other treatments for hypercalcemia (bisphosphonates, calcitonin, mithramycin) may be helpful but require further investigation.
VII. See Chapter 48 for treatment of renal failure.

Monitoring of Animal

I. Monitor serum calcium, acid-base status, and kidney function SID.
II. Repeat electrocardiographic evaluations if cardiac failure or arrhythmias were diagnosed initially.
III. Monitor for secondary infections owing to immunosuppression from chemotherapy or glucocorticoid therapy.

CANCER-ASSOCIATED HYPOGLYCEMIA

Definition

I. Decreased serum/plasma glucose concentration occurs in association with neoplastic disease.
II. Blood glucose concentration is <60 to 70 mg/dL (Ogilvie, 2000; Bergman, 2002).

Causes and Pathophysiology

I. Pancreatic beta-cell tumors (insulinoma) may produce hypoglycemia by inappropriate secretion of insulin.
II. Tumors other than pancreatic beta cell tumors may also result in hypoglycemia.
A. Examples include leiomyosarcoma, renal adenocarcinoma, hepatocellular neoplasms, hemangiosarcoma, salivary gland adenocarcinoma, melanoma, mammary carcinoma, primary pulmonary adenocarcinoma, and lymphoid leukemia (Morrison, 2002; Braund, 2003; Battaglia et al. 2005).
B. Tumors may produce an insulin-like substance, such as insulin-like growth factor (IGF) II.
C. Excessive consumption of glucose by the tumor occurs rarely.
D. Hepatic dysfunction or failure from destruction by the neoplasm may result in hypoglycemia.
E. Combinations of the preceding causes also occur.

Clinical Signs

I. Clinical signs are secondary to low glucose concentrations or to counterregulatory mechanisms mediated by the sympathetic system and adrenal gland (Braund, 2003).
II. Neurological signs are most common and typically occur if glucose is <45 to 50 mg/dL.
III. Neurological signs may arise from polyneuropathy (Dyer, 2004).

IV. Clinical signs worsen with precipitous drops in the concentration of glucose.
  A. Seizures
  B. Confusion, ataxia
  C. Weakness, lethargy, fatigue, collapse
  D. Muscle twitching
V. Clinical signs may also be related to the primary tumor.

Diagnosis

I. Decreased serum/plasma glucose concentration
  A. Persistently low fasting glucose concentration
  B. May need to fast for 24 to 48 hours to have reproducible results
II. ± Increased blood insulin concentration
  A. It is measured concurrently with glucose concentrations.
  B. Increased insulin concurrent with fasting hypoglycemia (<60 mg/dL) is strong evidence of an insulinoma.
III. Increased insulin to glucose ratio (I:G ratio) (Stockham and Scott, 2002)
  A. I:G ratio (μU insulin/mg glucose) = insulin concentration (μU/mL) ×100 ÷ glucose (mg/dL).
  B. Normal values must be determined by each laboratory.
  C. Increased I:G ratio with hypoglycemia suggests insulin is contributing to the hypoglycemia.
  D. Increased I:G ratio with hyperglycemia or normoglycemia suggests insulin resistance.
  E. Amended I:G ratio is not considered valid in dogs and cats (Stockham and Scott, 2002; Braund, 2003).
IV. To detect the causative neoplastic disease: diagnostic imaging, laboratory testing, biopsy, and histopathology

Differential Diagnosis

I. Iatrogenic hypoglycemia: insulin overdose
II. Malnutrition
III. Gastrointestinal disease
IV. Liver insufficiency
V. Adrenocortical insufficiency
VI. Sepsis

Treatment

I. Treat or eliminate the associated neoplasm.
II. Institute frequent feeding (3 to 6 meals daily) of a high complex carbohydrate, protein, and fat diet.
III. Prednisone 0.5 to 1 mg/kg PO BID may be used to increase glucose concentrations in dogs.
IV. Diazoxide 5 to 13 mg/kg PO BID may be useful in dogs with inoperable or metastatic insulinoma, but it is expensive (Nelson, 2000).
V. Intravenous infusion of a 5% dextrose solution immediately increases glucose concentrations, but infusion of more concentrated solutions may result in rebound hyperinsulinemia and profound hyperglycemia.

Monitoring of Animal

I. Regularly monitor the animal for clinical signs of hypoglycemia.
II. Monitor blood glucose concentration initially every 2 weeks, and then every 4 to 6 weeks once glucose concentrations are normal.
III. Prognosis is guarded to poor in dogs with insulinoma because of the high risk for recurrence and metastasis.

CANCER-ASSOCIATED HYPERGLYCEMIA

Definition

I. Increased serum/plasma glucose concentration occurs in association with neoplastic disease.
II. Blood glucose concentration is greater than the upper limit of normal (generally >110 to 130 mg/dL).

Causes and Pathophysiology

I. Tumors that may be associated with hyperglycemia include growth hormone-secreting pituitary tumors, adrenocortical tumors, glucagonomas, and vascular hamartomas (Padgett et al., 1997; Stockham and Scott, 2002b; Capen, 2002; Zerbe and Washabau, 2000; Feldman, 2000).
II. Hyperglycemia is caused by the production of hormones that stimulate release and synthesis of glucose, or by resistance to insulin.

Clinical Signs

I. Clinical signs are usually secondary to the primary tumor or hormone produced by the tumor.
II. Animals with growth hormone-producing acidophil adenomas may have acromegalic features.
III. Animals with functional adrenocortical tumors may have clinical signs of hyperadrenocorticism.
IV. Animals with glucagonomas may have cutaneous changes (superficial necrolytic dermatitis).

Diagnosis

I. Increased serum/plasma glucose concentrations are suspicious.
  A. Persistently increased fasting glucose concentrations (>130 mg/dL)
  B. Hyperglycemia refractory to insulin therapy
II. Diagnostic imaging, laboratory testing, biopsy, and histopathologic analysis assist in the detection of the underlying neoplastic disease.
III. Hormone determinations (glucagon, cortisol, growth hormone) may reveal a direct hormonal cause for the hyperglycemia.

Differential Diagnosis

I. Diabetes mellitus secondary to pancreatic islet injury or destruction
II. Insulin resistance unassociated with neoplastic disease
III. Iatrogenic hyperglycemia: glucocorticoids, megestrol acetate, dextrose, glucagon, ketamine, xylazine, streptozocin
IV. Stress or excitement: transient hyperglycemia

Treatment and Monitoring

I. The primary goal is treatment and/or elimination of the associated neoplasm.

II. Monitor blood glucose concentrations SID after elimination of the primary neoplasm, then every 2 weeks after concentrations stabilize.

MAST CELL-ASSOCIATED SYNDROMES

Definition

I. Mast cell-associated syndromes arise from increased concentrations of histamine and other products of mast cell tumors (Fox et al., 1990; Morrison, 2002; Kraegel and Madewell, 2000; Misdrop, 2004; Teske, 2004).
II. Syndromes most often described include gastroduodenal ulceration, localized cutaneous reactions, and systemic reactions.
III. These syndromes occur most often in dogs.

Causes and Pathophysiology

I. Dogs with mast cell tumors (MCT) typically have increased circulating concentrations of histamine (Fox et al., 1990).
II. Massive release of histamine from mast cell tumors may occur during surgical removal, trauma, or chemotherapy.
III. Gastroduodenal ulceration may occur.
   A. Histamine (H) interacts with H_2 receptors in the parietal cells of the stomach and stimulates secretion of gastric acid.
   B. Increased acidity in the stomach may result in ulceration of the stomach, duodenum, and esophagus.
   C. Histamine may also damage vascular endothelium, possibly causing ischemic necrosis of the GI mucosa.
IV. Release of histamine and other substances from mast cell granules may result in local recruitment of inflammatory cells and other cutaneous changes.
V. Marked release of histamine may also result in hypotensive shock that typically occurs with manipulation and treatment of large neoplasms, multiple tumors, and advanced stages of mast cell cancer.

Clinical Signs

I. Systemic signs
   A. Anorexia, inappetence
   B. Emesis
   C. Abdominal pain
   D. Hematochezia, melena
   E. Shock
II. Localized skin changes
   A. Poor wound healing
   B. Erythema, hemorrhage
   C. Pruritus
   D. Swelling
   E. Ulceration

Diagnosis

I. Clinical signs and physical examination findings may be suggestive.
II. Cutaneous MCT is often diagnosed by cytological examination of fine-needle aspirates.
III. Histological evaluation is necessary for proper grading of the tumor.
IV. Noncutaneous MCT often requires histopathology and other diagnostic tests.
V. Assays for plasma histamine are not usually necessary or widely available.

Differential Diagnosis

I. Other causes of GI bleeding, abdominal pain, anorexia
II. Other cutaneous tumors: histiocytoma, plasmacytoma, etc.
III. Other causes of circulatory shock and hypotension

Treatment

I. The primary goal is treatment and/or elimination of the tumor.
II. Pretreatment with H_1 and H_2 receptor blockers may be necessary to minimize the negative effects of massive histamine release during surgical removal.
   A. H_1 receptor blockers: diphenhydramine 1 mg/kg IM
   B. H_2 receptor blockers
      1. Ranitidine 0.5 to 2 mg/kg PO, SC, IV BID to TID
      2. Cimetidine 4 to 6 mg/kg PO, SC, IV TID to QID
      3. Dogs: famotidine 0.1 to 1 mg/kg PO, IV SID to BID
      4. Cats: nizatidine 2 to 5 mg/kg SID PO or 1 to 3 mg/kg SC, IM, IV TID
III. Proton pump inhibitors such as omeprazole or lansoprazole may be given to dogs at 1 to 2 mg/kg PO SID (maximum 20 mg/day) for cases of severe gastric ulceration (Hall, 2000).
IV. Sucralfate 0.5 to 1 g PO BID to QID may also be used in dogs for gastric ulcers, but must be administered 30 to 60 minutes after H_2 blockers to minimize interference with their absorption.
V. Prednisone 1 to 2 mg/kg PO SID to BID is used to minimize edema and inflammation at the site of the tumor, and possibly to inhibit tumor growth and granule formation (Bergman, 2002; Rogers, 1996).
VI. Palliative radiation therapy may be useful if complete removal of the tumor is not possible.

Monitoring of Animal

I. Monitor regularly for impaired wound healing after removal of MCTs.
II. Monitor for continued histamine-related problems, such as gastroduodenal ulceration, delayed wound healing, etc.

ZOLLINGER-ELLISON SYNDROME

Definition and Causes

I. Zollinger-Ellison syndrome is gastroduodenal ulceration associated with increased gastrin blood concentrations.
II. Excessive secretion of gastrin occurs from gastrin-secreting pancreatic tumors (gastrinomas).
III. Gastrin increases the secretion of acid in the stomach.

Clinical Signs

I. Anorexia, weight loss
II. Vomiting

III. Abdominal pain
IV. Depression, lethargy
V. Hematochezia, hematemesis, melena

Diagnosis

I. Suspicious clinical signs and physical findings
II. Determination of basal blood gastrin concentrations
  A. Increased in dogs and cats with gastrin-secreting tumors (normal = 3.65 ng/L in dogs, <18 pg/mL in cats [Garcia-Sancho et al., 2005; Goldstein et al., 1998]).
  B. Not entirely specific for gastrinoma, as basal gastrin may be increased with renal failure, chronic gastritis, liver disease, small intestinal resection, and during therapy with H_2 receptor blockers
  C. Stimulation tests possibly necessary for confirmation of the diagnosis
    1. These tests require additional investigation in dogs and cats.
    2. Secretin and calcium stimulation tests induce increases in gastrin with gastrinomas but not in normal animals.
  D. Assays for gastrin not widely available
III. Other tests to diagnose the neoplasm: diagnostic imaging, serum biochemical analyses, biopsy, histopathology

Differential Diagnosis

I. Other nonneoplastic causes of GI bleeding, abdominal pain, anorexia
II. Other neoplastic causes of gastroduodenal ulceration, such as mast cell tumors

Treatment and Monitoring

I. The primary goal is treatment and/or elimination of the tumor.
II. Correct any electrolyte, acid-base, and fluid disorders.
III. Start H_2 receptor blockers.
  A. Ranitidine 0. to 2 mg/kg PO, SC, IV BID to TID
  B. Cimetidine 4 to 6 mg/kg PO, SC, IV TID to QID
  C. Dogs: famotidine 0.1 to 1 mg/kg PO, IV SID to BID
  D. Cats: nizatidine 2 to 5 mg/kg SID PO or 1 to 3 mg/kg SC, IM, IV TID
IV. Sucralfate 0.5 to 1g PO BID to QID may be used in dogs to promote healing of gastric ulcers, but must be administered 30 to 60 minutes after H_2 blockers to minimize interference with their absorption.
V. Proton pump inhibitors such as omeprazole or lansoprazole may be given in dogs at 1 to 2 mg/kg PO SID for severe gastric ulceration (Hall, 2000).
VI. Prognosis in dogs and cats is grave owing to a high incidence of metastasis.

CANCER-ASSOCIATED CACHEXIA

Definition

I. It is general physical wasting and malnutrition associated with cancer (Ogilvie, 2000).
II. Cachexia may be defined as >20% weight loss; however, weight loss of 10% should be thoroughly investigated (Greco, 2000).

Causes and Pathophysiology

I. Cancer-associated cachexia is a derangement of lipid, protein, and carbohydrate metabolism in animals with cancer (Morrison, 2002; Ogilvie, 2000).
II. The chemical mediators have not been entirely defined; however, changes in cytokines and hormones such as interferon, TNF, interleukin-1, IL-6, insulin, and growth hormone may be involved.
III. There is a net loss of energy in the body.
IV. Tumor cells have a high rate of glucose consumption.
  A. Consumption occurs at the expense of the animal.
  B. Less glucose is available for healthy cells.
  C. Increased lactic acid concentrations occur from glycolysis in tumor cells.
  D. Lactic acid is converted to glucose by the animal's nonneoplastic tissues at a net loss of energy.
  E. Some animals may have concurrent insulin resistance that results in less glucose entering nonneoplastic cells.
V. Circulating concentrations of amino acids used for gluconeogenesis are also decreased.
  A. Protein catabolism is greater than protein synthesis.
  B. Indicators of severe protein catabolism include the following:
    1. Muscle wasting
    2. Decreased albumin concentrations
    3. Impaired healing of wounds
    4. Secondary infections from compromised immune function
VI. Derangements in fat metabolism also occur.
  A. Body fat is decreased owing to lipolysis, as the body tries to oxidize lipids for energy.
  B. Cancer cells do not utilize lipids as well as noncancerous cells.

Clinical Signs

I. Anorexia
II. Decreased body weight
III. Muscle wasting
IV. Weakness, fatigue

Diagnosis

I. Suspicious clinical signs, especially in the absence of malnutrition, malabsorption, cardiac disease
II. Tests to diagnose neoplasia: diagnostic imaging, laboratory testing (CBC, serum biochemical analyses), biopsy, histopathology, etc.

Differential Diagnosis

I. Malnutrition
II. Anorexia of nonneoplastic cause: dental disease, CNS disease, intoxication (e.g., aspirin, ethylene glycol, rodenticides)
III. Gastrointestinal malabsorption
IV. Severe parasitism
V. Chronic diarrhea, vomiting, or both
VI. Heart disease
VII. Diabetes mellitus, hyperthyroidism
VIII. Protein-losing nephropathy

Treatment

I. The primary goal is treatment or elimination of the tumor.
II. The secondary goal is to increase intake of nutrients.
III. Institute measures to increase appetite.
  A. Warm, aromatic foods
  B. Diazepam 0.05 to 0.15 mg/kg IV SID to QOD in cats (Bergman, 2002)
  C. Cyproheptadine 1 to 2 mg PO SID to BID in cats (Bergman, 2002)
IV. Nutritional supplementation includes the following (Ogilvie, 2000):
  A. Diets with highly bioavailable protein, modest amounts of simple carbohydrates, and n-3 fatty acids (Hill's n/d; Hill's Pet Nutrition, Inc., Topeka, Kan.)
  B. Increased fiber content
V. Increase frequency of feeding or consider enteral feeding.
VI. Provide parenteral nutrition if necessary.
VII. Avoid lactate and glucose-containing fluids during fluid therapy.

Monitoring of Animal

I. Monitor body weight on a weekly basis.
II. Repeat CBC every 2 weeks and serum biochemical profiles monthly to monitor general health and evaluate for opportunistic infections and anemia.
III. Document food intake at home and while hospitalized.
IV. Prognosis is poor.

CANCER-ASSOCIATED FEVER

Definition and Causes

I. Fever is an increase in body temperature above the expected normal temperature for that species.
II. Endogenous or exogenous pyrogens act on the thermoregulatory center in the anterior hypothalamus to elevate the body temperature (Miller, 2000).
III. Excessive heat production or inadequate heat loss occur to meet the new temperature "set-point."
IV. Fever develops from the presence of cancer in the body.
V. Fever of unknown origin (FUO) is a term typically used for fever that persists for a period ≥2 to 3 weeks and for which a cause has not been identified.
  A. With transient, self-limiting causes, fever usually resolves within 2 weeks.
  B. There are numerous causes of FUO, including cancer.
VI. Fever must be differentiated from other causes of hyperthermia, such as excessively high ambient temperatures (i.e., heat stroke), vigorous exercise on a hot day, excessive exercise, and injury to the thermoregulatory center.

Pathophysiology

I. Neoplasms produce cytokines and other chemical mediators that act on the thermoregulatory center to result in fever.
II. Specific immune-mediated reactions to the tumor or generalized inflammatory reactions to tumor necrosis may also elicit release of cytokines and chemical mediators.

Clinical Signs

I. Increased body temperature
II. Clinical signs associated with the neoplastic process
III. Weight loss or cachexia
IV. Anorexia and dehydration
V. Lethargy

Diagnosis

I. Rule out other causes of fever.
II. Diagnostic imaging, laboratory testing, biopsy, fluid analyses (e.g., joints, cerebrospinal fluid, abdominal fluid, urine), and histopathologic analysis help to diagnose neoplastic disease and to rule out other causes of fever.

Differential Diagnosis

I. Immune-mediated diseases (e.g., immune-mediated polyarthritis), noninfectious inflammatory diseases
II. Infections: bacterial, fungal, viral, parasitic
III. Tissue injury: trauma, infarction, ischemia
IV. Drugs: tetracycline (cats), levamisole (cats), bleomycin, colchicine, halothane, succinylcholine

Treatment

I. Primary treatment is directed at eliminating or controlling the neoplastic process.
II. If the fever exceeds 41° C (106° F), cool the animal.
  A. Bathe with cool water.
  B. Excessively cold water may interfere with release of heat because of vasoconstriction of the cutaneous vasculature.
  C. Consider cool water enemas or cool water gastric lavage.
III. Nonsteroidal antiinflammatory drugs may be given as antipyretics if fever persists.
  A. Dogs: aspirin 5 to 10 mg/kg PO SID to BID
  B. Cats: aspirin 3 to 6 mg/kg PO every 2 to 3 days

Monitoring of Animal

I. Measure and document the body temperature SID to QID (Bergman, 2002).
II. Monitor response to antitumor therapy and for recurrence and metastasis of the tumor.

HYPERGLOBULINEMIA

Definition

I. Increased concentration of immunoglobulins in the blood from excessive production by neoplastic cells
II. Generally arises from a monoclonal (sometime biclonal) synthesis of immunoglobulin (Ig) M, IgG, or IgA

Causes

I. Multiple myeloma
II. Extramedullary plasmacytoma
III. Lymphoma
IV. Lymphocytic leukemia

Pathophysiology

I. Neoplastic lymphocytes produce excessive amounts of immunoglobulins, such as IgA, IgG, IgM, or light chains.
II. Markedly increased protein concentrations result in increased resistance to the flow of blood or hyperviscosity.
III. Increased serum viscosity may result in hyperviscosity syndrome (HVS).
  A. In dogs HVS has been associated most often with elevations of IgM because of its larger size compared with IgG and IgA.
  B. Slow blood flow and distention of small blood vessels (e.g., retinal vessels) occur.
  C. Delivery of oxygen and nutrients to tissues is inadequate.
    1. Hypoxic injury to tissues results.
    2. Organs most commonly affected are the central nervous system, eyes, and kidneys (Morrison, 2002).
    3. Cardiac disease may occur secondary to hypoxic injury and excessive cardiac workload.
    4. Renal disease may be complicated by amyloidosis and light chain proteinuria (Bence-Jones proteinuria).
IV. Immunoglobulins produced by the neoplastic cells may interfere with coagulation and result in increased bleeding.
  A. Inhibition of platelet function
  B. Interference with clotting factors

Clinical Signs

I. Some clinical signs are directly related to the physical presence of the neoplasm.
II. Neurological abnormalities develop secondary to hyperviscosity
  A. Lethargy and weakness
  B. Seizures
  C. Dementia, depression
  D. Ataxia
  E. Anorexia and weight loss: common in cats with multiple myeloma
III. Abnormal bleeding also occurs with hyperviscosity.
  A. Epistaxis
  B. Mucosal hemorrhages
  C. Petechiae, ecchymoses
  D. Excessive bleeding at sites of venipuncture or injections
IV. Ocular abnormalities include hyphema, retinal hemorrhage, retinal detachment, and tortuosity and distention of retinal vessels.
V. Polyuria/polydipsia may develop from impaired renal function secondary to glomerular amyloidosis, decreased renal perfusion, or Bence-Jones proteinuria.

Diagnosis

I. Confirm and characterize the hyperglobulinemia.
  A. Increased total protein and globulin levels on serum biochemistry profile
  B. Serum protein electrophoreses
    1. Electrophoresis: monoclonal spike, sometimes biclonal spikes
    2. Immunoelectrophoresis: exact immunoglobulin identified
II. Search for an underlying cause.
  A. CBC, blood smear evaluation, and fine-needle aspirates of lesions, bone marrow, and lymph nodes
    1. Marked leukocytosis and neoplastic lymphocytes with leukemia
    2. Neoplastic plasma cells in lymph nodes, bone marrow, or masses
    3. Cytopenias from bone marrow infiltration
    4. Inflammatory leukograms with opportunistic infections
  B. Serum biochemistry analyses
    1. Evidence of renal insufficiency (azotemia with inappropriately concentrated urine) may be detected.
    2. Hypercalcemia may occur with some neoplasms.
  C. Urinalysis
    1. Bence Jones test: detects light chains in the urine
    2. Immunoelectrophoresis: identifies immunoglobulin light chains
  D. Other tests to consider
    1. Diagnostic imaging
    2. Fluid analyses
    3. Histopathology
    4. Coagulation assays
    5. Ophthalmologic examination

Differential Diagnosis

I. Infection with *Ehrlichia* spp. may cause monoclonal protein spikes on electrophoresis assays (See Chapter 115).
II. Other causes of hyperviscosity include primary or secondary polycythemia (see Chapter 64).

Treatment

I. Direct treatment at the elimination or control of the primary neoplasm.
II. Phlebotomy and administration of isotonic fluids may be necessary in severe cases.
III. Plasmapheresis is helpful for severe cases but is a complicated procedure.
IV. Antimicrobials may be needed to prevent or treat secondary infections from immunosuppression.

Monitoring of Animal

I. Monitor for response to chemotherapy.
II. Osteolytic lesions of multiple myeloma may take months to partially resolve.
III. Decreased serum immunoglobulin and urinary light chain concentration may occur within 3 to 8 weeks, if chemotherapy is successful.
IV. Evaluate CBCs and coagulation parameters every 2 to 4 weeks to monitor for improvement.
V. The prognosis for dogs with multiple myeloma uncomplicated by hypercalcemia, Bence-Jones proteinuria, and marked bone lysis is generally good.
VI. The prognosis for cats with multiple myeloma is typically poor because of a limited response to chemotherapy.

OTHER PARANEOPLASTIC SYNDROMES

See Table 73-1.

TABLE 73-1

Other Paraneoplastic Syndromes

CLASS OF DISORDER	SPECIFIC DISORDER	CAUSES	CLINICAL SIGNS
Cutaneous paraneoplastic diseases (Adapted from Turek, 2003; Angarano and Brewer, 1993)	Superficial necrolytic dermatitis	Glucagonoma (dogs) Pancreatic carcinoma (cat) Rule out hepatopathy	Well-demarcated erythematous erosions and alopecia involving haired skin and pressure points, mucocutaneous junctions, perineum, feet, muzzle Hyperkeratosis of the footpad
	Nodular dermatofibrosis	Cystadenoma or carcinoma of the kidney Females develop leiomyomas of the uterus	Multiple masses and papules in the dermis and subcutaneous tissues Extremities preferentially affected Predilection for German shepherd dogs
	Paraneoplastic pemphigus	Thymic lymphoma Splenic sarcoma	Erosions in the oral and nasal mucosa, mucocutaneous junctions, and haired skin In haired skin lesions may begin as vesicobullous lesions
	Feminization in male dogs	Sertoli cell tumor	Gynecomastia, bilateral symmetrical alopecia, pendulous prepuce, linear preputial dermatosis Possible enlarged testicles Possible cryptorchid testicle
	Feline thymoma-associated exfoliative dermatitis	Thymoma	Erythema and scaling progressing to alopecia Ulcers and crusts may occur Sebaceous debris in ear canals, nail bed, and between digits Nonpruritic
	Feline paraneoplastic alopecia	Pancreatic and biliary carcinoma	Progressive, bilaterally symmetrical alopecia Nonpruritic Footpads may be erythematous, dry, fissured, and crusted Concurrent clinical signs of illness (inappetence, vomiting, weight loss)
	Necrosis of skin	Lymphoma, possibly others	Necrotic skin on the extremities May be symmetrical
Hematological, coagulation	Anemia	Multiple tumors	Weakness, pallor, decreased hematocrit Anemia may arise secondary to blood loss, bone marrow infiltration by neoplastic cells, chemotherapy, iron or vitamin deficiency, and hemolysis
	Thrombocytopenia or coagulopathies	Multiple tumors	Petechiae, hemorrhages decreased platelet counts, increased coagulation times
	Polycythemia	Renal neoplasms, hepatic neoplasms, nasal fibrosarcoma	Increased hematocrit, lethargy, depression, anorexia, polyuria, polydipsia, vomiting, weakness

Continued

TABLE 73-1

Other Paraneoplastic Syndromes—*cont'd*

CLASS OF DISORDER	SPECIFIC DISORDER	CAUSES	CLINICAL SIGNS
		Rule out polycythemia vera, and dehydration	
	Leukocytosis (nonleukemic)	Multiple tumors	Increased white blood cell counts
Neurological (Adapted from Dyer, 2004; Braund, 1990)	Myasthenia gravis	Thymoma, other mediastinal tumors	Muscle weakness, exercise intolerance, difficulty holding up the head, and closing mouth or eyelids Dysphagia, regurgitation Megaesophagus
	Polyneuropathies	Multiple tumors	No clinical signs or weakness, paresis, ataxia
Urinary, endocrine	Nephrogenic diabetes insipidus (Cohen and Post, 1999)	Intestinal leiomyosarcoma	Increased water consumption Inability to concentrate urine despite adequate antidiuretic hormone concentrations Polyuria, polydipsia
	Inappropriate secretion of ADH (Bergman, 2002; Ogilvie, 2000)	Lymphoma, carcinoma, meningeal sarcoma Rule out other nonneoplastic causes (e.g., vincristine, barbiturates)	No clinical signs Hyponatremia, anorexia, increased body weight (water retention), vomiting, weakness, seizures, coma
Musculoskeletal	Hypertrophic osteopathy (see Chapter 81)	Primary or secondary pulmonary tumors are the most frequent cause in dogs Other neoplastic and nonneoplastic conditions of the thorax and abdomen	Thickened, painful, possibly deformed extremities Extremities may be warm to the touch

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CHAPTER 74

Introduction

Ellen Miller

IMMUNE SYSTEM

I. The immune system is a complicated array of cellular and biochemical components designed to discriminate self from nonself.
II. Both the antigen-specific and antigen-nonspecific components of the immune system protect the individual from infectious agents, neoplastic cell growth, and noninfectious invaders.
III. The immune system has the ability to respond to a wide variety of antigens (diversity) that it is genetically preprogrammed before exposure to those antigens.
IV. The immune system can respond more rapidly when a particular antigen is recognized the second time (memory).
V. The immune system has the ability to distinguish self from nonself (discrimination).

NONSPECIFIC MECHANISMS

I. Nonspecific immunological mechanisms include physical barriers, granulocytes, monocytes, complement and other inflammatory cells, and mediators.
II. Physical barriers are the first line of defense against invaders and include the skin, respiratory mucociliary apparatus, and normal gastrointestinal flora.
III. Once the physical barriers have been penetrated, inflammatory cells move into the area and chemical mediators are released (see Chapter 65).
   A. The neutrophil contains azurophilic granules (e.g., defensins, myeloperoxidase, lysozyme, elastase, collagenase, cathepsin, lipases, ribonuclease, other proteinases) and specific granules (e.g., lysozyme, nicotinamide adenosine dinucleotide phosphate [NADPH] oxidase, collagenase, gelatinase, lactoferrin, histaminase, receptors for complement, fibrinogen, fibronectin).
      1. When circulating neutrophils detect chemoattractants, such as complement components, fragments of collagen, leukotriene (LT)B_4, prostaglandin (PG)D_2, platelet-activating factor (PAF), and interleukin (IL)-8, they marginate and emigrate into the site of inflammation.
      2. Once in the area of inflammation, neutrophils engulf bacteria, cellular debris, and foreign particulate matter, forming a phagosome that fuses with granules to create a phagolysosome.
      3. Degranulation of the granules into the phagolysosome results in release of proteins designed to kill bacteria or dissolve foreign material.
   B. Monocytes circulate in peripheral blood or reside (tissue macrophages) in almost every tissue of the body.
      1. They contain lysosomes that store the same enzymes as neutrophil lysosomes but are fewer in number.
      2. In general, phagocytosis is slower and engulfed material is broken down more slowly than with neutrophils.
      3. Macrophages produce the complement components: IL-1, IL-6, IL-12, IL-18, and tumor necrosis factor (TNF).
   C. Eosinophils are produced in the bone marrow under the influence of granulocyte-monocyte colony stimulating factor, IL-3, and IL-5.
      1. Granule contents are comparable to those of neutrophils; however, percentages of the different enzymes vary.
      2. Eosinophils engulf particles, form phagolysosomes, and undergo lysosomal degranulation, but bacterial killing power is less efficient than that of neutrophils.
      3. Eosinophils function to down-regulate the immediate hypersensitivity response and control parasitic infections.
   D. Basophils are produced in the bone marrow from myeloid progenitor cells.
      1. Basophils have receptors for immunoglobulin (Ig)E on their surface and participate in IgE-mediated reactions similar to mast cells.

2. Their granules contain histamine, heparin, serotonin, and other vasoactive substances.
3. When basophils degranulate, the end result is increased vascular permeability and an influx of serum proteins and effector cells.
4. When release of mediators occurs, systemic or local anaphylaxis occurs, depending on the magnitude of release and organ involved.

E. Mast cells are produced in the bone marrow and migrate to tissues where they develop under the influence of various cytokines.
1. Metachromatic granules contain preformed mediators (histamine, heparin, TNF, superoxide dismutase, peroxidase, and acid hydrolases) and precursors to synthesized mediators (prostaglandins and leukotrienes).
2. When an appropriate antigen binds to mast cell IgE, degranulation of mast cells occurs.
3. Two major groups of mast cells exist: those associated with the connective tissue and those that live at the mucosal surfaces.

F. Platelets are produced from megakaryocytes in the bone marrow.
1. They have a 10-day lifespan in the circulation.
2. Activation during the clotting cascade results in aggregation and release of granule contents that include arachidonate metabolites, growth factors, bioactive amines, PAF, and hydrolases.

G. Endothelial cells also play a role in the inflammatory response.
1. Although not really inflammatory cells, they are activated by IL-1, TNF, and interferon (IFN)-α and become more adhesive for monocytes and neutrophils.
2. They can also serve as antigen-presenting cells.

IV. The complement system is a multicomponent, biochemical system that produces specific proteins that destroy foreign invaders.
A. Complement bridges the nonspecific and specific arms of the immune system.
B. Complement system can be activated in several ways.
1. The classical pathway of activation is triggered when antibodies bind to an antigen.
2. The alternative pathway of activation does not require antibody and provides an immediate host defense mechanism in the absence of prior sensitization.

C. The end result of complement activation is a membrane attack complex that causes osmotic lysis and killing of the invader.

V. Cytokines are regulatory proteins produced by cells of the immune system.
A. ILs are cytokines that regulate the interaction between lymphocytes and other leukocytes.
B. IFNs are synthesized in response to viral infections and inhibit viral replication.
C. TNFs are derived from macrophages and T lymphocytes.
D. Growth factors or colony-stimulating factors stimulate the growth of new cells.
E. Chemokines are small proteins that act as chemoattractants or leukocyte activators in the inflammatory response.

VI. Arachidonic acid derivatives are substances produced by cyclooxygenation (PGs) or lipooxygenation (LTs) of arachidonic acid in phagocytic cells, mast cells, and platelets.
A. PGE_2, PGF_2, prostacyclin, and thromboxanes are proinflammatory molecules.
B. LTB_4, LTC_4, LTD_4, and LTE_4 are synthesized in mucosal mast cells.
C. LTB_4 is a potent chemoattractant, whereas the other three (collectively termed *slow-reacting substance of anaphylaxis*) induce smooth muscle contraction, bronchoconstriction, mucus secretion, and the wheal-and-flare response.

SPECIFIC MECHANISMS

I. Specific immunological mechanisms include B and T lymphocytes and their products.

II. T lymphocytes (T cells) are responsible for the cell-mediated portion of the immune system.
A. Helper T cells release cytokines that activate B and cytotoxic T lymphocytes.
B. Cytotoxic T cells directly lyse target cells (e.g., tumor cells, cells infected with virus).
C. Antigen bound to major histocompatibility proteins on the surface of macrophages (antigen-presenting cells) is recognized by the T-cell receptor.
D. Binding of antigen to the T-cell receptor leads to T-cell activation.
1. Helper T cells secrete IL-2, IL-4, IL-5, IL-10, IL-12, IL-13, and IL-18; IFN-α; and TNF.
2. These cytokines amplify the immune response by activating macrophages and B and T lymphocytes.

III. B lymphocytes (B cells) are responsible for the humoral portion of the immune response.
A. Activated B cells (plasma cells) produce immunoglobulin that is specific for a particular antigen.
B. The B-cell antigen receptor is immunoglobulin that is attached to the B-cell surface.
C. The immunoglobulins found in the dog and cat are IgA, IgE, IgG, and IgM.
1. IgA is secreted by plasma cells near mucosal surfaces and is responsible for limiting antigen access to the body.
2. IgE is also secreted by plasma cells located beneath body surfaces, is responsible for the immune response against parasites, and is also involved in allergic reactions.
3. IgG is made and secreted by plasma cells in the lymph nodes, spleen, and bone marrow and is the primary immunoglobulin involved in the systemic immune response.

4. IgM is also produced by plasma cells in the bone marrow, spleen, and lymph nodes and is the first antibody produced in response to antigenic stimulation.

D. B cells, usually with the help of T cells, are activated and divide in response to antigen.
1. A portion of these cells becomes plasma cells, actively secreting immunoglobulin.
2. The other portion becomes memory cells, waiting for a second exposure to the same antigen to be activated.

CLASSIC HYPERSENSITIVITY REACTIONS

I. These immunological reactions are designed to ward off microbial invaders and neutralize toxins; however, when directed at host tissues, they can cause significant damage.

II. Most immune-mediated diseases are classified into one or more of four different reaction types.

A. A type I reaction is the classic anaphylactic reaction.
1. This reaction is mediated by mast cells, eosinophils, basophils, and IgE, and can be a localized or systemic reaction, depending on the route and rate of administration of antigen.
2. Binding of antigen to surface IgE on mast cells results in production and release of vasoactive chemicals such as histamine, serotonin, proteases, LTs, and PGs.
3. Examples include urticaria and systemic anaphylactic shock caused by a penicillin allergy.

B. A type II reaction is a cytotoxic reaction.
1. When the antibodies bind antigen on the cell surface, complement is activated, resulting in generation of the membrane attack complex.
2. The cell bearing the antigen is then destroyed.
3. Examples include immune-mediated hemolytic anemia, immune-mediated thrombocytopenia, and pemphigus vulgaris.

C. A type III reaction is immune complex disease.
1. Type III reactions are mediated by IgG, IgM, complement, neutrophils, platelets, and arachidonic acid metabolites.
2. Antigen–antibody complexes are filtered out in organs with high blood flow and attract neutrophils and platelets.
3. Activation of neutrophils, platelets, and complement causes release of chemicals (e.g., proteases, free radicals, nitric oxide) that damage the affected organ.
4. Immune complexes may contain autoantibodies (antibodies against self-antigens) and may also cause damage even if antibodies are not directed against self-antigens (e.g., heartworm disease causing immune-mediated glomerulonephritis).
5. Examples include systemic lupus erythematosus and vasculitis.

D. A type IV reaction is a delayed-type hypersensitivity reaction.
1. This reaction is mediated by macrophages, lymphocytes, and their cytokines.
2. When antigen enters the body, some is taken up by specialized macrophages that migrate to the local lymph node.
3. Sensitized T cells interact with antigen and secrete IFN, IL-2, IL-8, and serotonin.
4. More T cells and macrophages are attracted to the area, and a granulomatous reaction develops.
5. Contact hypersensitivity (e.g., plastic dish dermatitis) is an example.

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CHAPTER 75

Immunodeficiency Disorders

Ellen Miller

CONGENITAL/DEVELOPMENTAL DISORDERS

Primary Ciliary Dyskinesia

Definition and Causes

I. Primary ciliary dyskinesia is characterized by defective ciliary action within the respiratory tract.
II. The cilia of the respiratory epithelial cells have an abnormal microtubule arrangement.

Pathophysiology

I. The microtubular arrangement within the cilia is abnormal and results in random or dyscoordinated movement.
II. This defect results in reduced clearance of organisms that normally gain entry into the respiratory tract.
III. Therefore the escalator action of the mucociliary apparatus is disrupted.
IV. The disorder is inherited as an autosomal recessive trait.

Clinical Signs

I. Severe and recurrent respiratory tract infections such as rhinosinusitis, bronchitis, bronchiectasis, and bronchopneumonia
II. Reported in border collies, English setters, Doberman pinschers, and golden retrievers
III. Accompanied by situs inversus and immotile sperm
IV. Results in recurrent respiratory infections leading to chronic bronchitis and bronchiectasis

Diagnosis and Differential Diagnosis

I. A definitive diagnosis is made by examining respiratory cilia with electron microscopy and identifying the ultrastructural abnormalities in the cilia.
II. Ciliary dyskinesia is suggested in young animals with chronic respiratory disease, with or without situs inversus.
III. Mucociliary scintigraphy detects impaired clearance.
IV. Electron microscopy of tracheal and nasal epithelial biopsies reveals absence of the central pair of microtubules within the cilia.

Treatment and Monitoring

I. Treatment is supportive and symptomatic.
II. Appropriate antibiotic therapy based on culture and sensitivity of respiratory samples is imperative.
III. Supportive care includes oxygen therapy, airway humidification, and respiratory physiotherapy.
IV. Prognosis is guarded.

Cyclic Hematopoiesis

Definition and Cause

I. Cyclic hematopoiesis is caused by an autosomal recessive trait resulting in regular, cyclic fluctuations in leukocyte, platelet, and red blood cell numbers.
II. A cyclic decrease occurs in the production of hematopoietic cells in affected animals.
III. Because clinical signs are usually associated with low leukocyte numbers, this syndrome has also been called *cyclic neutropenia*.

Pathophysiology

I. The defect may arise from abnormal purine metabolism in the stem cells (Jezyk, 1988).
II. Myeloperoxidase deficiency in the neutrophils results in defective bactericidal activity as well.
III. The defect is inherent within the bone marrow environment and may be related to a cyclic decrease in erythropoietin and colony stimulating factor secretion.
IV. Condition is inherited as an autosomal recessive trait.
V. Reactive amyloidosis may develop from recurrent infections.

Clinical Signs

I. The disorder primarily affects gray-coated collies, which rarely live past 3 years of age.
II. In addition to life-threatening bacterial infections, affected animals are weak, have stunted growth, and have poor wound healing.
III. Hemorrhage secondary to thrombocytopenia is frequent.
IV. Neonatal death is common.

Diagnosis and Differential Diagnosis

I. Finding the classic cyclic pattern of neutrophil numbers in a gray-coated collie
II. Ruling out other diseases that can result in neutropenia

Treatment and Monitoring

I. Granulocyte colony-stimulating factor 5 μg/kg SC BID
II. Bone marrow transplantation
III. Lithium carbonate 21 to 26 mg/kg/day PO
IV. Supportive care: appropriate antibiotic therapy, correction of dehydration, oxygen therapy
V. Prognosis: guarded

Chédiak-Higashi Syndrome

Definition and Causes

I. It is characterized by abnormally large azurophilic granules in a number of cell types, including leukocytes.
II. Cells of numerous tissues, including leukocytes, contain abnormal giant azurophilic granules.

Pathophysiology

I. Decreased neutrophil chemotaxis and killing
II. Reduced neutrophil chemotactic activity and intracellular killing of bacteria
III. Defective defense against tumors and viruses by natural killer cells
IV. Transmitted in an autosomal recessive pattern

Clinical Signs

I. Affected cats have a smoke-blue hair coat and yellow-green eyes.
II. Dilution of coat color (abnormal melanin granules), photophobia (abnormal retinal pigment granules), and hemorrhagic tendencies (abnormal platelet function) are most commonly noted.
III. Although cats may have increased bleeding tendencies, the immunosuppression is mild.
IV. Syndrome affects Persian cats.

Diagnosis and Differential Diagnosis

I. Diagnosis is based on the characteristic appearance of neutrophil granules on a blood smear (eosinophilic granules up to 2 μm in diameter in about 50% of the neutrophils).
II. Must be differentiated from other phagocytic defects or infectious diseases that cause granules in neutrophils, such as the rickettsial diseases.

Treatment and Monitoring

I. Symptomatic treatment: appropriate antibiotics based on culture and sensitivity results
II. Supportive care
III. Prognosis: fair to good

Pelger-Huét Anomaly

Definition and Causes

I. This apparently benign condition is associated with incomplete neutrophil segmentation.
II. It is a benign, congenital leukocyte developmental disorder.

Pathophysiology

I. Incomplete segmentation of neutrophils and eosinophils gives the appearance of a left shift; however, neutrophil function is normal.
II. It is transmitted in an autosomal dominant mode.

Clinical Signs

I. Clinical signs are absent, with the exception of small litter size.
II. Hemograms appear to have a chronic left shift, but toxic forms are not encountered.
III. It affects foxhounds, domestic shorthaired cats, and various other breeds of dogs (Knoll, 1997).

Diagnosis and Differential Diagnosis

I. Diagnosis is made by finding the classic blood smear changes (left shift) in an animal without clinical signs of disease.
II. Differential diagnoses include sepsis, bacteremia, and other infectious diseases resulting in a left shift.

Treatment and Monitoring

I. None is required.
II. See Chapter 65.
III. Prognosis is good.

Complement Component 3 Deficiency

Definition and Causes

I. Compliment component 3 (C3)—the third component of complement—is of crucial importance in the classic and alternative pathway of complement activation.
II. Affected animals fail to make C3.
III. C3 deficiency is inherited as an autosomal recessive trait.

Pathophysiology

I. Lack of C3 prevents bacterial opsonization, chemoattraction of neutrophils, and development of membrane attack complex.
II. Deficiency of C3 results in severe bacterial infections.

Clinical Signs and Diagnosis

I. Homozygous animals suffer from recurrent infections, especially gram-negative septicemias.
II. Animals experience recurrent bacterial infections of the skin, respiratory system, and urinary tracts.
III. Heterozygotes are clinically unaffected and have C3 concentrations approximately 50% of normal.
IV. Measurement of serum complement concentrations helps identify both homozygotes and heterozygotes.
V. The condition occurs in Brittany spaniels.

Treatment and Monitoring

I. Treatment is symptomatic and primarily aimed at control of bacterial infections with appropriate antibiotics and provision of IV fluid.
II. No specific treatment is available.
III. Monitoring of body temperature, appetite, and white blood cell count helps detect early infections.
IV. Prognosis is guarded for homozygotes.

Canine Granulocytopathy Syndrome (Leukocyte Adhesion Molecule Deficiency)

Definition and Causes

I. It is an inherited autosomal recessive trait resulting in defective neutrophil function.
II. Affected dogs fail to express adhesion molecules CD11b and CD18 so that neutrophils cannot egress from the bloodstream into tissues to fight infection.

Pathophysiology

I. Deficiency develops in the leukocyte adhesion molecule, an integrin that allows neutrophils to adhere to vascular endothelium and eventually migrate into areas of inflammation or infection.
II. Neutrophils have impaired aggregation, chemotaxis, and phagocytosis.

Clinical Signs

I. Clinical signs arise before 12 weeks of age.
II. Recurrent pyogenic infections develop, such as pyoderma, omphalophlebitis, and pneumonia.
III. Delayed wound healing may occur.
IV. Condition occurs in Irish setters.

Diagnosis and Differential Diagnosis

I. Neutrophil counts are very high (sometimes >200,000/μL).
II. Measurement of CD11 to CD18 adhesion protein concentrations in the neutrophil membrane is the only definitive diagnostic tool.
III. Diagnosis is usually made by finding compatible clinical signs in an Irish setter.

Treatment and Monitoring

I. Treatment is symptomatic and involves the use of appropriate antibiotics based on culture and sensitivity testing.
II. No specific treatment is available.
III. Prognosis is poor.

Severe Combined Immunodeficiency

Definition and Causes

I. Severe combined immunodeficiency arises from defects in both the T-cell and B-cell components of the immune system.
II. A mutation in the common chain of the receptor molecules for cytokines interleukin (IL)-2, IL-4, IL-7, IL-15, and IL-17 results in impaired cellular and humoral immunity.

Pathophysiology

I. A mutation in the gene coding for the IL-2 receptor results in severe defects in T-cell function.
II. Antibody production is restricted to immunoglobulin (Ig) M because the class shift in antibody production does not occur.
III. Decreased lymphocyte blastogenic responses are identified in affected animals.
IV. It is inherited as a sex-linked (X chromosome) trait.

Clinical Signs

I. Affected animals fail to thrive and show increased susceptibility to viral and bacterial diseases, such as pneumonia, enteritis, and septicemia.
II. Severe, recurrent infections such as *Pneumocystis* pneumonia, otitis, and stomatitis are common.
III. Affected puppies exhibit a failure to thrive.
IV. It is reported in basset hounds and Cardigan Welsh corgis (Somberg et al., 1994).

Diagnosis

I. Suspicious findings include thymic and lymphoid dysplasia, as well as hypoglobulinemia with normal IgM concentrations.
II. Mild lymphopenia and lack of lymphoid tissue are noted in affected animals.
III. Affected dogs have no IgG or IgA.

Treatment and Monitoring

I. Treatment is supportive and symptomatic, with antibiotics and IV fluid therapy being most important.
II. Bone marrow transplantation has been done experimentally.
III. Prognosis is grave; most affected dogs die by 16 weeks of age.

Selective Immunoglobulin A Deficiency

Definition and Causes

I. The disorder is characterized by reduced amounts of IgA in the serum and in secretions on mucosal surfaces, resulting in deficient mucosal immunity.
II. Failure to produce adequate amounts of IgA at the mucosal surface occurs because of a mutation of the gene encoding the immunoglobulin alpha chain.
III. Mode of inheritance is unknown.

Clinical Signs

I. Affected animals have normal IgG and IgM concentrations but have increased incidence of chronic respiratory and skin infections.
II. High incidence of atopy occurs in affected Chinese sharpeis.
III. Recurrent small intestinal diarrhea occurs in German shepherd dogs.
IV. Condition is known to occur in the beagle, Chinese sharpei, and German shepherd dog.

Diagnosis

I. Diagnosis is made by measuring immunoglobulin concentrations in serum or intestinal secretions using radial immunodiffusion.
II. Serum IgA concentrations are normal to decreased compared with normal dogs, whereas IgM and IgG concentrations are normal.
III. Depending on the breed, local IgA concentration at the mucosal surface may also be decreased.

Treatment and Monitoring

I. Treatment is symptomatic and aimed at controlling infections with appropriate antibiotic therapy.
II. No specific treatment is available.
III. Prognosis is generally good.

Growth Hormone Deficiency

Definition and Causes

I. Growth hormone (GH) deficiency is an immunodeficiency syndrome documented in dwarf weimaraners (Roth et al., 1980).
II. Congenital GH deficiency results in thymic dysgenesis and lymphocyte depletion.

Pathophysiology

I. Lack of GH results in failure of thymic development and impairment of cell-mediated immunity.
II. Lack of thymosin, normally produced by the thymic epithelium, causes failure of T-cell differentiation.
III. GH deficiency in the Weimaraner is associated with a small thymus and depletion of lymphocytes in the thymic-dependent portions of lymphoid organs.

Clinical Signs

I. Pups look normal at birth, but fail to thrive; they develop severe, recurrent respiratory and skin infections.
II. Condition is characterized by stunted growth, unthriftiness, and persistent infections.
III. Affected animals die within weeks to months after birth.

Diagnosis

I. Diagnosis is made by finding low-serum GH concentrations and thymic depletion.
II. Classic clinical signs of wasting in a young Weimaraner are supportive of the diagnosis.

Treatment and Monitoring

I. Pups respond to thymosin fraction 5 therapy (1 mg/kg SC SID for 7 days) with improved growth and lymphocyte function (GH appears to increase thymosin fraction 5 production).
II. Experimentally, administration of thymosin fraction 5 or bovine GH resolves clinical signs.
III. Without treatment the prognosis is grave.

ACQUIRED IMMUNODEFICIENCIES

Definition

I. In small animals, acquired disorders are more common than congenital disorders.
II. Acquired disorders may involve nonspecific or specific components of the immune system.

Causes and Pathophysiology

I. Disorders of nonspecific immunity
  A. Diabetes mellitus (DM) is associated with defects in phagocytosis, bacterial killing, and reduced levels of complement.
  B. Hyperadrenocorticism suppresses the immune system in several ways.
    1. Hyperadrenocorticism is associated with decreased complement levels.
    2. Decreased skin thickness and delayed wound healing may also occur.
    3. Neutrophils in animals with hyperadrenocorticism exhibit impaired phagocytosis.
    4. Decreased production of leukotrienes and prostaglandins (critical to the inflammatory response) also occurs.
  C. Hypothyroidism is associated with decreased neutrophil function, decreased sebum production, and keratinization alterations that reduce the barrier function of the skin.
II. Disorders of specific immunity
  A. Hyperadrenocorticism results in decreased lymphocyte function from hypercortisolemia; reduced antibody concentrations have also been documented in some animals.
  B. Systemic infections suppress the immune system in a variety of ways.
    1. Canine distemper virus causes direct cell (lymphocyte) lysis.
    2. Feline leukemia virus infections result in certain cellular dysfunctions.
    3. Viral products may be immunosuppressive (e.g., p15e from feline leukemia virus).
    4. Immune complex formation (blocking of normal immune responses) occurs with feline infectious peritonitis.
    5. Immunosuppression caused by bacterial infections is poorly understood.
  C. Failure of passive transfer results in reduced immunity in neonates.
    1. Most (90% to 95%) of the immunity transferred from the mother to the offspring is via the colostrum in dogs and cats.
    2. Failure of passive transfer seems to have little clinical effect in puppies and kittens as long as cleanliness is maintained.
  D. Neoplasia may be associated with immunosuppression.
    1. Immunosuppression is primarily associated with lymphoreticular malignancies in small animals.

2. With multiple myeloma, the incidence of fatal infections is very high.
3. Primary defect with other tumors is in cell-mediated immunity.
4. Altered immunity may be both a cause and an effect of neoplasia.
5. Tumor-associated immune complexes may "block" immune cells from performing their normal functions.
6. Tumor cells may secrete soluble suppressive factors that have yet to be identified.

Diagnosis

I. The diagnosis of secondary immunodeficiencies is approached by selecting tests that identify an underlying disease such as DM or hyperadrenocorticism.
   A. Hyperglycemia and glucosuria are noted with DM (see Chapter 44).
   B. An exaggerated response to adrenocorticotropic hormone or inappropriate suppression after dexamethasone administration is seen with hyperadrenocorticism (see Chapter 45).
   C. Low serum thyroxine concentration with high endogenous thyroid-stimulating hormone concentration is diagnostic for hypothyroidism (see Chapter 42).

II. Feline leukemia virus and feline immunodeficiency virus testing is warranted in all cats with increased incidence of infections.

III. Physical examination, radiography, and ultrasonography are all important in identifying cancer.

Treatment and Monitoring

I. Treatment is specific for the underlying disease.

II. Adequate control of the underlying disease often results in resolution of the immunodeficiency.

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CHAPTER 76

Immune-Mediated Diseases

Ellen Miller

GENERAL INFORMATION

I. Immune-mediated diseases are associated with all of the classic hypersensitivity reactions.
II. Allergic diseases of the skin (e.g., atopy, food allergy), respiratory tract (e.g., asthma in cats, bronchitis in dogs), and gastrointestinal (GI) tract (e.g., anaphylactic shock) are all immune-mediated diseases caused by a type I reactions.
III. Type II reactions are responsible for immune-mediated hemolytic anemia (IMHA) (see Chapter 64), immune-mediated thrombocytopenia (ITP) (see Chapter 67), and some of the autoimmune skin diseases (see Chapter 91).
IV. A type III reaction is responsible for systemic lupus erythematosus (SLE) and vasculitis.
V. Type IV reaction causes contact dermatitis.

ANAPHYLAXIS

Definition

I. Anaphylaxis is a severe, life-threatening, systemic manifestation of a type I hypersensitivity reaction.
   A. It occurs immediately after exposure to antigen in a sensitized animal.
   B. Mast cell- and basophil-bound immunoglobulin (Ig) E binds antigen, causing release of chemical mediators such as histamine, leukotrienes, and prostaglandins.
   C. With massive mediator release, anaphylactic shock occurs.
II. Anaphylactoid reactions are clinically similar to anaphylaxis; however, complement components (not IgE) mediate them.
III. Anaphylaxis is rare in dogs and cats.

Causes

I. Many antigens can cause anaphylactic reactions.
   A. Venoms from insects: bees, wasps, hornets, ants
   B. Drugs: antibiotics, L-asparaginase, vitamin K, IV radiopaque dyes, nonsteroidal antiinflammatory drugs, local anesthetics
   C. Vaccines: leptospiral bacterin
   D. Blood and plasma products
II. Usually the antigen is introduced parenterally.

Pathophysiology

I. After initial exposure to antigen, susceptible individuals produce IgE antibody.
II. IgE binds to receptors on mast cells and basophils.
III. Cross-linking of IgE by antigen binding results in cellular activation, degranulation, and release of chemical mediators.
   A. Primary granules contain preformed mediators such as histamine, heparin, eosinophil chemotactic factor, and proteases.
   B. Secondary mediators intensify and prolong the anaphylactic reaction.
      1. Secondary mediators are not preformed.
      2. These mediators are products of arachidonic acid metabolism and are of the prostaglandin and leukotriene families.
IV. Vasodilatation, increased vascular permeability, bronchoconstriction, platelet aggregation, pulmonary vasoconstriction, increased airway mucus, and cardiac depression occur.
V. Cardiovascular shock ensues, with the severity dependent on the antigen type, antigen amount, and route of exposure.

Clinical Signs

I. Signs of systemic anaphylaxis vary with the species.
II. The liver is the shock organ in the dog.
   A. Vomiting, diarrhea, and urination occur and progress to respiratory distress, collapse, and death if not treated.
   B. Postmortem findings include hepatic and GI venous engorgement and portal hypertension.
III. The respiratory and GI tracts are the shock organs in the cat.
   A. Anaphylactic reactions start with facial pruritus followed by dyspnea, salivation, vomiting, and diarrhea.
   B. Pathologic findings include bronchoconstriction, emphysema, pulmonary hemorrhage, and edema of the larynx.

Diagnosis

I. Diagnosis is based largely on history and physical examination.
II. Specific diagnostics are not available for systemic anaphylaxis.
III. Retesting the animal with the antigen is unwise.

Treatment

I. Treatment of systemic anaphylaxis depends on the organ system affected.
II. If the animal is dyspneic, establish an airway and administer oxygen.
  A. Insert an endotracheal tube or perform a tracheostomy.
  B. Administer bronchodilators.
III. Treat any hypotension aggressively.
  A. Place at least one large-bore IV catheter and administer isotonic crystalloid solutions at 50 to 150 mL/kg IV over several hours.
  B. If hypotension persists, administer epinephrine diluted to 0.1 mg/mL (1:10,000) at a dose of 0.05 to 0.1 mL/kg IV (maximum of 2.0 mL/dose).
  C. Consider giving dobutamine as a constant-rate infusion (2 to 5 μg/kg/minute IV) to maintain vascular pressure.
IV. Counteract chemical mediators with dexamethasone 1 to 2 mg/kg IV or prednisolone sodium succinate 10 to 25 mg/kg IV.
V. Administer atropine at 0.02 to 0.04 mg/kg IV, IM, if the animal is bradycardic.

Monitoring of Animal

I. Animals with systemic anaphylaxis should be monitored in the hospital for at least 24 hours.
II. Monitors systemic blood pressure, heart rate, hematocrit, blood glucose, and activated clotting times.
III. The animal can be discharged when it is stable (hemodynamically and clinically) and has been weaned off all fluid therapy.

URTICARIA AND ANGIONEUROTIC EDEMA

Definition

I. Urticaria (hives) is an acute, localized type I hypersensitivity reaction associated with pruritus.
II. Angioedema is similar to urticaria but involves the deeper subcutaneous tissues around the head and extremities, without producing pain or pruritus.

Causes

I. These disorders are caused by a type I hypersensitivity reaction.
II. Food or inhaled allergens, as well as parenterally administered antigens, can cause urticaria.
III. Nonimmunological causes include agents (e.g., cold, heat, pressure) that induce histamine release or activate complement.

Pathophysiology

I. Mechanisms are similar to those described previously under Anaphylaxis.
II. Wheal formation is caused by extravasation of fluid from vasodilation of capillaries.

Clinical Signs

I. Localized or generalized subdermal wheals
II. Swelling and edema of tissues of the head or extremities
III. Variable pruritus or self-mutilation
IV. Possible inspiratory stridor from laryngeal edema

Diagnosis

I. Diagnosis is usually based on history and physical examination findings.
II. Localized anaphylactic reactions are usually confirmed by intradermal skin testing or enzyme-linked immunosorbent assays for canine IgE.

Treatment

I. Treatment of localized anaphylaxis is less critical than systemic anaphylaxis.
II. Causative agent is removed, if possible.
III. Many cases resolve spontaneously without treatment.
IV. Antihistamines are administered, such as diphenhydramine 1 to 2 mg/kg IV, IM.
V. Prednisone (1 to 2 mg/kg PO SID to BID) beginning 12 to 24 hours after the reaction (with a rapid tapering dose) reduces delayed effects.

Monitoring of Animal

I. For animals with localized reactions, contact owners by phone SID for a few days to ensure that clinical signs have abated.
II. Avoid exposure to antigen in the future.

DRUG ALLERGY

Definition

I. Drug allergy is an immune-mediated hypersensitivity reaction caused by production of antidrug antibodies.
II. Sensitized T lymphocytes may also be produced and directed against a drug or its metabolites.

Causes

I. Large proteins contained in serum, vaccines, and biological extracts may be antigenic and cause allergic reactions.
II. Most drugs are not large enough in size to be allergenic but can act as haptens that covalently bind to larger host proteins, thereby causing a reaction.
III. The following drugs have been associated with allergic reactions:
  A. Sulfonamides
  B. Penicillins
  C. Cephalosporins
  D. Propylthiouracil
  E. Levamisole
  F. Gold salts
  G. L-asparaginase
  H. Doxorubicin
  I. Tetracyclines
  J. Methimazole
  K. Vaccines

IV. Some drugs of similar structure may cause cross-sensitivity, such as penicillin and cephalosporin.
V. Drug dose, duration of treatment, route of administration, and drug formulation affect the allergic reaction.
VI. Genetic factors may influence individual susceptibility, as in Doberman pinschers, in which sulfonamide reactions are common.

Pathophysiology

I. All four types of hypersensitivity reactions are implicated in drug reactions.
   A. In a type I reaction, the drug carrier binds to an IgE molecule, causing degranulation of mast cells and basophils.
   B. In a type II reaction, the antidrug antibody is IgG or IgM, which activates complement and causes cell lysis.
   C. In a type III reaction, the circulating drug carrier–antibody complexes are trapped in vascular endothelium, resulting in a neutrophilic inflammatory response.
   D. Tissue-fixed, drug-carrier complexes attract T lymphocytes, which release lymphokines and cause an inflammatory response.
II. Certain drug allergies may be manifestations of multiple hypersensitivity reactions.

Clinical Signs

I. Drug reactions occur only after an initial sensitization period of 5 or more days.
II. These reactions are seen in a small percentage of the population.
III. Reactions often mimic other immune-mediated diseases, such as IMHA, ITP, polyarthritis, and vasculitis.
IV. Clinical signs subside within days of discontinuing the drug.
V. Clinical signs recur with readministration of the drug.
VI. Specific clinical signs include the following:
   A. Fever
   B. Cutaneous manifestations (see Chapters 85 and 91)
      1. Urticaria
      2. Pruritus
      3. Erythema multiforme
      4. Allergic contact dermatitis
      5. Toxic epidermal necrolysis
   C. Polyarthritis
   D. Polymyositis
   E. Ataxia
   F. Glomerulonephritis
   G. Hematological manifestations: hemolytic anemia, thrombocytopenia, leukopenia, lymphadenopathy

Diagnosis

I. The diagnosis is usually made by taking a detailed history and finding the classic clinical signs (discussed previously).
II. Laboratory tests may reveal nonspecific, but suggestive, results.
   A. Rarely, a Coombs' test, antinuclear antibody (ANA) test, or rheumatoid factor test may be positive.
   B. Suppurative, nonseptic inflammation is found on cytology of joint fluid in cases of polyarthritis.
   C. Proteinuria and a urine protein:creatinine ratio >1.0 are noted with glomerulonephropathy.
   D. Immunoglobulin (immune complex) deposits may be identified with histopathology and immunohistochemistry or by immunofluorescence staining of affected tissues.
III. Drug challenge studies are not usually recommended.

Differential Diagnosis

I. Autoimmune disorders, such as SLE, IMHA, ITP, and immune-mediated polyarthritis, can have similar signs.
II. Infectious diseases, such as bacterial endocarditis, bacteremia, septic arthritis, fungal infections, and rickettsial diseases, are other considerations.

Treatment and Monitoring

I. Key treatment is drug withdrawal.
II. Administer antihistamines, epinephrine, IV fluids, and corticosteroids if the reaction is severe (see Anaphylaxis).
III. Blood transfusions or purified hemoglobin *(Oxyglobin)* therapy are occasionally necessary for IMHA and ITP (see Chapter 71).
IV. Prognosis is generally good for complete recovery.
V. Avoidance of the inciting drug and any cross-reacting drugs is imperative.

SYSTEMIC LUPUS ERYTHEMATOSUS

Definition

I. SLE is a multisystemic autoimmune disorder that may affect the joints, skin, kidneys, platelets, or erythrocytes.
II. Those most affected are young to middle-aged animals.
   A. No male or female predisposition exists.
   B. Many breeds can be affected, although German shepherd dogs are overrepresented.

Causes and Pathophysiology

I. Type III hypersensitivity reaction is responsible for the tissue damage.
   A. Autoantibodies in SLE are directed against intranuclear, intracytoplasmic, and cell surface antigens.
   B. Autoantibodies and self-antigens form immune complexes.
      1. Pathogenic immune complexes are formed in slight antigen excess and are medium-sized, soluble, and not readily phagocytosed.
      2. These immune complexes get trapped in the blood vessels of tissues with high circulatory volume, such as synovium and kidneys.
      3. When trapped, immune complexes attract neutrophils and platelets and fix complement.
II. Neutrophil lysosomal enzymes and complement products damage affected tissues.

Clinical Signs

I. The history is usually a chronic, progressive one of weight loss, anorexia, lameness, and dermatitis.

II. Physical examination findings are dependent on the systems affected.
  A. Skin lesions are variable and occur in one third of affected dogs (see Chapter 91).
    1. These include maculopapular, purpuric, vesiculobullous, or seborrheic eruptions.
    2. Patchy alopecia is also seen.
  B. Distal polyarthritis causing joint effusion, pain, and lameness is found in about two thirds of dogs with SLE (Grindem and Johnson, 1983).
  C. Other findings include muscle wasting, emaciation, and pale mucous membranes, with or without petechiation.

Diagnosis

I. Routine laboratory data may support a diagnosis of SLE.
  A. Complete blood count may show a nonregenerative anemia of chronic disease, a regenerative IMHA, an inflammatory leukogram, and possibly thrombocytopenia.
  B. A serum chemistry panel usually shows hyperglobulinemia and less commonly reveals an azotemia.
  C. Urinalysis indicates proteinuria approximately 50% of the time (Grindem and Johnson, 1983).
II. Specific tests for SLE include the ANA test and the lupus erythematosus (LE) clot test (Grindem and Johnson, 1983).
  A. ANA is the most sensitive and reliable test and is positive in 60% to 100% of dogs with SLE.
  B. LE clot test is positive in 60% to 80% of dogs with SLE.
  C. Coombs' test can be positive with IMHA, which occurs in about one third of affected dogs.
III. Biopsies of affected tissues may show classic histological lesions, including glomerular lesions, vasculitis, thrombosis, and dermatitis with pustule formation.
  A. Direct immunofluorescence techniques and immunohistochemistry techniques can localize the presence of immune complexes in specific tissues.
  B. Classically, skin biopsies show immunoglobulin deposition at the dermal–epidermal junction.
IV. Diagnosis of SLE in dogs must include at least one class I criterion and two or more class II criteria; drug-induced and infectious diseases must also be ruled out (Grindem and Johnson, 1983).
  A. Class I criteria include a positive ANA test or LE clot test.
  B. Class II criteria include clinical findings of polyarthritis, protein-losing nephropathy, hemolytic anemia, alopecia and dermatitis, or thrombocytopenia.

Differential Diagnosis

I. Because SLE is an immune-complex disease, other disorders that result in immune complex production can cause similar signs.
  A. Systemic bacterial infections, such as bacteremia, bacterial endocarditis, sepsis, and septic arthritis, can all mimic SLE.
  B. Systemic fungal infections are often chronic and can induce immune complex formation, resulting in polyarthritis, glomerulonephritis, and anemia.
  C. Neoplastic antigens may also form immune complexes and result in similar findings.
  D. Drug and vaccine reactions may mimic SLE.
II. Infectious and neoplastic diseases must be adequately ruled out because immunosuppression can be lethal to afflicted animals.

TABLE 76-1

Protocol for Reduction of Immunosuppressive Drugs in Animals with Systemic Lupus Erythematosus*

DAY	PREDNISONE/PREDNISOLONE DOSE	AZATHIOPRINE DOSE
1 to 7	2 mg/kg PO BID	1 mg/kg PO SID
8 to 28	2 mg/kg PO SID	1 mg/kg PO QOD
29 to 50	1 mg/kg PO SID	Same
51 to 72	0.5 mg/kg PO SID	Same
73 to 94	0.25 mg/kg PO SID	Same
95 to 116	0.25 mg/kg PO QOD	Same (given QOD with prednisone)
>117	0.25 mg/kg PO QOD	Discontinue

*Recheck the animal at every decrease in dose and continue if no signs recur.

Treatment

I. Prednisone or prednisolone 1 to 2 mg/kg PO BID is the mainstay of therapy.
II. A cytotoxic drug, such as azathioprine at 2 mg/kg PO SID for 7 days then QOD, can be used in combination with immunosuppressive doses of prednisone.

Monitoring of Animal

I. Examine the animal every 3 to 4 weeks (more frequently if not responding well to therapy or experiencing severe side effects from the drugs).
II. Decrease the dose of prednisone gradually once the animal is in remission (Table 76-1).
  A. Monitor for improvement in red blood cell count, platelet count, hyperglobulinemia, and proteinuria.
  B. Relapses may occur that require increased doses of prednisone and the addition of other immunosuppressive drugs.
III. Long-term prognosis is guarded because the disease is often refractory to treatment and can be progressively more difficult to control.

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CHAPTER 77

Immunoproliferative Disorders

Bradley R. Schmidt

REACTIVE CONDITIONS

General Considerations

Definition

I. Appropriate or inappropriate benign expansion of cells of the immune system
II. Result from exposure to an exogenous or endogenous antigen

Causes

I. Infectious diseases: bacterial, viral, fungal, rickettsial, parasitic, protozoal
II. Allergic disease
III. Autoimmune disease
IV. Reactive histiocytosis
V. Nonimmunoproliferative or nonlymphoid neoplasms

Pathophysiology

I. Reactive conditions result from polyclonal immune cell proliferation.
II. Reactive conditions generally resolve when the inciting cause is identified and removed.

Clinical Signs

I. Clinical signs are usually nonspecific and result from the primary disease process.
II. Signs may include the following:
   A. Lethargy, anorexia, fever
   B. Lymphadenomegaly, splenomegaly
   C. Uveitis
   D. Central nervous system signs
   E. Cutaneous lesions: inflammatory lesions, petechial hemorrhages, plaques, edema

Diagnosis

I. Complete blood count (CBC), serum biochemistry, and urinalysis results are variable and dependent on the underlying cause.
   A. Red blood cell indices may reveal the following:
      1. Anemia of chronic disease: normocytic, normochromic, nonregenerative
      2. Regenerative anemia associated with hemolysis, possible agglutination or spherocytes with immune-mediated hemolysis
      3. Blood loss anemia
      4. May be normal
   B. White blood cells and platelets may be normal, increased, or decreased.
   C. Hyperglobulinemia (when present) is generally polyclonal but may be monoclonal in certain disease processes (e.g., ehrlichiosis, leishmaniasis, feline infectious peritonitis).
   D. Urinalysis may reveal proteinuria secondary to glomerular disease.
II. Needle biopsy or histopathology of lymph nodes or other organs often reveals a benign proliferation of lymphocytes, plasma cells, and other inflammatory cells.
III. Occasionally, specific pathologic processes (e.g., blood parasites, fungal organisms, neoplastic processes) may be identified in aspirates or on histopathology.
IV. Additional diagnostic tests such as flow cytometery and immunohistochemistry are helpful to distinguish between benign and malignant proliferative diseases.

Differential Diagnosis

I. All causes listed previously
II. Neoplastic processes: lymphoma or multiple myeloma

Canine Reactive Histiocytic Diseases

Definition

I. Conditions include cutaneous histiocytosis (CH) and systemic histiocytosis (SH), which are charaterized by benign, reactive, nonneoplastic proliferation of histiocytes.
II. CH is a benign, nodular proliferation of histiocytes within the skin and subcutis, with no systemic involvement.
III. SH is a benign proliferation of histiocytes in multiple organs, such as skin, lymphoid organs, bone marrow, spleen, nasal cavity, eyelids, sclera, lungs, and liver.

Causes

I. They arise from reactive histiocytic proliferation of interstitial histiocytic cells.
II. SH may be inherited in Bernese mountain dogs.

III. Clinical behavior and response to immunosuppressive agents support a dysregulated immune interaction between dendritic cells and T cells.
IV. An immune response to antigens may initiate the process (Moore and Affolter et al., 2005).

Pathophysiology

I. CH results in multiple cutaneous and subcutaneous lesions that may ulcerate and become infected.
   A. The Bernese mountain dog, beagle, collie, golden retriever, and German shepherd dog may be overrepresented.
   B. CH often occurs in younger dogs.
II. In addition to cutaneous lesions, SH may cause organ dysfunction from cellular infiltration and may progress to a hemophagocytic syndrome resulting in blood cytopenias.
   A. SH primarily affects Bernese mountain dogs but can occur in other breeds.
   B. Generally, SH affects young to middle-aged (2 to 8 years) male dogs, but females may also be affected.

Clinical Signs

I. With CH, multiple cutaneous and subcutaneous nodules occur predominantly on the head, neck, perineum, scrotum, and extremities.
   A. Ulcerations of the skin and secondary sepsis may develop.
   B. Regional lymph nodes may be involved.
   C. Lesions are not epidermotropic, which helps distinguish CH from cutaneous histiocytomas.
II. Multiple cutaneous plaques or nodules similar to CH also occur with SH, but other organ systems are generally involved, such as lymph nodes, eyes, and nasal mucosa.
III. Clinical signs for CH and SH may spontaneously wax and wane; however, the disorders are usually progressive unless therapy is instituted.

Diagnosis

I. Histopathology reveals a reactive process consisting of diffuse infiltration of histiocytic cells and a mixed population of neutrophils and lymphocytes.
   A. Minimal or no atypia is seen in CH.
   B. Mild atypia may be seen in SH.
II. Immunohistochemical stains are useful in confirming histiocytic origin and distinguishing these conditions from histiocytoma, histiocytic sarcoma (HS), and malignant histiocytosis (MH) (Moore and Alfolter, 2005).
III. Because CH and SH are clinically similar, additional diagnostics tests (abdominal ultrasonography, thoracic radiography, lymph node aspiration and biopsy, bone marrow aspiration) are needed to identify systemic involvement.
IV. Results of routine laboratory tests are variable, depending on the organs involved.
   A. CBCs and biochemistry profiles are usually normal with CH.
   B. Anemia, leukopenia, or thrombocytopenia may be seen secondary to hemophagocytic syndrome associated with SH.
V. Underlying infectious processes, such as fungal infections, must also be investigated.

Differential Diagnosis

I. Neoplasia
   A. Histiocytic tumors: cutaneous histiocytoma, HS, MH
   B. Other discrete round-cell tumors: lymphosarcoma, mast cell tumors
II. Fungal or atypical infections: ruled out with special stains
III. Idiopathic sterile nodular panniculitis
IV. Nodular granulomatous episcleritis and other causes of uveitis (see Chapters 98 and 99)

Treatment

I. Spontaneous remissions have been reported in a few animals with CH, but relapses are common and immunosuppressive therapy is generally required.
   A. Prednisone 1 to 2 mg/kg PO BID may be effective in some dogs.
      1. Continue at this dosage until remission, then taper.
      2. Long-term maintenance therapy with low-dose prednisone may be required.
   B. Other animals require additional therapy with azathioprine 2 mg/kg PO SID or cyclosporine 5 mg/kg PO SID to BID, with doses tapered as lesions resolve.
   C. Leflunomide may be considered at 2 to 4 mg/kg PO SID, with desired trough plasma levels of 20 μg/mL (Cannon et al., 2000).
   D. Combination of tetracycline and niacinamide (250 to 500 mg of each PO TID) may be useful as maintenance therapy once remission is obtained (Rosychuck, 2002).
II. SH is often poorly responsive to immunosuppressive therapy; however, corticosteroids, azathioprine, cyclosporine, and leflunomide may be tried.

Monitoring of Animal

I. Prognosis is guarded to fair for dogs with CH.
II. Although the clinical course of SH frequently waxes and wanes, the prognosis is poor for most dogs because of the overall progressive course and the chronic debilitating nature of the disease.
III. Monitor CBCs and biochemistry profiles for abnormalities secondary to the disease and/or immunosuppressive therapy.
IV. Monitoring blood levels of cyclosporine or leflunomide is recommended.

NEOPLASIA

Histiocytoma and Langerhans Cell Histiocytosis

Definition and Cause

I. Cutaneous histiocytoma is a benign proliferation of Langerhans cells.
II. Langerhans cell histiocytosis (LCH) is a rare condition that histologically resembles histiocytoma but has a more aggressive behavior.

III. In cats, feline progressive histiocytosis is rare and resembles LCH.
IV. The cause of these conditions is unknown.

Pathophysiology

I. Histiocytoma generally affects younger dogs but may occur in older dogs.
   A. It is usually a solitary cutaneous lesion, but multiple lesions are possible.
   B. Histiocytomas generally undergo spontaneous regression; however, metastasis to lymph nodes and lungs occurs rarely.
II. Cutaneous lesions in LCH may be confluent, and the condition usually progresses rapidly with metastasis.
III. Cats with progressive histiocytosis are middle-aged or older, and the disease is often progressive, with metastasis to internal organs.

Clinical Signs

I. Dogs usually have a solitary cutaneous nodule.
   A. Nodules are pink and hairless.
   B. Nodules are round, smooth, and possibly ulcerated.
   C. Multiple lesions are possible.
II. Cats have solitary to multiple cutaneous nodules that may be ulcerated.
III. Lymphadenomegaly and systemic clinical signs are only associated with the rare metastatic forms of this disease complex.

Diagnosis

I. Histologically, large histiocytes are accompanied by lymphocytes, neutrophils, and other inflammatory cells.
II. Epidermotropism and epidermal invasion are not features of CH and may aid in the diagnosis.
III. Immunohistochemical stains are useful in distinguishing histiocytoma from lymphoma, CH, and SH (Moore and Affolter, 2005).

Differential Diagnosis

I. Other round-cell tumors: lymphoma, mast cell tumors, plasmacytoma
II. Other histiocytic diseases
III. Xanthomas in cats

Treatment

I. In young dogs, histiocytomas generally regress spontaneously.
   A. Immunosuppressive agents may interfere with regression and are avoided.
   B. Surgical removal may be considered in cases in which lesions become traumatized or fail to regress.
   C. Many lesions, particularly nonregressing or nonresectable lesions in older dogs, respond to cryotherapy.
II. Treatment for metastatic lesions has not been reported.
III. No successful treatment has been reported for feline progressive histiocytosis.

Monitoring of Animal

I. Prognosis is good for most dogs with histiocytoma.
II. Prognosis is guarded to poor for dogs with metastatic histiocytoma or LCH.
III. Prognosis is poor for cats with progressive histiocytosis.

Malignant Histiocytosis and Histiocytic Sarcoma

Definition and Cause

I. MH is a systemic proliferation of malignant histiocytes, with rapid infiltration of multiple organs.
II. HS is a histiocytic neoplasm originating from a single site; when metastasis occurs, the disease is termed *disseminated HS*.
III. MH and disseminated HS are similar and may be difficult to differentiate.
IV. Both conditions usually affect Bernese mountain dogs, but can occur in other breeds, such as the rottweiler, flat-coated retriever, and golden retriever.
V. Male dogs are more commonly affected.
VI. Cause of this condition is unknown; however, it may have a polygenic mode of inheritance in the Bernese mountain dog.
VII. These conditions have been reported rarely in cats.

Pathophysiology

I. Proliferation of malignant histiocytes occurs in the periarticular tissues, spleen, liver, skin, lymph nodes, lung, and bone marrow of affected dogs.
II. Other organs may be affected, such as bones and the nervous system.
III. Infiltration with malignant histiocytes causes organomegaly and possible dysfunction.

Clinical Signs

I. Anorexia, depression, lethargy, fever, and cachexia are commonly seen.
II. Lymphadenomegaly and hepatosplenomegaly may be recognized on physical examination.
III. Other signs related to multiorgan infiltration may also occur.

Diagnosis

I. Histologically, a diffuse infiltration of malignant histiocytic cells occurs in multiple organs with phagocytosis of erythrocytes and leukocytes.
II. Immunohistochemistry stains may help to differentiate these disorders from SH, CH, and other tumors, such as lymphoma, mast cell tumors, and sarcomas.
III. CBC and serum biochemistry results are variable and often include anemia, thrombocytopenia, hypoalbuminemia, and elevated liver enzymes.
IV. Bone marrow aspiration may reveal histiocytic infiltration and erythrophagocytosis.
V. Radiography and ultrasonography may reveal lymphadenopathy, pulmonary masses, splenomegaly, and hepatomegaly.
VI. Hyperferritinemia occurs in malignant histiocytosis.

Differential Diagnosis

I. Large-cell lymphoma and other histiocytic diseases are the major differential considerations.
II. Differential diagnoses for pulmonary lesions include a primary lung tumor and granulomatous pulmonary disease.

Treatment

I. Surgery alone or combined with radiation therapy may be curative for localized HS.
II. In dogs with MH and disseminated HS, doxorubicin-based chemotherapy (liposomal doxorubicin) or CCNU (lomustine) may induce short-term responses.

Monitoring of Animal

I. Prognosis is guarded to favorable for dogs with localized HS.
II. Prognosis is generally poor in both dogs and cats with MH or disseminated HS.

Multiple Myeloma and Waldenström's Macroglobulinemia

Definition and Causes

I. *Multiple myeloma* and *Waldenström's macroglobulinemia* are defined as systemic neoplastic proliferation B cells in bone marrow or other organs, with high levels of a myeloma (M) protein in the bloodstream.
II. In dogs with multiple myeloma, the M protein is usually immunoglobulin (Ig) G or IgA, and cells typically range from poorly to well-differentiated plasma cells.
III. In cats with multiple myeloma, the M protein is typically IgG.
IV. Primary macroglobulinemia (Waldenström's macroglobulinemia) is a neoplastic proliferation of immune cells with excessive production of IgM.
    A. Cells do not have the typical plasmacytoid features and are more similar to the cells of small, lymphocytic lymphoma of the intermediate type.
    B. Skeletal lesions are rare.

Pathophysiology

I. Increased production of immunoglobulins may lead to the following:
    A. Bleeding diatheses secondary to decreased platelet aggregation and adhesiveness, and possible prolongation of thrombin and partial thromboplastin times
    B. Hyperviscosity syndrome secondary to increased production of IgM, IgA, or IgG
    C. Renal failure secondary to immunoglobulin light chains (Bence Jones proteinuria)
    D. Amyloidosis
    E. Cryoglobulinemia
II. Bone marrow infiltration may cause anemia, leukopenia, and thrombocytopenia.
III. Plasma cell dysfunction leads to immunodeficiency and increased susceptibility to infection.
IV. Hypercalcemia may arise from increased osteoclast activating factor secreted by the neoplastic plasma cells.
V. Bone infiltration can cause pathologic fractures, neurological signs, and bone pain.
    A. Most common bones involved are the vertebrae, long bones, ribs, and pelvis.
    B. Osteolysis is uncommon in primary macroglobulinemia and is less common in cats.

Clinical Signs

I. Vague clinical signs (anorexia and lethargy) may be seen.
II. Hepatosplenomegaly is a common finding in dogs and cats.
III. Renomegaly and lymphadenopathy are also reported in the cat (Patel et al., 2005).
IV. Skeletal pain may be a presenting sign.
V. Neurological signs may arise secondary to vertebral masses, primary neoplastic infiltration, or hyperviscosity syndrome; signs may include vision loss.
VI. Polyuria and polydipsia may occur secondary to renal dysfunction, hyperviscosity syndrome, or hypercalcemia.
VII. Bleeding tendencies, such as petechiation and ecchymoses may be noted.
VIII. Cardiac murmurs and arrhythmias occur from increased cardiac workload and myocardial hypoxia.
IX. Pyothorax, ascites, and peritonitis have been found in some affected cats (Patel et al., 2005).

Diagnosis

I. CBC
    A. It may be normal.
    B. Mild normochromic, normocytic anemia is usually present.
    C. Leukopenia secondary to bone marrow infiltration may be detected.
    D. Thrombocytopenia is variable (mild to marked).
II. Serum biochemistry profile
    A. Marked elevation in serum globulins (>9 g/dL) is typical.
        1. Total serum protein may be normal if there is a concurrent decrease in serum albumin or protein loss through the kidneys.
        2. Serum viscosity is generally >7 relative to water.
    B. Hypercalcemia is seen in 5% to 20% of affected dogs and cats (Hammer and Couto, 1994; Patel et al., 2005).
    C. Azotemia secondary to renal failure may be present.
    D. Increased liver enzymes are seen with hepatic infiltration.
III. Urinalysis
    A. Heat precipitation and electrophoresis of urine are performed to identify light chains (Bence Jones proteins).
    B. Standard urine dipsticks are not capable of this determination.
IV. Serum protein electrophoresis (to characterize hyperglobulinemia)
    A. Monoclonal gammopathy is a common finding.
    B. Biclonal gammopathy may occur in both dogs and cats (Peterson and Meininger, 1997; Patel et al., 2005).

C. In rare cases, excessive globulins are not produced (MacEwen et al., 1984; Marks et al., 1995).

V. Bone marrow evaluation: critical in diagnosis of multiple myeloma
   A. Plasma cell population greatly exceeds 20% of nucleated cells in both dogs and cats with multiple myeloma.
   B. Because the malignant plasma cells may be morphologically normal, a bone marrow core biopsy is helpful to identify clusters of plasma cells (consistent with malignancy) versus diffuse plasma cell infiltrates (suggestive of a reactive process, such as a rickettsial disease).
   C. Plasma cell atypia is supportive in cases with plasma cell counts less <20%.
   D. Decreased numbers of erythroid and myeloid cells may be present.

VI. Survey of skeletal radiographs
   A. Up to two thirds of dogs have osteolytic skeletal lesions in the vertebrae, long bones, ribs, or pelvis (Hammer and Couto, 1994).
   B. Bone scintigraphy may not be a sensitive test in these lesions.
   C. Bony lesions are not as common in dogs with primary macroglobulinemia or in cats.

VII. Cats: most feline leukemia negative

Differential Diagnosis

I. Diagnosis of multiple myeloma requires at least two of the following:
   A. Bone marrow infiltration with plasma cells
   B. Osteolytic bone lesions
   C. Monoclonal gammopathy
   D. Bence Jones proteinuria
   E. Visceral organ infiltration and plasma cell atypia in cats

II. If the previous criteria are not met, consider the following:
   A. Extramedullary plasmacytoma
   B. Other causes of monoclonal gammopathy: ehrlichiosis, leishmaniasis, feline infectious peritonitis, amyloidosis, B-cell lymphoma
   C. For osteolytic lesions: primary bone tumors, osteomyelitis
   D. For hyperglobulinemia: other causes of chronic antigenic stimulation (usually polyclonal)

Treatment

I. Goals of therapy are to ameliorate clinical signs, to reduce serum globulin levels and Bence Jones proteinuria by 50%, and to stabilize osteolytic lesions.

II. Melphalan and prednisone are recommended for dogs and cats with multiple myeloma.
   A. Melphalan is started at 0.1 mg/kg PO SID for 10 days, followed by 0.05 mg/kg PO SID continuously.
   B. Prednisone is given at 0.5 mg/kg PO SID for 10 days, followed by 0.5 mg/kg PO QOD.

III. Doxorubicin, cyclophosphamide, and vincristine in combination or as single agents have been used; however, they are not consistently more effective than melphalan and prednisone (Kisseberth et al., 1995).

IV. Ancillary therapy may be considered.
   A. Palliative radiation therapy may help alleviate bone pain and spinal cord compression.
   B. Antibiotics are recommended until remission is obtained.
   C. Plasmapheresis may be considered to remove excess immunoglobulins.
   D. Therapy for hypercalcemia is instituted when indicated (see Chapter 73).
      1. Saline diuresis and furosemide are the mainstays of therapy.
      2. Mithramycin and bisphosphonates may be considered for refractory cases.

V. Chemotherapy protocols for lymphoma or chlorambucil 0.2 mg/kg PO SID may be used in dogs with primary macroglobulinemia.

Monitoring of Animal

I. A positive response is usually seen in 1 to 2 months.
   A. Monitoring of serum protein levels, repeating serum protein electrophoresis, and bone marrow aspirate are recommended to assess response to therapy.
   B. Melphalan can cause neutropenia and thrombocytopenia, so monitor a CBC and platelet count every 30 to 60 days.

II. Prognosis is variable.
   A. Median survival is 540 days in dogs (Matus et al., 1986).
      1. Poor prognostic variables include a lack of response to therapy, hypercalcemia, Bence Jones proteinuria, pancytopenia, and renal failure.
      2. Dogs with primary macroglobulinemia successfully treated with chlorambucil had a median survival of 11 months (MacEwen and Hurvitz, 1977).
   B. Prognosis for cats is worse (Fox et al., 1999).
      1. Median survival time is 87 (1 to 1395) days.
      2. Average survival when treated with melphalan and prednisone is 183 days (if animal survived 2 weeks after the diagnosis).

Extramedullary Plasmacytoma

Definition and Cause

I. Extramedullary plasmacytoma is any neoplastic proliferation of plasma cells that does not fulfill the diagnostic criteria for multiple myeloma.

II. It is a common tumor in dogs, but is rare in cats.

III. Cocker spaniels may be overrepresented.

IV. Three forms are described in dogs.
   A. Skin and oral mucosal tumors
   B. Gastrointestinal (GI) masses
   C. Solitary osseous plasmacytoma (SOP)

V. In the cat the most common site is the skin, while the oral cavity, abdominal cavity, eye, and brain may also be affected.

VI. The cause is unknown.

Pathophysiology

I. Skin and oral mucous membranes are the most common sites in the dog.
   A. Not usually associated with excessive immunoglobulin production
   B. Systemic disease runcommon
   C. Usually benign
II. The GI tract is another potential site.
   A. Solitary or multifocal masses in the rectum, intestine, stomach or esophagus
   B. May secrete immunoglobulins
   C. Usually metastatic within the abdomen
III. SOP may progress to multiple myeloma.
IV. In the cat, extramedullary soft-tissue plasmacytomas and SOP can be associated with paraprotein secretion; metastasis is a frequent occurrence.

Clinical Signs

I. Oral and cutaneous forms are often solitary, pink, hairless, and ulcerated masses in the mouth or on the skin of the head and ears.
II. GI tumors may cause vomiting, melena, and hematochezia.
III. Osseous tumors may cause bone pain and/or fractures.

Diagnosis

I. Biopsy of the lesion demonstrates malignant proliferation of plasma cells.
II. Evaluate affected animals for multiple myeloma.
III. Diagnosis of extramedullary plasmacytoma is made when criteria for multiple myeloma are not met.

Differential Diagnosis

I. Multiple myeloma
II. Differential diagnoses for GI plasmacytoma: lymphoma, osteosarcoma, fibrosarcoma, other tumors, inflammatory diseases
III. Cutaneous plasmacytoma: lymphoma, histiocytoma, mast cell tumor, other cutaneous masses (see Chapter 89)

Treatment and Monitoring

I. Considerations in animals with canine oral and cutaneous plasmacytoma are as follows:
   A. Excisional surgery is the treatment of choice and is curative in most cases.
   B. Radiation therapy or cryotherapy may be effective for nonresectable tumors.
II. Considerations in animals with canine GI plasmacytoma or SOP are as follows:
   A. For GI plasmacytoma, long-term survival may be achieved in some cases with a combination of surgery and chemotherapy (melphalan and prednisone; see Multiple Myeloma).
   B. Local control of SOP may be possible with surgery and/or radiation therapy; however, most lesions progress to multiple myeloma within 6 months.
   C. Ancillary therapy includes antibiotics and plasmapheresis if severe hyperglobulinemia is present.
III. Treatment for feline extramedullary plasmacytomas is not well defined, but treatments similar to those used in the dog can be tried; prognosis is guarded because of the high incidence of metastasis.

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CHAPTER 78

Diseases of the Thymus

Bradley R. Schmidt

BENIGN DISEASES

Thymic Hypoplasia

Definition

I. Decreased size of the thymus from aplasia or hypoplasia
II. Arises secondary to reduced numbers of lymphocytes and/or the epithelial framework

Causes

I. Genetic disorders
  A. Thymic atrophy of Mexican hairless dogs leading to reduced T-cell function in adults
  B. Thymic aplasia in cats resulting in hairlessness in Birman kittens
  C. Autosomal recessive, severe, combined immunodeficiency of Jack Russell terriers
  D. Severe, combined immunodeficiency in a colony of basset hounds
  E. Growth hormone deficiency resulting in thymic hypoplasia in Weimaraners
  F. Acrodermatitis with immunodeficiency in bull terriers
II. Acquired disorders
  A. Infectious diseases: canine distemper virus, canine parvovirus, feline panleukopenia virus, and feline retroviral infections
  B. Environmental conditions: malnutrition in puppies and kittens, toxin exposure, radiation therapy, chemotherapy, corticosteroid administration

Pathophysiology

I. Thymic aplasia is failure of differentiation of all thymic elements.
II. Thymic hypoplasia involves lack of development or loss of thymocytes.

Clinical Signs

I. Immunodeficiency develops and results in recurrent viral, fungal or bacterial infections of the skin or the respiratory and gastrointestinal tracts of young animals.
II. Signs attributable to the primary cause, such as vomiting and diarrhea, occur with canine parvovirus or feline panleukopenia virus.
III. "Fading" syndrome of puppies and kittens (neonatal death) may be the only presenting sign.
IV. Stunted growth is seen in some animals.

Diagnosis and Differential Diagnosis

I. Laboratory testing for viral causes is recommended, especially in fading puppies and kittens.
II. The congenital form is considered in affected Mexican hairless dogs and Birman cats.
III. History of malnutrition or environmental exposure to toxins, radiation therapy, chemotherapy, or corticosteroids may be noted with acquired forms.
IV. Primary differential consideration is nonthymic-related immunosuppression.

Treatment

I. Treat the specific cause, if possible.
II. Antibiotic, antifungal, and antiviral therapy may be warranted.
III. Immunomodulating drugs, cytokine therapy, and bone marrow transplantation have been attempted; however, the results have not been consistently effective.
IV. Severe immunosuppression is usually fatal because of overwhelming sepsis or organ dysfunction.
V. Future treatments may include gene replacement therapy.

Thymic (Mediastinal) Cysts

Definition

I. There are benign fluid-filled and cystic structures in the cranial mediastinum (see Chapter 20).
II. Thymic cysts are uncommon in dogs and cats.

Cause and Pathophysiology

I. Cystic structures arise from pleural, lymphatic, bronchogenic, or thymic structures.
II. Fluid is generally clear and of low cellularity.
III. Condition is likely congenital.

Clinical Signs

I. Thymic cysts are usually an incidental finding with no clinical signs.
II. Clinical signs relating to a space-occupying mass may be present, such as regurgitation or coughing.

Diagnosis

I. Radiographically, a soft-tissue density in the cranial mediastinum is seen.
II. Ultrasonography identifies a fluid-filled or cystic structure.
III. Fine-needle aspiration of the cyst reveals a clear, acellular fluid.

Differential Diagnosis

I. Thymoma
II. Other cranial mediastinal tumors

Treatment and Monitoring

I. No therapy is required if the animal is asymptomatic.
II. Ultrasound-guided aspiration of the mass is often curative and may be attempted in symptomatic animals.

Thymic Hemorrhage

Definition and Causes

I. It is spontaneous hemorrhage occurring in the involuting thymus in young dogs.
II. Thymic hemorrhage is uncommon in the dog and rare in the cat.
III. Causes are not well defined.

Clinical Signs

I. Clinical signs arise from acute blood loss within the mediastinum and include pallor, tachycardia, and weakness.
II. Hemothorax may also occur and may induce tachypnea or dyspnea (see Chapter 19).

Diagnosis

I. Thoracic radiography and ultrasonography of the cranial mediastinum reveal a mass or diffuse thickening secondary to hemorrhage and hematoma formation.
II. Coagulation profile is normal.
III. Definitive diagnosis requires exploratory surgery.

Differential Diagnosis

I. Mediastinal tumors (rare in young dogs)
II. Other causes of anterior thoracic bleeding: trauma, clotting abnormalities

Treatment

I. Supportive care with IV fluids, evacuation of any free blood in the chest, and respiratory support
II. Whole blood transfusion if indicated (see Chapter 71)

Monitoring of Animal

I. Prognosis is guarded because fatal hemorrhage may occur.
II. Animals that do recover have a good prognosis.

NEOPLASTIC DISEASES

Thymoma

Definition and Cause

I. Thymoma is a neoplastic proliferation of the epithelial component of the thymus, with varying degrees of benign lymphocytic infiltration.
II. It is generally seen in older animals and is more common in dogs than cats.
III. The underlying cause is unknown, but German shepherd dogs appear to be predisposed.

Pathophysiology

I. Thymoma may be malignant or benign.
II. Malignancy is based primarily on clinical behavior rather than histologic findings.
   A. Benign thymoma is more common, usually encapsulated, and surgically removable.
   B. Malignant thymoma is less common and is generally locally invasive.
   C. Hemorrhage, pleural effusion, and metastasis may be present with malignant thymomas.
III. Thymoma may be categorized as lymphocytic-predominant or epithelial-predominant.
IV. Cystic thymoma has been recognized in cats.

Clinical Signs

I. Clinical signs are related to the presence of a space-occupying mass and pleural effusion and may include regurgitation, cough, dyspnea, and muffled cardiac and respiratory sounds.
   A. Precaval syndrome (edema of the head, neck, and possibly forelimbs) may be noted in some animals.
   B. In cats, the cranial thorax may be noncompressible.
II. Peripheral nerve entrapment may result in laryngeal paralysis or Horner's syndrome.
III. Paraneoplastic syndromes are often associated with thymoma in the dog but occur less commonly in the cat.
   A. Myasthenia gravis resulting in megaesophagus and weakness
   B. Hypercalcemia resulting in weakness, anorexia, polyuria, and polydipsia
   C. Polymyositis
   D. Exfoliative dermatitis in cats (see Chapter 73 and 93)

Diagnosis

I. Radiography and ultrasonography reveal a cranial mediastinal mass that may be cystic.
II. Computed tomography is helpful in staging the tumor but cannot differentiate thymoma from other mediastinal masses.
III. Needle biopsy reveals mature lymphocytes and variable numbers of mast cells, eosinophils, macrophages, and neutrophils.
   A. Some thymomas contain large lymphocytes, making it difficult to distinguish from lymphoma.
   B. Epithelial cells are not always noted, especially in lymphocytic-predominant thymoma.
IV. Histopathology may be needed to distinguish thymoma from lymphoma.
V. Immunohistochemical stains, polymerase chain reaction (PCR) assays, and flow cytometry are also helpful in distinguishing thymoma from lymphoma.

Differential Diagnosis

I. Mediastinal lymphoma
   A. The condition is characterized by immature or large lymphocytes, in contrast to mature lymphocytes of lymphocytic-predominant thymomas
   B. Multicentric involvement is a possibility.
II. Thymic cysts
III. Other anterior thoracic or anterior mediastinal masses: hematoma, squamous cell carcinoma, ectopic thyroid tumors

Treatment

I. Surgery is the treatment of choice for noninvasive tumors.
II. Radiation therapy may be tried for invasive tumors, incompletely resected tumors, or as palliation.
III. Chemotherapy may be considered for palliative purposes.
   A. Prednisone alone or in combination with cyclophosphamide and vincristine may offer partial remissions by reducing the benign lymphoid component of the tumor.
   B. Platinum-containing agents or doxorubicin may decrease the epithelial component of the tumor.

Monitoring of Animal

I. Growth of the tumor may be slow in some animals, allowing prolonged survival with no therapy.
II. Prognosis is good with surgical removal of benign thymomas in animals that have no paraneoplastic syndromes.
   A. Dogs have a median survival of 16 to 19 months (Atwater et al., 1994).
   B. Cats have a median survival of 21 months (Gores et al., 1994).
III. Prognosis is guarded to poor for animals with invasive thymoma; however, radiation therapy may be beneficial (response rate in cats and dogs of 74%) even though complete remissions are rare (Smith et al., 2001).
   A. Median survival time in dogs after radiation therapy is 248 days.
   B. Median survival time in cats after radiation therapy is 720 days.
IV. Prognosis is guarded for animals with paraneoplastic signs, especially megaesophagus.
V. Dogs with lymphocytic-predominant lymphomas may have a longer survival.
VI. Metastasis has been reported in cats with cystic thymoma (Patnaik et al., 2003).

Thymic Lymphoma

Definition

I. Thymic lymphoma is neoplastic proliferation of lymphocytes within the thymus.
II. Many thymic lymphomas are actually lymphomas of the anterior mediastinal lymph nodes.
III. It may occur alone or be part of multicentric lymphoma.

Cause and Pathophysiology

I. The cause in dogs is unknown.
II. Thymic lymphoma may cause hypercalcemia, especially in dogs.
III. The tumor is frequently associated with the feline leukemia virus (FeLV) in young cats.

Clinical Signs

I. Clinical signs are related to the presence of a space-occupying mass and pleural effusion (see Thymoma).
   A. Precaval syndrome (edema of the head, neck, and possibly forelimbs) may be noted in some animals.
   B. Cranial thorax may not be compressible, and palpable tumor may extend beyond the thoracic inlet, especially in cats.
II. Clinical signs associated with hypercalcemia are polyuria, polydipsia, weakness, and anorexia.

Diagnosis

I. Radiography or ultrasonography usually reveals a cranial mediastinal mass ± pleural effusion.
II. Computed tomography is helpful in staging the tumor but cannot differentiate between lymphoma and other mediastinal masses.
III. Needle biopsy or fluid analysis shows large lymphoblasts; however, a definitive diagnosis may require histopathology, immunohistochemistry, flow cytometry, and PCR assays of biopsy specimens.
IV. Phenotyping often demonstrates a T-cell origin.

Differential Diagnosis

I. Thyoma: characterized by mature lymphocytes and PCR, flow cytometry, and immunohistochemistry negative for lymphoma
II. Thymic cysts
III. Other causes of anterior thoracic and mediastinal masses: hematoma, squamous cell carcinoma, and ectopic thyroid tumors

Treatment

I. Combination chemotherapy is used as described for lymphoma (see Chapter 69).
II. Radiation therapy may offer rapid local remissions.
III. Therapy for hypercalcemia is recommended (see Chapter 73); however, hypercalcemia generally resolves if remission is obtained.

Monitoring of Animal

I. Cats
   A. Prognosis is variable depending on stage of the tumor.
   B. Thymic and mediastinal lymphoma has poor survival times (2 to 3 months); however, survival is longer in FeLV-negative cats (17.5 months) (Mooney et al., 1989; Withrow and MacEwen, 2001).
II. Dogs
   A. Presence of a large cranial mediastinal mass and hypercalcemia warrants a poor prognosis (Rosenberg et al., 1991).

B. Longer survival times are possible if hypercalcemia is absent.

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CHAPTER 79

Introduction

Nicholas J. Trout

BASIC CONSIDERATIONS

I. Dysfunction of the musculoskeletal system can produce pain, distortion, deviation, and disruption to bones, cartilage, muscles, ligaments, and tendons.
II. Most commonly, changes are noticed as a variation in movement or gait (lameness).
III. Severity of lameness can be categorized but may not correlate with the severity of underlying cause.
   A. Subtle: ligament sprain, strain, tendonitis, tenosynovitis
   B. Weight-bearing lameness: hip dysplasia with secondary degenerative joint disease, angular limb deformities, panosteitis
   C. Toe-touching lameness: hypertrophic osteodystrophy, acute cranial cruciate ligament rupture
   D. Nonweight bearing: long bone fracture, elbow luxation, footpad foreign body
IV. Appreciation of the dysfunction necessitates a familiarity with normal anatomy and a reproducible, systematic approach to the examination of the entire musculoskeletal system.
V. Lameness from neurological dysfunction can be differentiated from a musculoskeletal cause by a complete neurological examination.

CLINICAL APPROACH

I. Speed of onset of dysfunction frequently affects the musculoskeletal examination, which includes the following:
   A. Detailed history (anamnesis)
   B. Observation of how the animal sits, stands, and moves through different gaits
   C. Physical palpation and manipulation for abnormalities
   D. Ancillary diagnostic tests
II. Musculoskeletal disorders requiring emergency surgery are uncommon.
   A. Traumatic spinal fracture or luxation may require immediate stabilization.
   B. Septic arthritis may require immediate drainage and lavage.
   C. Open fractures with extensive soft tissue trauma and contamination may require debridement, protection, and stabilization; however, immediate, definitive surgical fixation is unusual.
   D. Life-threatening problems must be addressed first.
   E. History of concurrent disease(s) may affect the choice of diagnostic tests or treatment.
   F. Complete blood count, biochemical profile, urinalysis, and thoracic radiographs are obtained for all trauma victims as part of a minimum data base.
   G. Plain radiographs are used to identify soft tissue and osseous abnormalities using at least two standard views (mediolateral, craniocaudal), as well as oblique or tangential views when necessary.
   H. In cases of possible spinal injury, the entire spinal column is radiographed (initially without sedation or anesthesia).
III. Musculoskeletal disorders requiring urgent or nonelective surgery are more common and include most open and articular fractures and traumatic joint luxations.
   A. The animal must be stable (as defined by a minimum data base) before considering therapeutic options.
   B. Chemical restraint may be needed to obtain diagnostic radiographs of the affected and the contralateral, unaffected limb (for comparison).
IV. The majority of musculoskeletal disorders requiring evaluation are nonurgent or elective problems, such as biceps tenosynovitis, elbow dysplasia, immune-mediated polyarthropathy, and panosteitis.
   A. History taking is tailored to the individual problem and includes the following:
      1. Signalment: age, weight, breed, gender
      2. Owner assessment of problem

3. Duration of problem, speed of onset, association with trauma or exercise, relationship of signs to time of day

B. Determine the course of the problem and the influence of rest and medication.

C. Consider prior musculoskeletal history with information regarding the dam, sire, siblings, diet, and any exercise regimen.

D. More subtle degrees of lameness necessitate a more careful evaluation of the animal.
   1. Observation of how the animal sits, rises, stands, and moves through different gaits
   2. Serial palpation before and after exercise
   3. Use of sedation or anesthesia to complete palpation of a painful area in a fractious animal
   4. Use of additional diagnostic tools to define specific problems

DIAGNOSTIC TOOLS

I. Certain radiographic studies have become increasingly common in the investigation of certain musculoskeletal disorders.
   A. PennHIP films to evaluate hip dysplasia in young dogs
   B. Dorsal acetabular rim views of the pelvis to assess candidates for triple pelvic osteotomy
   C. Hyperextended and hyperflexed views of an unstable joint to define instability
   D. Preoperative stifle radiographs to define the angle of the tibial plateau for tibial plateau leveling osteotomy and the position of the straight patella ligament in stifle extension for tibial tuberosity advancement procedures

II. Arthrocentesis can be used to obtain synovial fluid for cytological evaluation to better define septic, degenerative, immune-mediated, or traumatic arthritides.

III. Ultrasonography provides useful information regarding lesions of tendons and muscular attachments to bone.

IV. Computed tomography helps delineate obscure skeletal abnormalities.

V. Magnetic resonance imaging is better at defining soft tissue abnormalities.

VI. Nuclear scintigraphy can be used to localize osseous lesions that are difficult to define with plain radiography.

VII. Arthroscopy has become the technique of choice to define and treat a variety of joint related disorders.

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CHAPTER 80

Diseases of Joints and Ligaments

Michael P. Kowaleski

CONGENITAL/DEVELOPMENTAL DISORDERS

Avascular Necrosis of the Femoral Head (Legg-Calvé-Perthes Disease)

Definition and Causes

I. It is defined as noninflammatory, aseptic necrosis of the femoral head that occurs predominantly in adolescent, small breed dogs.
II. Interruption of blood flow to the femoral head occurs for an unknown reason.
III. Possible causes include hereditary factors, increased intra-articular pressure, infarction of the femoral head, hormonal factors, and anatomic conformation.
IV. A recessive mode of inheritance has been proposed in the Manchester terrier (Vasseur et al., 1989).

Pathophysiology

I. Initial change is osteonecrosis of the proximal femoral epiphysis, with viable articular cartilage.
II. Continued weight bearing results in microfractures of the necrotic trabeculae, subchondral bone collapse, subchondral cleft formation, and ischemic damage to the physis.
III. Normal metaphyseal bone responds and revascularization of the femoral head occurs; however, the femoral epiphysis is mechanically weakened and susceptible to collapse and fragmentation under normal physiologic loads.
IV. Resulting deformity of the femoral head leads to joint incongruity and osteoarthritis of the hip joint.

Clinical Signs

I. Initial sign is progressive pelvic limb lameness unassociated with trauma in a young, small-breed dog.
   A. Lameness slowly worsens over 6 to 8 weeks and may progress to a nonweight bearing.
   B. Acute-onset lameness is presumably related to a previously undiagnosed mild lameness that acutely progresses from sudden collapse of the epiphysis.
II. Average age at onset is 5 to 8 months (range of 3 to 13 months) (Gambardella, 1993).
III. Bilateral in 12% to 17% of cases (Gambardella, 1993).

Diagnosis

I. Physical examination reveals discomfort with flexion, extension, rotation, and abduction of the hip joint.
II. Radiography is essential to establish a diagnosis.
   A. Incongruency and widening of the coxofemoral joint space progressing to subluxation
   B. Flattening of the femoral head
   C. Foci of decreased density of the femoral head and neck (moth-eaten appearance)
   D. Irregular indentation of the subchondral bone of the femoral head, periarticular osteophyte formation
III. Histopathologic examination of the resected femoral head and neck is confirmatory.

Differential Diagnosis

I. Medial patellar luxation
II. Proximal femoral physeal fracture
III. Traumatic hip luxation
IV. Canine hip dysplasia

Treatment

I. Femoral head and neck excision is the treatment of choice.
II. Total hip replacement can be considered, depending on the size of the dog.
III. In bilateral cases the worst hip (clinically) is operated on first, followed by the second hip (generally in 4 to 6 weeks).

Monitoring of Animal

I. Postoperatively, low-impact activities are initiated that encourage use of the limb (e.g., leash walking, swimming).
II. Passive range-of-motion exercises may be needed if weight bearing does not begin within 10 to 14 days.
III. Radiographs are repeated if lameness develops in the opposite pelvic limb.

Patellar Luxation

Definition and Causes

I. Patellar luxation is intermittent or permanent displacement of the patella from the femoral trochlear sulcus.
II. It is associated with a malalignment of the quadriceps muscles, patella, and patellar tendon, as well as femoral and/or tibial deformities.

Pathophysiology

I. Medial malalignment of the quadriceps mechanism in growing dogs with medial patellar luxation can cause sufficient pressure on the medial distal femoral growth plate to retard growth, whereas reduced pressure laterally allows accelerated growth.
II. Deformities associated with medial luxation include distal femoral varus, external femoral torsion, and medial displacement of the tibial tuberosity.
III. Patellar luxation causes reduced pressure on the trochlear sulcus of the femur, allowing excessive growth of the articular cartilage and underlying bone, leading to a shallow or absent trochlear groove.
IV. Lateral luxation is associated with coxa valga (excessive angle of inclination of the femoral neck) and excessive anteversion angle (external rotation of the proximal femur with respect to the distal femur).

Clinical Signs

I. Medial luxation is a developmental disorder in small-breed dogs, may occur secondary to trauma in any breed, and is increasing in frequency in large-breed dogs.
II. Lateral luxation is seen most commonly in large-breed dogs.
III. Most animals have intermittent weight-bearing lameness and occasionally hold the limb in a flexed position for several steps.

Diagnosis

I. Grade I
   A. Patella may be luxated manually with the joint in extension, but reduction occurs when digital pressure is released.
   B. It is usually an incidental finding but may be associated with occasional lameness.
II. Grade II
   A. Patella can be luxated manually with the joint in extension, especially with rotation of the foot in the direction of luxation.
   B. Reduction occurs with flexion and rotation of the foot opposite to the direction of luxation.
   C. Patella luxates spontaneously and intermittently, and the gait ranges from "skipping" to non–weight-bearing.
III. Grade III
   A. Patella is permanently luxated; manual reduction is possible, but reluxation occurs when pressure is released or the stifle is flexed.
   B. Lameness ranges from weight-bearing to non–weight-bearing.
IV. Grade IV
   A. Patella is permanently luxated and cannot be manually reduced.
   B. Limb is non–weight-bearing if unilateral or the animal moves in a crouched posture if bilateral.

Differential Diagnosis

I. Avascular necrosis of the femoral head
II. Coxofemoral luxation
III. Cranial cruciate ligament rupture
IV. Distal femoral physeal fracture

Treatment

I. Grade I patellar luxations do not require surgical treatment unless lameness is frequent or progressive.
II. Grade II luxations commonly require surgery if episodes of lameness are frequent or severe.
   A. A combination of surgical procedures is performed to address each abnormality present.
   B. Deepening of the femoral trochlear sulcus is accomplished using trochlear wedge recession, trochlear block recession, trochleoplasty, or trochlear chondroplasty (Slocum and Slocum, 1993; Johnson et al., 2001).
   C. Tibial tuberosity transposition is done to align the quadriceps mechanism.
   D. Joint capsule imbrication is performed on the side opposite the luxation.
   E. Retinacular and joint capsule–releasing incision is made on the side of the luxation.
III. Grade III luxations require a combination of the previously discussed procedures and possibly femoral and/or tibial corrective osteotomy to address angular or torsional deformities.
IV. Grade IV luxations often also require corrective osteotomy of the femur and/or tibia.
   A. Prognosis for return of pet to a functional level is fair to good.
   B. Stifle joint arthrodesis may be required with poor return to function.

Monitoring of Animal

I. Postoperatively, low-impact activities are initiated that encourage use of the limb (e.g., leash walking, swimming).
II. Passive range-of-motion exercises may be needed if weight bearing does not begin within 10 to 14 days.
III. Physical examinations are repeated at 2 and 6 weeks to assess limb function and ensure the patella is stable.
IV. Radiographs are obtained to assess bony healing at 6 to 8 weeks.

Shoulder and Elbow Luxation

Definition and Causes

I. Congenital shoulder and elbow luxation are likely hereditary in origin.
II. Luxation of the shoulder or elbow can occur secondary to trauma.
III. Congenital medial shoulder luxation occurs most frequently in small and miniature breed dogs (e.g., Shetland sheepdog, toy poodle).
IV. Congenital elbow luxation has been reported in the Boston terrier, Yorkshire terrier, English bulldog, miniature poodle, Pomeranian, and pug.

Pathophysiology

I. The cause of congenital luxations is not known.
II. Congenital or developmental joint laxity may lead to luxation and hypoplastic joint surfaces.

Clinical Signs

I. Medial shoulder luxation: congenital or traumatic
   A. Affected limb is carried in flexion with foot rotated outward.
   B. Greater tubercle is palpable medial to the normal position.
II. Lateral shoulder luxation
   A. It is generally traumatic; large breeds are affected most.
   B. Affected leg is carried in flexion with foot rotated internally.
   C. Greater tubercle is palpable lateral to the normal position.
III. Elbow luxation
   A. Congenital elbow luxation results in lateral rotation of the proximal ulna, as well as subluxation or luxation of the humeroulnar joint.
   B. Most traumatic elbow luxations are lateral because of the large medial epicondylar ridge.
   C. Limb is abducted, externally rotated, and held in slight flexion.
IV. Congenital forms: possibly bilateral

Diagnosis

I. Malarticulation and displacement of normal bony landmarks are classic findings.
II. Diagnosis is confirmed radiographically.
III. Additional radiographic findings are flattening of the joint surfaces and angular or torsional deformities of the humerus, ulna, or radius.

Differential Diagnosis

I. Fractures of elbow or shoulder
II. Physeal trauma: fracture or growth deformity

Treatment

I. Congenital shoulder and elbow luxations
   A. Closed reduction and coaptation are generally unsuccessful.
   B. Surgical reduction and stabilization may result in acceptable joint function.
   C. Closed reduction and percutaneous fixation have been described in dogs (Dassler and Vasseur, 2003).
   D. Arthrodesis may be required if joint function is unacceptable.
II. Traumatic medial shoulder luxation
   A. Conservative management
      1. Closed reduction and cage rest for 2 to 3 weeks
      2. Reduction and placement of the limb in a Velpeau sling for 2 to 3 weeks to distract the humeral head laterally
   B. Surgical management: medial transfer of biceps brachii tendon and joint capsule imbrication
   C. Salvage procedures: excision arthroplasty of the humeral head, resection of the glenoid, shoulder arthrodesis
III. Traumatic lateral shoulder luxation
   A. Conservative management
      1. Closed reduction and cage rest for 2 to 3 weeks
      2. Closed reduction and placement of the limb in a spica splint or sling for 2 to 3 weeks
   B. Surgical management
      1. Lateral transfer of biceps brachii tendon and joint capsule imbrication
      2. Prosthetic glenohumeral ligament reconstruction using nonabsorbable suture material and bone anchors or tunnels in the scapular and humeral neck
   C. Salvage procedures: excision arthroplasty of humeral head, resection of glenoid, shoulder arthrodesis
IV. Traumatic elbow luxation
   A. Conservative management
      1. Closed reduction under general anesthesia
      2. Application of spica splint for 10 to 14 days
   B. Surgical management
      1. Open reduction is indicated if instability is present after closed reduction or for chronic or irreducible elbow luxations.
      2. Torn collateral ligaments may be primarily repaired, and a screw, washer, and heavy-gauge suture may be used to create a prosthetic collateral ligament.
      3. Spica splint is applied for 10 to 14 days.

Monitoring of Animal

I. Passive range-of-motion exercises are initiated, followed by low-impact activity once the coaptation has been removed.
II. Radiographs are repeated in 4 to 6 weeks to assess status of joint reduction and stability of implants.

Canine Elbow Dysplasia

Definition and Causes

I. Canine elbow dysplasia is a group of developmental diseases that researchers believe is caused by incongruity between the humerus, radius, and ulna.
II. Manifestations include fragmented medial coronoid process (FMCP) of the ulna, ununited anconeal process (UAP) of the ulna, and osteochondritis dissecans (OCD) of the medial portion of the humeral condyle.
III. In the past, decreased radius of curvature of the ulnar trochlear notch was the suggested cause.
IV. Recently, elbow incongruity from asynchronous growth between the radius and ulna has been implicated as the cause (Schultz and Krotscheck, 2003).

Pathophysiology

I. Lagging radial growth and a relatively long ulna may stress the medial coronoid process and humeral condyle, resulting in FMCP and, potentially, OCD of the humeral condyle.
II. A relatively long radius may increase the load on the anconeal process, preventing normal fusion of this center of ossification.
III. Dogs with unilateral UAP have a slightly longer radius on the affected side (Sjöström et al., 1995).

Clinical Signs

I. FMCP and OCD
  A. Thoracic limb lameness, initially evident at 5 to 8 months of age, is seen in retrievers, Bernese mountain dogs, and rottweilers.
  B. Dogs may not be presented until 1 to 2 years of age, after development of osteoarthritis.
  C. Lameness is worse after exercise, and joint effusion and periarticular fibrosis may be palpable.
    1. Lameness is usually unilateral, even if both joints are affected.
    2. Stiff or stilted gait may be observed if bilateral lameness is present (shortened stride).
  D. Pain is evident with supination or pronation of the pes, simultaneous flexion and extension of the joint, and palpation of the medial coronoid process.

II. UAP
  A. The anconeal process normally fuses with the proximal ulna by 20 to 24 weeks of age, so diagnosis of UAP before this may be premature.
  B. Large-breed dogs, especially the German shepherd dog, basset hound, and St. Bernard are affected.
  C. Signs of thoracic limb lameness, elbow abduction, and external rotation of the foot become apparent at 5 to 8 months of age.
  D. Crepitus, joint effusion, and periarticular thickening of the elbow may be noted.

Diagnosis

I. FMCP
  A. Presumptive diagnosis is based on typical history and clinical signs.
  B. Radiographs of both elbows are taken, because the disease is commonly bilateral.
    1. Radiographic findings are nonspecific; presence of osteoarthritis is suggestive of FMCP.
    2. Osteophytosis and superimposition of the radial head on the coronoid process make identification of the FMCP difficult.
    3. Obtain lateral and craniocaudal views; a flexed lateral view exposes the anconeal process to assess for osteophytosis.
    4. The craniolateral-caudomedial −15-degree oblique view (with 30 degrees of flexion) may help visualize the medial coronoid.
    5. Blunting of the coronoid, visible fragments, and osteophytes of coronoid process, anconeal process, or radial head may be visible.
    6. The earliest radiographic changes are osteophytes on the anconeal process.
    7. Later signs include subchondral bone sclerosis, articular and periarticular osteophytosis, joint space narrowing, joint effusion, and periarticular soft-tissue thickening; these signs indicate secondary degenerative joint disease (DJD).
  C. Definitive diagnosis can be made with arthroscopy, computed tomography, magnetic resonance imaging, or arthrotomy.

II. OCD
  A. An oval to triangular subchondral bone defect is evident in the medial portion of the humeral condyle in the craniocaudal radiographic projection.
  B. Earliest radiographic changes are similar to those of FMCP.

III. UAP
  A. Clinical signs, age, and breed allow for a tentative diagnosis.
  B. Flexed, lateral radiograph reveals an irregular radiolucent line between the anconeal process and the olecranon.
  C. Radiographs of the contralateral elbow may be useful for comparison.
  D. Bilateral UAP occurs in 11% to 47% of cases (Schultz and Krotscheck, 2003).

Differential Diagnosis

I. These conditions produce similar signs and can be differentiated radiographically.
II. Combinations of OCD, FMCP, and UAP may occur.
III. Humeroulnar subluxation resulting from premature physeal closure can be differentiated radiographically.
IV. Other diseases of the thoracic limb in young dogs are OCD of the shoulder and panosteitis.

Treatment

I. FMCP and OCD
  A. Medical management
    1. Asymptomatic dogs or those with severe DJD may be treated medically.
    2. Weight control, exercise moderation, nonsteroidal antiinflammatory drugs (NSAIDs), chondroprotective agents, and nutritional management are the cornerstones of treatment.
    3. Rest (2 to 3 weeks) and NSAIDs (Table 80-1) are used during episodes of lameness, followed by return to moderate regular exercise.
  B. Surgical management

TABLE 80-1

Nonsteroidal Antiinflammatory Drugs Approved for the Treatment of Osteoarthritis in Dogs

DRUG (BRAND NAME)	DOSE AND FREQUENCY
Carprofen *(Rimadyl)*	2.2 mg/kg PO BID
Deracoxib *(Deramaxx)*	1 to 2 mg/kg PO SID
Etodolac *(EtoGesic)*	10 to 15 mg/kg PO SID
Firocoxib *(Previcox)*	5 mg/kg PO SID
Meloxicam *(Metacam)*	0.1 mg/kg PO SID
Tepoxalin *(Zubrin)*	10 mg/kg PO SID

1. Indications include persistent lameness and mild DJD.
2. Some dogs with moderate or severe DJD may also benefit from loose fragment removal.
3. The joint is explored either arthroscopically or via arthrotomy; loose fragments of the FMCP or OCD lesion are removed, followed by debridement of the subchondral bone bed.
4. Surgical treatment does not halt the progression of osteoarthritis; therefore continued medical therapy is indicated.

II. UAP
   A. Removal of the anconeal process is an acceptable method of treatment but may lead to elbow instability and osteoarthritis.
   B. Surgical reconstruction and procedures that enhance fusion of the anconeal process may be preferred.
      1. Dynamic proximal ulnar osteotomy may allow fusion of the anconeal process in young (6 to 12 month) dogs.
      2. Dynamic proximal ulnar osteotomy and lag screw fixation may be required in older (>1 year) dogs and in dogs with loose attachment of the anconeal process to the olecranon (Schultz and Krotscheck, 2003).

Monitoring of Animal

I. FMCP and OCD
   A. Exercise is restricted for 4 to 6 weeks, followed by gradual return to normal activity.
   B. Prognosis for full function is guarded because of progressive DJD regardless of treatment.
   C. Most dogs are functional pets and have intermittent lameness.
   D. Osteoarthritis requires lifelong medical management.

II. UAP
   A. A soft, padded bandage is applied for 3 to 5 days from the digits to the middiaphysis proximal to the incision to minimize postoperative swelling.
   B. The dog is confined to leash walks for 6 weeks, then gradually returned to normal activity over the next 6 weeks.
   C. Radiographs are repeated in 4 to 6 weeks to assess fusion of the anconeal process and healing of the ulnar osteotomy (if performed).

Canine Hip Dysplasia

Definition and Causes

I. Canine hip dysplasia is an abnormal development of the hip joint with varying degrees of joint laxity that permits subluxation of the femoral head early in life.

II. Researchers agree that hip dysplasia is genetically mediated; however, the exact mechanism is unknown.

III. Environmental factors, such as increased energy and calcium intake, also play an important role (Todhunter and Lust, 2003).

Pathophysiology

I. If muscle development and rate of growth lag behind the development of skeletal structures, then the limit of the supporting structures is exceeded and joint laxity occurs.

II. Severity depends on the degree of overloading of the joint during its development.

III. Changes in cartilage, supporting soft tissue, and muscles cause alterations in bony architecture.

IV. Coxofemoral joint laxity leads to subluxation of the femoral head, which causes cartilage damage, release of degradative enzymes, and loss of cartilage matrix.

V. The end result is osteoarthritis (DJD).

Clinical Signs

I. Pelvic limb lameness is worse after exercise and varies from mild and intermittent to non–weight-bearing.

II. Decreased flexion and extension of the hip during a walk or trot and a "bunny-hopping gait" while running are common findings.

III. Pelvic limb muscle atrophy, joint laxity, and pain during range-of-motion examination of the coxofemoral joint are typical findings.
   A. Ortolani sign is a palpable click elicited as the subluxated hip reduces with abduction.
   B. Ortolani sign is often positive in young dogs with mild to moderate degenerative changes and is consistent with hip laxity and dysplasia.
   C. As the degeneration progresses, the acetabulum fills with new bone and the Ortolani sign becomes negative.
   D. A negative Ortolani sign can be a normal finding or indicative of advanced DJD.

Diagnosis

I. Radiographic changes range from mild subluxation of the femoral head to severe DJD.
   A. In young dogs (<10 months), subluxation is often the main abnormality.
   B. In dogs >10 months, evidence of DJD is typically present.
      1. Flattening of the femoral head
      2. Shallow acetabulum
      3. Osteophytosis of the femoral neck, femoral attachment of the joint capsule and acetabular margins
      4. Narrowing of the joint space
      5. Subchondral sclerosis of the femoral head and acetabulum

II. Stress radiographic techniques (e.g., PennHIP method) are useful to demonstrate laxity of the hip joint, which is a predictor of future DJD (Smith et al., 1990).

Differential Diagnosis

I. Cranial cruciate ligament rupture

II. Traumatic luxation

III. Degenerative myelopathy (older dogs)

IV. Femoral head, neck, or proximal femoral physeal fracture (younger dogs)

V. Infectious or inflammatory arthritis

Treatment

I. Medical management involves the following:
   A. Weight loss is important because it decreases loading of joints and muscles; the goal is a thin and athletic frame (body condition score of 2.5 to 3.5).
   B. Daily low-impact activity aids in weight loss and helps improve muscle mass, joint range of motion, and exercise tolerance.
   C. NSAIDs are administered as needed (see Table 80-1) (Bergh and Budsberg, 2005).
      1. Never administer NSAIDs with other NSAIDs (including aspirin) or corticosteroids.
      2. When switching from one NSAID (particularly aspirin) to another, wait a few days (according to the manufacturer's recommendations).
   D. Chondroprotective agents may mitigate inflammation and enhance reparative processes.
      1. Glucosamine hydrochloride 22 mg/kg PO SID, *with*
      2. Chondroitin sulfate 8.8 mg/kg PO SID
   E. Diets containing high levels of omega-3 fatty acids and eicosapentaenoic acid may help improve clinical signs associated with DJD.

II. Once the animal is refractory to medical management or is disabled by the condition, surgical therapy is indicated.
   A. An exception is the triple pelvic osteotomy (TPO), in which delay may preclude the animal from being a good candidate.
   B. Surgical management is divided into treatments that aim to diminish the progression of DJD and salvage procedures that remove the original hip joint.

III. Juvenile pubis symphysiodesis is electrocautery of the pubic symphysis to induce its premature closure (Dueland et al., 2001).
   A. The resulting asymmetrical closure of the pelvic symphysis (pubic is closed, ischial is not) and continued growth of the sacrum and ilium result in acetabular ventroversion, which enhances femoral head capture.
   B. Procedure is experimentally effective but must be performed at an early age (12 to 16 weeks).
   C. It is difficult to identify which dogs will benefit at such an early age.

IV. TPO increases the acetabular coverage of the femoral head.
   A. The ideal candidate is young (5 to 12 months), has minimal or no radiographic evidence of DJD, and has adequate femoral head capture.
   B. Femoral head capture is subjective assessment of dorsal acetabular rim wear, and is assessed by performing the Ortolani maneuver and determining the angle at which the femoral head reduces into the acetabulum (angle of reduction), as well as the angle at which it subluxates (angle of subluxation).
   C. The quality of femoral head capture may also help determine if the dorsal acetabular rim is excessively worn or able to maintain the hip in reduction postoperatively.
   D. Arthroscopic examination of the hip joint allows a more thorough evaluation of the joint before surgery.
   E. TPO entails osteotomy of the pelvis at the pubis, ischium, and ilium; external rotation (ventroversion) of the free acetabular segment; and stabilization of the ilial osteotomy with plate fixation, to provide more dorsal coverage to the femoral head and preventing continued subluxation.

V. Femoral head ostectomy (FHO) is a salvage procedure in which the femoral head and neck are removed and a scar tissue "joint" subsequently forms.
   A. Animals treated with this procedure have a limited range of motion, a mildly abnormal gait, and persistent muscle atrophy.
   B. Although range of motion is diminished, most animals <20 kg function well; results in animals ≥20 kg are less reliable.

VI. Total hip arthroplasty (THA) provides the animal with a prosthetic femoral component and acetabular cup.
   A. Currently, component systems are either cemented in place or are cementless in design.
   B. THA results in normal or near normal gait, muscle mass, and range of motion.
   C. THA is a sophisticated procedure that demands strict asepsis and precise surgical technique if a successful result is to be obtained.

Monitoring of Animal

I. Animals treated medically are monitored to assess efficacy of therapy and limb function.
   A. Initially, reevaluation is performed at monthly intervals.
   B. If the response to treatment is favorable, then the dog is reevaluated every 3 to 4 months and at times of disease flare-up.

II. Surgically treated animals undergo exercise restriction and are monitored for common complications as follows:
   A. Juvenile pubis symphysiodesis: progression of DJD
   B. TPO
      1. Exercise is restricted for 4 to 6 weeks.
      2. Radiography is conducted at 4 to 6 weeks postoperatively to assess bony healing.
      3. If clinically indicated, surgery may be performed on the contralateral side once bony healing is adequate on the initial side (typically 4 to 6 weeks).
      4. Long-term function is good despite progression of DJD (Rasmussen et al., 1998).
   C. FHO
      1. Initiate low-impact activities (e.g., leash walking, swimming) after 2 weeks.
      2. Passive range-of-motion exercises may be needed if weight bearing does not begin within 10 to 14 days.
      3. Gradual return to normal activities is encouraged during weeks 2 to 8.
   D. THA
      1. Walk the animal outside on a leash (for eliminations only) for the first 4 weeks.
      2. Duration of leash walks is increased progressively during weeks 5 to 8.
      3. Short episodes of off-leash activity are allowed during weeks 9 to 12.

4. Radiographs are taken at week 12 to assess implants, then yearly.
5. Most (92% to 95%) animals have good or excellent function postoperatively (Olmstead, 1987).

Osteochondrosis and Osteochondritis Desiccans

Definition and Causes

I. Osteochondrosis (OC) is failure of endochondral ossification and refers to the disease in general.
II. OCD is a combination of dissecting lesions of articular cartilage, communication of synovial fluid into subchondral bone, and synovitis (Schultz and Krotscheck, 2003).
III. Factors that have been implicated include nutrition (e.g., excessive nutrition, dietary calcium, protein), genetics, exercise, environmental factors, and trauma (e.g., excessive mechanical loading).

Pathophysiology

I. A defect in endochondral ossification results in a focal area of abnormal subchondral bone formation.
II. The overlying cartilage fails to ossify, resulting in focal retention of cartilage.
III. The thickened region of cartilage becomes necrotic and weak, and breaks down under normal loading conditions or secondary to trauma.
   A. Early in the disease process, OC affects only the epiphyseal cartilage and the animal is asymptomatic.
   B. Once a fissure occurs in the thickened cartilage, it extends through the necrotic cartilage to the subchondral bone, allowing access of the synovial fluid to the subchondral bone.
   C. This latter stage seems to correspond to the onset of clinical signs, at which time the disease is termed *OCD.*
IV. OCD results in two distinct joint abnormalities.
   A. Joint incongruity secondary to malformation of cartilage and subchondral bone
   B. Joint mouse formation
V. Cartilage flaps that remain attached may ossify, with the resulting bone remaining viable as long as the flap is attached.
VI. Detached cartilage flaps may survive in the joint fluid, grow in size, and mineralize or ossify if they attach to the joint capsule.

Clinical Signs

I. Common sites are the caudomedial humeral head (shoulder), distal humerus (elbow), trochlear ridge of the talus (hock), and femoral condyle (stifle).
II. Shoulder lesions often occur in large breed dogs, 4 to 8 months of age.
   A. Males are affected more commonly than females.
   B. Many dogs are clinically affected in only one limb, but lesions are bilateral in 43% to 65% of cases (Bloomberg and Lewis, 1998).
   C. Thoracic limb lameness may be noted before or after exercise.
   D. Pain is elicited with shoulder extension; crepitus, deltoid and spinatus muscle atrophy may be found.
III. Hock lesions typically occur in young (5 to 8 months) large-breed dogs, especially the rottweiler, Labrador retriever, and bullmastiff.
   A. OCD of the medial trochlear ridge is most common, whereas the lateral trochlear ridge OCD often occurs in rottweilers.
   B. Pelvic limb lameness is characterized by a shortened stride and hyperextension of the tarsocrural joint.
   C. Thickening of the tarsus occurs, especially if the medial trochlear ridge of the talus is involved.
IV. Stifle lesions occur in large-breed dogs that are 5 to 7 months of age.
   A. Lameness varies from mild to severe.
   B. Joint effusion, muscle atrophy, and crepitus may be evident.

Diagnosis

I. Normal cartilage is not visible radiographically unless significant dystrophic calcification has occurred.
II. Radiographically, an OCD lesion is a flattened or saucer-like "divot" in the subchondral bone.
III. Shoulder radiographs reveal a flattening of the humeral head in a properly positioned lateral view.
IV. An arthrogram of the shoulder may be needed if the lesion is not evident or if cartilage has migrated into the biceps tendon sheath.
V. Radiographic identification of hock lesions may be difficult because of the location of the lesion on the trochlear ridge.
   A. An extended dorsoplantar projection may reveal the defect in the trochlear ridge.
   B. A dorsolateral-plantar-medial 45-degree oblique projection in full extension outlines the medial trochlear ridge of the talus.
   C. A skyline view of the talus may identify a lesion on the center of the trochlear ridge of the talus.
VI. Slight flattening and sclerosis of the subchondral bone of the femoral condyle is evident in a caudocranial view of the stifle.
VII. Do not confuse the extensor fossa of the femur for an OCD lesion.

Differential Diagnosis

I. Panosteitis
II. Traumatic joint injury
III. Septic or inflammatory arthritis
IV. Other causes of thoracic limb lameness: elbow dysplasia
V. Other causes of pelvic limb lameness: cranial cruciate ligament rupture, hip dysplasia

Treatment

I. As the relative size of the osteochondral defect increases, the resulting joint incongruity also increases; therefore a small defect in a large joint (shoulder) has less of an affect than in a small (hock) or complex (elbow or stifle) joint.

A. Surgical treatment can result in normal or near-normal function in large joints with relatively small lesions (shoulder).
B. Function is improved, but clinical signs are not always alleviated in complex or small joints (elbow, hock, stifle).

II. Goals of surgery are to surgically debride the osteochondral defect, with minimal damage to the joint.
A. Arthrotomy or arthroscopy can be used.
B. Debride the lesion to the level of subchondral bleeding bone, using a curette, hand bur, or motorized shaver.
C. Debride the edge of the lesion peripherally until normal cartilage is reached, ensuring the edges are perpendicular to the subchondral bed.
D. Microfracture can be used to create vascular access channels from the lesion to the underlying subchondral bone.

III. Long-term medical management with weight control, exercise moderation, NSAIDs, chondroprotective agents, and nutritional changes are also helpful (see Osteoarthritis).

IV. Rest (2 to 3 weeks) and NSAIDs are used for recurrent episodes of lameness, followed by return to moderate regular exercise.

Monitoring of Animal

I. In the case of hock or stifle OCD, a soft, padded bandage is applied for 3 to 5 days from the digits to the middiaphysis proximal to the incision to minimize postoperative swelling.

II. The dog is confined to leash walks for 6 weeks, then gradually returned to normal activity over the next 6 weeks.

III. Degree of DJD in the joint before surgery has an inverse effect on long-term function.

IV. Dogs with OCD of the hock may fare well without surgery, because of the relatively large size of typical hock lesions and the tendency for significant preoperative DJD.

DEGENERATIVE DISORDERS

Osteoarthritis

Definition and Causes

I. Osteoarthritis (i.e., DJD) is a syndrome of pathologic changes in diarthrodial or synovial joints accompanied by signs of pain and disability.

II. It develops secondary to trauma, or from application of normal forces on abnormal joints, such as with hip dysplasia or cranial cruciate ligament disease.

III. Other less common causes include sepsis, prolonged joint immobilization, inflammatory joint disease, or developmental diseases (e.g., OCD).

Pathophysiology

I. All joint tissues are involved, including articular cartilage, joint capsule, subchondral bone, ligaments, and muscle.

II. Initially, degradative enzymes are released from chondrocytes, synoviocytes, and inflammatory cells.

III. The earliest form of articular cartilage damage is fibrillation or roughening of the cartilage surface.

IV. Once the superficial layer of cartilage loses its integrity, the deeper layers are exposed to progressively higher loads, leading to fissure formation.

V. Cartilage destruction leads to altered biomechanical function of the joint, which perpetuates the degradative process and worsens functional impairment and discomfort (Todhunter and Johnston, 2003).

Clinical Signs

I. Signs include slowly progressive, episodic or persistent lameness, pain, and disability.
A. Stiffness is often noted after periods of rest.
B. Stiffness and lameness partially or fully resolve with activity in most cases.
C. Lameness is exacerbated by strenuous activity, particularly if the activity is followed by a period of rest.

II. Discomfort is noted during range-of-motion examination of the joints.

III. Periarticular fibrosis, bony crepitus, joint effusion, and muscle atrophy are common findings.

Diagnosis

I. History and clinical findings allow a presumptive diagnosis.

II. Radiography reveals joint effusion, periarticular osteophytosis, muscle atrophy, and subchondral bone sclerosis.
A. Joint space narrowing may occur from cartilage thinning; however, most radiographs are not obtained under weight-bearing conditions, so this finding must be interpreted with caution.
B. Joint subluxation and luxation may also be seen.

III. Synovial fluid analysis is consistent with DJD (Table 80-2).

Differential Diagnosis

I. Trauma

II. Developmental joint disease

III. Inflammatory joint disease

TABLE 80-2

Interpretation of Synovial Fluid Analysis

CONDITION	TOTAL CELL COUNT ($\times 10^3$/L)	MONONUCLEAR CELLS (%)	NEUTROPHILS (%)
Normal	0.0-3.0	90-100	0-10
Nonsuppurative Inflammation			
Degenerative osteoarthritis	0.0-3.5	90-100	0-10
Suppurative Inflammation			
Nonerosive arthritis	4.4-370	5-85	15-95
Erosive arthritis	3.0-38	20-80	20-80
Bacterial arthritis	110-267	1-10	90-99

Treatment

I. Prevention of osteoarthritis is preferable, but the condition is usually well established before diagnosis.
II. Medical management of osteoarthritis involves five basic treatments.
  A. Weight loss decreases loading of joints and muscles, and the goal is a thin and athletic frame.
  B. Daily low-impact activity aids in weight loss and helps improve muscle mass, joint range of motion, and exercise tolerance.
  C. NSAIDs are administered as needed (see Table 80-1) (Bergh and Budsberg, 2005).
  D. Chondroprotective agents may mitigate inflammation and enhance reparative processes.
    1. Glucosamine hydrochloride 22 mg/kg PO SID, *with*
    2. Chondroitin sulfate 8.8 mg/kg PO SID
  E. Diets containing high levels of omega-3 fatty acids and eicosapentaenoic acid may help improve the clinical signs.
III. Surgical management is indicated in selected cases.
  A. If joint instability exists (e.g., cranial cruciate ligament rupture), then surgical stabilization mitigates clinical signs.
  B. Joint replacement is very effective in alleviating clinical signs but is routinely performed only in the hip (THA).
  C. Total elbow and knee arthroplasties may be performed.
  D. Excision arthroplasty may be performed in selected joints.
    1. FHO
    2. Resection of the glenoid excision arthroplasty of the humeral head: data on outcome lacking
  E. Arthrodesis may be performed in selected joints to salvage limb function.
    1. Partial or total carpal and or tarsal arthrodeses are well tolerated and result in acceptable limb function.
    2. Shoulder, stifle, and elbow arthrodesis result in significant mechanical lameness but may diminish clinical discomfort.

Monitoring of Animal

I. NSAIDs are administered only as needed at the lowest effective dose.
II. Reexamine the animal every 1 to 4 months to assess the efficacy of therapy and to monitor for any complications of treatment (Bergh and Budsberg, 2005).
  A. Perform a complete blood count and biochemical profile before initiating therapy.
  B. Laboratory tests are repeated every few months while the animal is on NSAIDs to monitor for hematological, hepatic, and renal abnormalities.
III. Perform follow-up radiographs 8 to 12 weeks after surgery in animals treated with surgical procedures.

Cranial Cruciate Ligament Rupture

Definition and Causes

I. Disruption of the cranial cruciate ligament (CCL) results in stifle instability and secondary DJD.
II. An acute mechanical overload from trauma can cause disruption of a normal CCL.
III. More commonly, a progressive deterioration of the ligament coupled with a normally high level of mechanical stress results in rupture.

Pathophysiology

I. The CCL ligament limits cranial tibial subluxation, internal rotation of the tibia, and stifle hyperextension.
II. Rupture results in stifle joint instability, which causes DJD and meniscal damage.
III. Meniscal injury occurs in approximately 20% to 80% of cases (Vasseur, 2003).
  A. The lateral meniscus is seldom damaged because of its mobility.
  B. The medial meniscus is commonly damaged because the structure is relatively immobile.
    1. Medial meniscal injury results from either crushing or tearing.
    2. Meniscal injury leads to further instability and synovitis.

Clinical Signs

I. Lameness can vary from mild and intermittent (partial tear) to non–weight-bearing (complete rupture and/or meniscal tear).
II. Non–weight-bearing lameness is often noted at the time of ligament rupture, followed by partial weight bearing within 48 to 72 hours.
III. Pain is elicited with palpation, manipulation, and full extension of the stifle joint.
IV. Stifle effusion, periarticular fibrosis (medial buttress formation), positive cranial drawer test, positive tibial compression test, bony crepitus, and muscle atrophy may be noted.
V. A meniscal click may be evident with flexion of the stifle, if the meniscus is torn.
VI. Bilateral CCL rupture may result in difficulty, inability, or unwillingness to rise and can be confused with neurological disease or myopathy.

Diagnosis

I. Stifle joint palpation is the most reliable noninvasive test.
II. Positive cranial drawer and/or tibial compression tests are diagnostic.
  A. To perform the cranial drawer test, position the animal in lateral recumbency.
    1. Place the thumb of the proximal hand behind the lateral fabella and the index finger on the patella.
    2. Place the thumb of the distal hand behind the fibular head, and place the index finger on the tibial tuberosity.
    3. Check the tibia for cranial movement with respect to the femur throughout a range of motion (from 30 degrees short of full extension to 90 degrees of flexion).
    4. In the adult, no cranial drawer is present.

5. In the juvenile, 3 to 4 mm of cranial drawer may be present; it ends with an abrupt stop and is symmetrical in both stifles.
6. Cranial drawer in flexion is consistent with a partial CCL rupture.

B. To perform the tibial compression test, position the animal in lateral recumbency.
1. Grasps the metatarsus with the distal hand.
2. Extend the index finger of the proximal hand down the straight patellar tendon, with the fingertip on the tibial tuberosity.
3. Monitor for cranial tibial translation as the hock is flexed.

III. Radiographic findings are consistent with DJD.
A. Effacement of the infrapatellar fat pad, with soft tissue opacity in the lateral view, is consistent with stifle joint effusion.
B. Periarticular or peritrochlear osteophytosis may be detected.
C. Osteophytosis of the base or apex of the patella, distal aspect of the fabella, and cranial intercondyloid area of the tibia may be noted.
D. Cranial tibial subluxation may be seen.
E. Medial buttress formation may be seen on the caudocranial view.

IV. Stifle arthrotomy or arthroscopy may be used to confirm the diagnosis.

Differential Diagnosis

I. Patellar luxation
II. Stifle OCD
III. Avulsion of the long digital extensor tendon
IV. Caudal cruciate ligament rupture
V. Hip dysplasia

Treatment

I. Very small dogs (<5 kg) and most cats may only require medical management (see Osteoarthritis).
II. Larger dogs, obese cats, and active small dogs benefit from stifle stabilization.
III. Extracapsular techniques use elements outside the joint to provide stability.
A. Lateral suture (lateral retinacular imbrication)
B. Fibular head transposition
IV. Intracapsular techniques use an intraarticular graft (patellar tendon or biceps fascia) to stabilize the joint.
A. Under-and-over fascial technique
B. Over-the-top procedure
V. Osteotomy procedures alter joint biomechanics to lessen or eliminate the cranial tibial thrust force, thereby eliminating the need for the cranial cruciate ligament.
A. Tibial plateau–leveling osteotomy
B. Tibial-closing wedge osteotomy
C. Tibial tuberosity advancement
VI. In young dogs, avulsion of the femoral origin or (more commonly) the tibial insertion of the CCL may occur; if the avulsed fragment is large enough, then it may be reduced and stabilized with internal fixation.
VII. If medial meniscal injury is present, the damaged portion (partial meniscectomy) or the entire meniscus (medial meniscectomy) is removed.

Monitoring of Animal

I. Institute medical management and monitoring for osteoarthritis in all animals.
II. A bandage may be placed after an arthrotomy to minimize postoperative swelling and edema.
III. Evaluate limb function and stifle stability 6 to 8 weeks postoperatively.
IV. Radiographically evaluate bony healing 6 to 8 weeks after osteotomy procedures.
V. Begin low-impact activity (e.g., leash walking) at weeks 2 to 4 and continue until lameness resolves (typically by weeks 6 to 8).
VI. The risk for contralateral CCL rupture in cases without a known traumatic event is high (Vasseur, 2003).
VII. Most procedures result in 90% of affected animals returning to good (occasional lameness) or excellent (no discernable lameness) function (Vasseur, 2003).
VIII. Deterioration of limb function after stifle stabilization may be the result of latent meniscal injury, which requires arthroscopic or open meniscectomy (partial or complete).

INFECTIOUS ARTHRITIS

Bacterial Arthritis

Definition and Causes

I. Bacterial joint infection results in arthritis.
II. Hematogenous spread of bacteria may occur from the respiratory, urinary, and digestive tracts; umbilicus; and endocardium, primarily in young or immunocompromised animals.
III. Exogenous sources are the most common and include trauma, surgical procedures, and intraarticular injections.
IV. Common organisms include staphylococci, streptococci, and coliforms.

Pathophysiology

I. Bacterial contamination of the synovium results in edema, hyperemia, and infiltration of neutrophils.
II. Inflammation of the synovium leads to capillary rupture and local areas of necrosis.
III. Lysosomal enzyme and enzyme by-products released by the synovial cells and neutrophils cause degradation of the cartilage matrix and collagen.

Clinical Signs

I. Joint effusion, periarticular swelling, and discomfort are found in one or more joints.
A. Hematogenous spread typically involves multiple joints.
B. Exogenous infections usually involve one joint.
II. Severe, weight-bearing or non–weight-bearing lameness occurs.

III. Pyrexia may be present.
   A. Systemic signs are often present in hematogenous cases.
   B. Systemic signs are uncommon in exogenous cases.

Diagnosis

I. Tentative diagnosis is based on clinical findings, particularly a history of recent joint surgery.
II. Definitive diagnosis is based on results of joint fluid analysis (see Table 80-2).
   A. Reduced viscosity
   B. Increased white blood cell (WBC) count
   C. Predominance of neutrophils
III. Joint fluid culture is commonly negative; however, inoculation of blood culture medium facilitates growth of the causative organism (Montgomery et al., 1989).

Differential Diagnosis

I. Trauma
   A. Ligamentous injury
   B. Intraarticular fracture
   C. Periarticular or physeal fracture
   D. Periarticular or intraarticular neoplasia
II. Other infectious arthritides
   A. Calicivirus infection of cats (Dawson et al., 1994)
   B. Mycoplasmosis
   C. Coronavirus
   D. Fungal infections: rare, usually associated with adjacent fungal osteomyelitis or immunocompromise

Treatment

I. Systemic antimicrobial therapy is initiated immediately after samples are obtained for fluid analysis and culture.
II. A broad-spectrum, bactericidal agent is started pending the results of culture, followed by long-term (6 to 8 weeks) oral administration.
   A. Cefazolin 20 to 25 mg/kg IV, IM TID to QID
   B. Cephalexin 11 to 33 mg/kg PO TID
   C. Enrofloxacin 5 to 20 mg/kg PO SID or 2.5 to 10 mg/kg PO BID (mature dogs)
   D. Tetracycline 15 to 20 mg/kg PO TID for 4 weeks or doxycycline 5 to 10 mg/kg PO BID for 4 weeks for *Borrelia* spp., rickettsiae, *Mycoplasma* spp., bacterial L-forms
III. Joint lavage is essential to decompress the joint and remove cellular and enzymatic agents that exacerbate cartilage damage.
   A. Fine-needle aspiration or ingress-egress drainage is rarely sufficient.
   B. Arthrotomy or arthroscopy, surgical debridement, and copious (5 L) lavage is recommended in the following cases (Bubenik and Smith, 2003):
      1. Postoperative infection
      2. Septic joints left untreated for >72 hours
      3. Septic joints that have not responded to antibiotics alone for 72 hours
      4. Penetrating wounds
IV. Severe infections may necessitate management of the joint as an open wound, with daily sterile bandage changes until the wound is fully granulated.

Monitoring of Animal

I. Parenteral (ideally) or oral antibiotic therapy, based on the results of culture and sensitivity, is continued for a minimum of 4 weeks or at least 2 weeks beyond resolution of clinical signs.
II. Residual lameness may be treated as outlined previously for Osteoarthritis.

Borreliosis (Lyme Disease)

See Chapter 113.

Ehrlichiosis

See Chapter 115.

Rocky Mountain Spotted Fever

See Chapter 115.

IMMUNE-MEDIATED ARTHRITIS

Nonerosive Arthritides

Definition and Causes

I. These inflammatory diseases are characterized by periarticular inflammation, without radiographic or histological evidence of joint destruction in their early stages.
II. The most common nonerosive immune-mediated arthropathies are idiopathic polyarthritis, systemic lupus erythematosus (SLE), polyarthritis of chronic disease, and drug-induced polyarthritis (Davidson, 2003).

Pathophysiology

I. Immune complex deposition in the synovial membrane results in synovitis.
II. Mononuclear cell infiltration occurs in the synovium.
III. Neutrophils migrate from synovial capillaries into the synovium.
IV. The inflammatory process results in weakening of the intraarticular and periarticular ligamentous structures and leads to joint instability.
V. In these cases, osteoarthritis may arise from chronic joint instability rather than the initial inflammatory process.

Clinical Signs

I. Lameness affects one or more limbs.
   A. The distal limb joints (carpus, tarsus, interphalangeal joints) are most often affected.
   B. Monoarticular disease is most commonly seen in the elbow.
II. Pain, joint effusion, periarticular fibrosis, periarticular soft tissue swelling, and palpable joint hyperthermia may occur.
III. Clinical signs may be intermittent or persistent and shift from limb to limb.
IV. SLE is often accompanied by abnormalities in other organs (see Chapters 76, 91, and 104).

Diagnosis

I. Radiographic findings are limited to joint effusion and periarticular fibrosis in the early stages.
II. Radiographic findings in late stages are similar to those of erosive polyarthritis (periarticular osteophytosis, joint space collapse).
III. Synovial fluid analysis is consistent with suppurative inflammation (see Table 80-2).
IV. Lupus erythematosus cell assays may be positive.
V. Serological testing for antinuclear antibody (ANA) may be positive.
VI. Serological testing for rheumatoid factor and infectious agents is negative.

Differential Diagnosis

I. Erosive arthritides
II. Infectious arthritides
III. Osteoarthritis

Treatment and Monitoring

I. Prednisone (1 to 2 mg/kg PO BID for 10 to 14 days) is used as the initial treatment.
II. In mild cases chronic administration of NSAIDs may control clinical signs (see Table 80-2).
III. If synovial fluid WBC counts drop to <4000 cells/μL, then the prednisone dose is slowly tapered over several weeks to 1 mg/kg PO QOD.
IV. If remission continues on reduced doses for 1 to 3 months, then elimination of prednisone can be considered.
V. In refractory canine cases, a cytotoxic drug may be added to the prednisone.
   A. Cyclophosphamide 1.5 to 2.5 mg/kg PO SID for 4 consecutive days each week (discontinued 1 month after remission, after 4 months of therapy, or if hemorrhagic cystitis develops)
   B. Azathioprine 2 mg/kg PO SID for 14 to 21 days, then 1 to 2 mg/kg PO QOD for 1 month beyond remission
   C. Methotrexate 2.5 mg/m^2 PO SID
VI. Arthrodesis may be considered for irreversibly damaged joints.

Erosive Arthritides

Definition and Causes

I. These arthritides are characterized by periarticular inflammation, with destruction of articular cartilage and bone.
II. They include rheumatoid arthritis (RA), erosive polyarthritis of greyhounds (EPG), and feline chronic progressive polyarthritis.

Pathophysiology

I. Specific causes have not been identified.
II. In RA, host immunoglobulin (Ig) G becomes antigenic and IgM (rheumatoid factor) is formed in response.
III. Immune complex deposition in the synovium causes synovitis.
IV. Destruction of the articular cartilage and bone results from the ensuing inflammatory process.

Clinical Signs

I. RA usually affects adult, small-breed dogs.
II. EPG affects greyhounds 3 to 30 months of age.
III. Feline chronic progressive polyarthritis affects cats 1 to 5 years of age.
IV. Lameness may occur in one or more limbs.
V. The most commonly affected joints are the distal limb joints, such as the carpus, tarsus, and interphalangeal joints.
VI. Pain, joint effusion, periarticular fibrosis, periarticular soft tissue swelling, and palpable joint hyperthermia may be noted.
VII. Clinical signs may be intermittent or persistent and shift from limb to limb.

Diagnosis

I. Radiographic findings include joint space collapse, periarticular fibrosis, periarticular soft tissue swelling, subchondral bone cysts, and periarticular osteophytosis.
II. In chronic cases, joint subluxation or luxation may be present.
III. Synovial fluid analysis is consistent with suppurative inflammation (see Table 80-2).
IV. Rheumatoid factor assays are positive in 25% to 75% of cases (Davidson, 2003).
V. ANA analysis must be negative for a diagnosis of RA.
VI. Animals with a positive ANA analysis probably have SLE.

Differential Diagnosis

I. Nonerosive arthritides
II. Infectious arthritides
III. Osteoarthritis

Treatment

I. Prednisone (1 to 2 mg/kg PO BID for 10 to 14 days) is used as the initial treatment.
II. In mild cases chronic administration of NSAIDs may control clinical signs (see Table 80-2).
III. In refractory cases a cytotoxic drug may be added to the prednisone (see Nonerosive Arthritis).
IV. In dogs, weekly injections of sodium aurothioglucose (1 mg/kg IM) have been successful for RA.
V. Arthrodesis may be considered in irreversibly damaged joints.

Monitoring of Animal

I. Complete resolution is rare, but remission may be achieved with 3 to 6 months of therapy.
II. CBC and platelet counts are monitored every 1 to 3 weeks in animals on cytotoxic therapy, depending on the dosage.
III. If synovial fluid WBC counts drop to <4000 cells/μL and clinical remission occurs, then dosages are slowly tapered over several weeks.
IV. Reexamination is recommended at 1- to 6-month intervals to assess for recurrence.
V. Treatment of EPG has been unrewarding, and the prognosis is poor.

VI. Cats are monitored at yearly intervals for infection with feline leukemia virus if treated with cytotoxic agents.

NEOPLASIA

Synovial Sarcoma

Definition and Causes

I. Synovial sarcoma is a malignant neoplasm that arises from primitive, undifferentiated, mesenchymal tissue adjacent to synovial membranes (Fox et al., 2002).
II. The etiology is unknown.
III. Presence and growth of the intraarticular tumor results in an inflammatory arthropathy and joint destruction.

Clinical Signs

I. Progressive lameness in a single limb is a classic sign.
II. Large-breed dogs are most commonly affected.
III. Joint effusion, periarticular soft tissue swelling, edema of the limb, and discomfort with manipulation of the limb are common.

Diagnosis

I. Radiographic findings may include intraarticular soft tissue opacity, subchondral and epiphyseal bone lysis, periarticular osteophytosis, soft tissue calcification, and an irregular periosteal reaction.
II. Definitive diagnosis requires arthroscopic or open biopsy, as well as histological examination.
III. Reliability of differentiating synovial sarcoma from other soft tissue sarcomas or round-cell neoplasia via histopathologic examination or immunohistochemistry is questionable (Fox et al., 2002).

Treatment

I. Limb amputation: local excision not possible
II. Chemotherapy: efficacy not well established

Monitoring of Animal

I. Monitor for local recurrence and distant metastasis.
II. The metastatic rate for synovial sarcoma is 40% to 50% (Vail et al., 1994).

TRAUMATIC DISORDERS

Caudal Cruciate Ligament Rupture

Definition and Causes

I. Trauma is the typical cause of this rare condition.
II. Force applied to the tibia in the caudal direction may cause isolated rupture because it prevents caudal subluxation of the tibia.
III. More commonly, this structure is damaged in association with collateral ligament rupture or stifle luxation.

Clinical Signs

I. Acute-onset lameness is seen after known or possible trauma (Johnson and Olmstead, 1987).
II. Stifle pain and joint effusion may be seen.
III. Caudal drawer sign, tibial sag, and an avulsion fragment (radiographically) may be evident in some cases.
   A. Caudal drawer sign must be carefully differentiated from a cranial drawer sign.
   B. Caudal drawer sign is present if the tibia moves from a neutral position to a position of caudal subluxation.

Diagnosis

I. Caudal drawer sign
II. Confirmed surgically by arthrotomy or arthroscopy

Differential Diagnosis

I. Cranial cruciate ligament rupture
II. Stifle collateral ligament rupture
III. Stifle luxation
IV. Meniscal injury
V. Patellar luxation

Treatment

I. Clinical signs may resolve with conservative treatment with cage rest and NSAIDs for 8 weeks.
II. In large dogs or cases of persistent lameness, extracapsular stabilization is recommended.
   A. Extracapsular suture stabilization
   B. Popliteal tenodesis

Monitoring of Animal

I. After surgery, restrict exercise for 6 to 8 weeks, then gradually return the animal to normal activity during weeks 8 to 16.
II. Prognosis for isolated rupture of the caudal cruciate ligament is good.

Stifle Luxation (Deranged Stifle)

Definition and Causes

I. Stifle subluxation is a complete or partial rupture of the stifle collateral ligaments or a combination of rupture of the stifle collateral ligaments and the cruciate ligaments (stifle luxation).
II. Severe trauma to the stifle joint is the cause.

Pathophysiology

I. Ligament injuries (sprains) can be mild (first degree), more severe with stretching and rupture of ligament fibers (second degree), or result in tearing or avulsion of the ligament (third degree).
II. Only third-degree and some second-degree injuries require surgical therapy.
III. Isolated rupture of the collateral ligaments is rare in small animals (Vasseur, 2003).
IV. Most injuries involve rupture of the medial and/or lateral collateral ligaments and the cranial and/or caudal cruciate ligaments.
   A. Most commonly affected ligaments are the medial collateral cranial cruciate ligament and the caudal cruciate ligament.

B. Lateral collateral ligament becomes lax with stifle joint flexion, which may spare it from damage.

Clinical Signs

I. Stifle effusion, pain, and angular deviation may be evident.
II. Damage to the medial collateral ligament results in a valgus instability.
III. Damage to the lateral collateral ligament results in a varus instability.
IV. Damage to the cruciate ligaments results in cranial and/or caudal drawer.

Diagnosis

I. Meticulous physical examination under anesthesia allows determination of which ligaments are involved.
II. Results of palpation may be confusing, and joint exploration is frequently required to confirm individual ligament involvement.

Differential Diagnosis

I. Cranial cruciate ligament rupture
II. Bacterial arthritis
III. Intraarticular or periarticular fracture

Treatment

I. Reconstruction of each of the involved ligaments
   A. The collateral ligaments can be primarily repaired, or a prosthetic ligament can be created from bone anchors or screws and heavy-gauge monofilament suture.
   B. The stifle can be stabilized as for cranial and/or caudal cruciate ligament rupture.
II. Transarticular stabilization
   A. Transarticular pin placement for small dogs or cats
   B. Rigid transarticular fixator application
   C. Hinged transarticular fixator placement
   D. External coaptation
   E. Arthrodesis

Monitoring of Animal

I. Institute medical management and monitoring for DJD.
II. A bandage may be placed to minimize postoperative swelling and edema after arthrotomy.
III. Evaluate limb function and stifle stability 6 to 8 weeks postoperatively.
IV. Low-impact activity is recommended, beginning at week 2 to 4 and continuing until lameness has resolved—typically by week 6 to 8.
   A. In animals treated with external skeletal fixation, remove the fixation device 4 to 6 weeks postoperatively.
   B. Institute low-impact activity after fixator removal.

Traumatic Joint Luxation

Definition and Causes

I. Traumatic joint luxation is the complete separation of two articulating joint surfaces.
II. Severe trauma is the typical cause of joint luxation.
III. Traumatic episode results in the disruption of the normal stabilizers of the joint, including the joint capsule, collateral ligaments, and other associated ligaments.
IV. Commonly affected joints include the shoulder, elbow, carpus, hip, stifle, tarsus, metacarpophalangeal and tarsophalangeal joints, and interphalangeal joints.

Clinical Signs and Diagnosis

I. Lameness of the affected limb can vary from mild to non–weight-bearing.
II. Clinical signs and history of trauma allow a presumptive diagnosis.
III. Physical examination findings are confirmatory in many cases.
   A. Discomfort with manipulation
   B. Excessive mobility
   C. Soft tissue swelling
   D. Abnormal limb length, with affected limb shorter
IV. Radiography confirms the luxation.

Differential Diagnosis

I. Intraarticular or periarticular fracture
II. Bacterial arthritis
III. Neoplasia

Treatment

I. Closed reduction and coaptation
II. Open reduction
III. Carpus
   A. Isolated collateral ligament injuries may be treated with primary repair or placement of a prosthetic ligament.
   B. Most injuries require partial carpal arthrodesis or pancarpal arthrodesis.
IV. Hip
   A. Closed reduction
      1. It is indicated for acute luxation (<3 to 5 days) in animals with normal hip conformation and no intraarticular fractures.
      2. Maintain reduction with an Ehmer sling for 3 to 4 weeks.
   B. Open reduction
      1. It is indicated when the femoral head does not seat well in acetabulum, the hip has reluxated after closed reduction, the hip has been chronically luxated, and intraarticular fractures or hip dysplasia are present.
      2. Open reduction techniques include toggle pin, extracapsular prosthesis, and iliofemoral suture.
   C. Salvage techniques
      1. FHO
      2. THA
V. Tarsus
   A. Isolated collateral ligament injuries may be treated with primary repair or placement of a prosthetic ligament.
   B. Many injuries require partial or total tarsal arthrodesis.
VI. Metacarpal, metatorsal, tarsophalangeal, and interphalangeal joints
   A. Closed reduction and external coaptation
   B. Primary ligamentous repair

C. Arthrodesis
D. Digit amputation

VII. Shoulder and elbow (see Congenital and Degenerative Disorders)

Monitoring of Animal

I. Instruct the owner to monitor bandages and slings SID-BID.
II. Restrict exercise for 4 to 8 weeks after bandage or sling removal to allow remodeling of ligamentous structures.
III. In surgical cases, obtain radiographs 6 to 8 weeks post-operatively to assess reduction, progression of osteoarthritis, and implant stability.

Physeal Injury

See Chapter 81.

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CHAPTER 81

Diseases of Bone

Nicholas J. Trout

DEVELOPMENTAL DISORDERS

Panosteitis

Definition and Causes

I. Panosteitis is an acquired self-limiting disease that affects the long bones of rapidly growing, large-breed dogs.
II. The cause is unknown.
III. German shepherd dogs are one of several breeds that are predisposed (La Fond et al., 2002).

Pathophysiology

I. Increased osteoblast and fibroblast activity leads to degeneration and necrosis of bone marrow fatty tissue in the diaphyseal and metaphyseal regions, with replacement by fibrous connective tissue.
II. It is frequently associated with the nutrient foramen of long bones.
III. Medullary hypertension and vascular congestion may cause secondary endosteal and periosteal new bone formation (Demko and McLaughlin, 2005).
IV. New bone resorption returns the marrow to normal.

Clinical Signs

I. Typically a large- or giant-breed dog develops an acute lameness in a single limb or has a shifting, intermittent lameness.
II. Affected dogs are more commonly males, 5 to 18 months of age (range, 2 months to 5 years) (Montgomery, 2003).
III. Pain is elicited on deep palpation of the diaphysis and metaphysis of affected long bones.
IV. Most commonly affected bones are the ulna, radius, humerus, femur, and tibia, in that order.
V. Severely affected dogs may have pyrexia, anorexia, and lethargy.

Diagnosis

I. History, signalment, clinical signs, and physical examination findings suggest the condition.
II. Radiography may reveal several findings.
   A. "Cotton ball" appearance (radiodense blurring) of the trabecular pattern in the medullary canals and an endosteal reaction are seen.
   B. Smooth periosteal reaction gives the appearance of cortical thickening.
   C. Radiographs are frequently unrewarding because clinical signs precede these changes by 7 to 10 days.
III. Nuclear scintigraphy is a better diagnostic tool (Schwarz et al., 2004).

Differential Diagnosis

I. Elbow dysplasia
II. Hip dysplasia
III. Hypertrophic osteodystrophy
IV. Osteochondroses
V. Trauma

Treatment

I. Therapy consists of supportive care and analgesia.
II. Nonsteroidal antiinflammatory drugs (NSAIDs) are used during the acute phase of the disease, together with exercise restriction and weight reduction (if merited).
   A. Carprofen 2.2 mg/kg PO BID
   B. Meloxicam 0.1 mg/kg PO SID
   C. Deracoxib 1 to 2 mg/kg PO SID

Monitoring of Animal

I. Warn the owners that the lameness commonly shifts to another limb, but usually resolves permanently once the animal reaches skeletal maturity.
II. Secondary complications are rare.

Hypertrophic Osteodystrophy

Definition and Causes

I. Hypertrophic osteodystrophy (metaphyseal osteopathy) is a disease of the long bones of young, growing, large- and giant-breed dogs that causes metaphyseal trabecular disruption.
II. The cause is unknown.
III. The condition is not caused by a deficiency of vitamin C or excessive vitamin D, dietary mineral, or calories.
IV. Links to vaccination for canine distemper virus remain unproven (Harrus et al., 2002; Crumlish et al., 2006).

Pathophysiology

I. Disturbance of the metaphyseal blood supply leads to delayed ossification of the physeal hypertrophic zone.
II. Inflammation and necrosis may occur secondary to metaphyseal trabecular microfractures.

Clinical Signs

I. Metaphyseal limb swelling often involves all four limbs, but is more noticeable in the thoracic limbs.
II. Male dogs are affected more than female dogs and are usually 2 to 8 months of age.
III. In the acute form, transient, episodic, low-grade lameness occurs, with pyrexia and hot, swollen, painful limbs.
IV. Peracute cases may have lethargy, dehydration, and severe pain on palpation of the affected area.
V. Severe physeal damage rarely leads to angular limb deformities.

Diagnosis

I. History, signalment, clinical signs, and physical examination findings are often suggestive of the condition.
II. Radiographs reveal a pathognomonic pseudophyseal line adjacent to the physis on the metaphyseal side of the bone.
III. Laboratory findings are invariably unremarkable.
IV. Rare hypocalcemia is of unknown significance.

Differential Diagnosis

I. Panosteitis
II. Septic arthritis
III. Rickets
IV. Osteomyelitis
V. Trauma

Treatment

I. Therapy consists of supportive care and analgesia.
II. Correct an inappropriate diet and withdraw excessive supplements of vitamin C, vitamin D, or minerals.
III. NSAIDs are used during the acute phase of the disease.
   A. Carprofen 2.2 mg/kg PO BID
   B. Meloxicam 0.1 mg/kg PO SID
   C. Deracoxib 1 to 2 mg/kg PO SID
IV. Rest, confinement, use of soft bedding, and turning of the animal every 4 to 6 hours is done as necessary.
V. Severe cases may require more intensive management with prednisolone at 0.25 to 0.5 mg/kg PO SID (after ruling out the possibility of a bacterial infection), fluid therapy, and nutritional care.
VI. If lameness persists because of angular limb deformities, then surgical correction may be necessary.

Monitoring of Animal

I. Relapses can occur in growing dogs.
II. Most mild and moderate cases recover completely.
III. Owners may elect euthanasia of severely affected animals or ones that experience multiple relapses.

Craniomandibular Osteopathy

Definition and Cause

I. Craniomandibular osteopathy is a proliferative bone disease that primarily affects the mandible, zygomatic arches, and tympanic bullae of growing dogs.
II. The cause is unknown.

Pathophysiology

I. Existing lamellar bone undergoes resorption and replacement by new, woven bone.
II. Woven bone may be replaced by mature bone, but permanent distortion of bony architecture is common.

Clinical Signs

I. It is commonly seen in terrier breeds, 3 to 8 months of age, with males and females equally affected.
II. Difficult mastication, with secondary weight loss and dehydration, may occur.
III. Pain is detected when manually opening the animal's mouth and on deep palpation of affected flat bones.
IV. Decreased range of motion is present in the temporomandibular joint.
V. Intermittent fever may be observed.
VI. The disease may be seen in other breeds, such as the Pyrenean mountain dog, Shetland sheepdog, Labrador retriever, Great Dane, English bulldog, Doberman pinscher, and boxer.
VII. A similar condition, calvarial hyperostosis syndrome, is reported in the bullmastiff (Pastor et al., 2000; McConnell et al., 2006).

Diagnosis

I. History, signalment, clinical signs, and physical examination findings allow a tentative diagnosis.
II. Radiographs reveal bilaterally symmetrical, periosteal proliferation along the mandible and tympanic bullae.
III. Bone biopsy is rarely necessary; however, histopathologic examination demonstrates osteoclastic resorption of lamellar bone, replacement of bone marrow by vascular fibrous tissue, and formation of coarse trabecular bone.

Differential Diagnosis

I. Myositis
II. Temporomandibular joint malalignment or malformation
III. Osteomyelitis
IV. Neoplasia

Treatment

I. Treatment consists of supportive care and analgesics until the animal reaches skeletal maturity.
II. NSAIDs may be useful.
   A. Carprofen 2.2 mg/kg PO BID
   B. Meloxicam 0.1 mg/kg PO SID
   C. Deracoxib 1 to 2 mg/kg PO SID
III. Soft or liquefied food helps to reduce painful chewing.
IV. Gastrostomy or esophagostomy tubes may be necessary if the animal is unable to eat.
V. Rostral mandibulectomy allows affected dogs to lap gruel.
VI. Euthanasia may be indicated in severely affected dogs.

Monitoring of Animal

I. Schedule periodic physical and radiographic examinations of the animal (every 6 to 8 weeks) until skeletal maturity.
II. Warn owners of the possibility of relapses until skeletal maturity.

III. Prognosis is guarded when excessive bony proliferation of the bullae and mandible causes pain and poor condition.

Multiple Cartilaginous Exostoses

Definition and Causes

I. Multiple cartilaginous exostoses (osteochondromatosis) are proliferations of cartilage-capped exostoses arising from the surface of bones formed by endochondral ossification (Jacobson and Kirberger, 1996).
II. The exact cause is unknown, although a familial tendency has been reported in dogs (Chester, 1971).
III. Exostoses have been associated with feline leukemia virus infection in cats (Poole, 1993).

Pathophysiology

I. Chondrocytes displaced from the periphery of a long bone physis create an immature, independent growth plate perpendicular to the long axis of the bone.
II. In dogs, exostoses enlarge until skeletal maturity, when they stop growing.
III. In cats, exostoses can grow after skeletal maturity.

Clinical Signs

I. Exostoses only cause clinical signs if they have a compressive effect on adjacent structures.
II. Signs may be mild (e.g., lameness if they encroach on a tendon or ligament) or severe (e.g., paralysis from spinal cord compression).
III. Limb exostoses are often bilateral (Poole, 1993).
IV. Exostoses can be asymptomatic, incidental findings.
V. Affected dogs are typically young (6 to 18 months), whereas cats are older (2 to 4 years).

Diagnosis

I. Palpation of a firmly attached swelling associated with a rib, vertebrae, or long bone is characteristic.
II. Survey radiographs of the entire skeleton can be useful to locate smaller lesions before they become clinically significant.
III. Radiographs reveal the following:
   A. Outgrowths of bone contiguous with the periosteal surface from which they arise
   B. Varying amounts of hyaline cartilage within the exostoses producing a mottled appearance
   C. Smooth or irregular, sessile or pedunculated outgrowths
IV. Histological evaluation of a biopsy is characterized by a hyaline cartilage cap covering a base of cancellous bone.

Differential Diagnosis

I. Neoplasia
II. Trauma
III. Hypervitaminosis A (cats)
IV. Calcinosis circumscripta

Treatment

I. Although the heritable nature of the disease has not been proven, sterilization of affected animals is recommended.
II. Surgical removal is indicated if the exostosis produces secondary clinical signs from compression.
III. In cats, surgical excision may only be palliative because malignant transformation can occur.

Monitoring of Animal

I. In asymptomatic cases, perform a physical examination and radiographic evaluation every 6 months to define whether the lesion is static or enlarging.
II. Prognosis in dogs depends on the age of the animal at the time of diagnosis (more guarded if young animals with multiple lesions), as well as the number, location, and resectability of the lesions.
III. Prognosis in cats is poor because of the potential for malignant transformation.

Radial and Ulnar Growth Deformities

Definition and Causes

I. Radial and ulnar growth deformities occur as developmental abnormalities from total or partial fusion of the distal ulna, as well as from distal radial or proximal radial physes.
II. They can lead to asynchronous growth of the radius and ulna, with abnormal conformation of the forelimb.
III. Physeal abnormalities can arise from the following:
   A. Direct or indirect trauma
   B. Hypertrophic osteodystrophy: can bridge the growth plate
   C. Retained ulnar cartilaginous core
      1. Retarded endochondral ossification at the distal ulnar physis leads to slowed growth similar to a traumatic physeal closure.
      2. Retained ulnar cartilaginous cores do not always produce a disturbance in longitudinal growth.
   D. Chondrodystrophic breeds: relative retardation of the growth of the ulna compared with the radius
IV. Antebrachial angular and length deformities can affect the antebrachiocarpal joint and cubital joint, leading to subluxation and degenerative joint disease.

Pathophysiology

I. Proximal ulnar physis contributes only to olecranon length (15% of total length) and closes at 5 to 8 months of age; premature closure causes no significant abnormalities (Carrig and Wortman, 1981).
II. Distal ulnar physis contributes longitudinal growth distal to the elbow (approximately 85% of total length) and closes at 6 to 8 months.
III. Distal ulna physis grows more actively than the distal radius (>15%) and contributes as much growth as the proximal and distal radial physes combined.
IV. Proximal radial physis contributes 30% to 40% of total length and closes at 5 to 8 months of age (Carrig and Wortman, 1981).
V. Distal radial physis contributes about 60% to 70% of total length and closes at 6 to 9 months of age (Carrig and Wortman, 1981).

VI. As a paired set of bones, the radius and ulna must undergo synchronous, unrestricted growth to maintain proper alignment of the antebrachium and shared articular surfaces.

Clinical Signs

I. Signs include varying degrees of forelimb lameness, abnormal limb length, angulation (valgus, varus), and internal or external rotation along the long axis of the radius and ulna.
II. Joint pain, crepitus, and swelling with restricted range of motion are seen.
III. Signs are typically unilateral when initiated by trauma and are bilateral in young, large- or giant-breed dogs secondary to retained ulnar cartilaginous cores.

Diagnosis

I. Radiography is required to confirm the diagnosis and identify the exact lesions.
II. See Table 81-1 for diagnostic features.

Differential Diagnosis

I. Poor conformation
II. Carpal and elbow ligament and/or tendon laxity

Treatment and Monitoring

I. See Table 81-1 for therapeutic options.
II. Physical examination to assess limb conformation and range of movement in the elbow and antebrachiocarpal joints, together with radiographic evaluation of the bones and joints, is undertaken every 1 to 2 weeks in immature animals.
III. After corrective surgery, evaluate the animal clinically and radiographically every 2 to 4 weeks, depending on the underlying problem, type of surgery, and age of the animal.

INFECTIOUS DISORDERS

Osteomyelitis

Definition and Causes

I. Osteomyelitis is inflammation of bone marrow, cortex, and possibly periosteum (Johnson and Hulse, 2002; Herron, 1993)
II. Most commonly, bacteria cause osteomyelitis; however, other causes include fungi such as *Coccidioides immitis* (southwestern states) and *Blastomyces dermatitidis* (southeastern and central states), parasites, viruses, foreign bodies, and corrosion of metal implants.
III. Gram-positive organisms are more common in canine osteomyelitis (Dernell, 1999).
  A. *Staphylococcus* spp.
  B. *Streptococcus* spp.
  C. *Escherichia coli*
  D. *Proteus* spp.
IV. In the majority of cases a single organism is identified.
V. Anaerobic bacteria are uncommon isolates, but failure of standard treatments may reflect their presence.

Pathophysiology

I. Bacterial exposure may arise from exogenous contamination at the time of the original injury (e.g., puncture wound, open fracture, shearing injury), at the time of fracture repair, or from hematogenous seeding.
  A. Hematogenous infection is uncommon in small animals.
  B. Hematogenous infection can localize in the metaphysis of immature animals, in the epiphysis (sinusoidal venous sludging), or in the subchondral bone of adult animals.
II. Fungal infections usually occur secondary to pulmonary inoculation.
III. Factors affecting osteomyelitis secondary to exogenous sources include the following:
  A. Extent of soft tissue damage and alteration of blood supply
  B. Inoculation of bacterial flora
  C. Stability of fracture after repair
  D. Formation of a biofilm (glycocalyx): promotes bacterial attachment to bone or foreign bodies, and protects the bacteria from phagocytes, antibodies, and antibiotics
  E. Systemic or local factors that influence immune surveillance, metabolism, or local vascularity (Fossum and Hulse, 1992)

Clinical Signs

I. Acute osteomyelitis
  A. Signs are noted within 3 weeks (most often within 5 days) of injury, concurrent illness, or fracture repair.
  B. Soft tissue heat, swelling, pain, and lameness are common.
  C. Pyrexia, depression, and anorexia may be noted.
II. Chronic osteomyelitis
  A. Onset of signs months to years after an injury, previous illness or fracture repair
  B. Draining sinus tracts
  C. Pain and lameness
  D. Pyrexia, depression, anorexia uncommon

Diagnosis

I. History, clinical signs, radiography, and laboratory findings are suggestive.
II. Radiographic changes are generally not present until 2 weeks postinfection.
III. Radiography may reveal soft tissue swelling, irregular periosteal reactions, increased medullary density, and bony sequestration walled off by vascular new bone (involucrum).
IV. Fistulography may reveal a draining tract that leads to a bony lesion.
V. Leucocytosis with a neutrophilic left shift is expected with acute osteomyelitis but is often absent in chronic osteomyelitis.
VI. Deep, fine-needle aspirates or a biopsy is obtained for aerobic and anaerobic bacterial culturing.
VII. Do not take cultures from draining tracts.

TABLE 81-1

Frequency, Effects, and Treatment of Radius and Ulna Growth Deformities

	DISTAL ULNAR PHYSEAL CLOSURE	DISTAL RADIAL PHYSEAL CLOSURE	PROXIMAL RADIAL PHYSEAL CLOSURE
Frequency			
	Common	Uncommon	Very uncommon
Effects			
	Bowstring effect on radius causes cranial bowing, carpal valgus and external rotation of carpus, as well as humeroulna subluxation and carpal subluxation Degenerative joint disease	Entire physis closed (symmetrical): usually no growth deformity but can lead to bowstring effect on ulna with carpal varus, internal rotation of carpus, radial head subluxation (if closure occurs early) Closure of lateral physis (asymmetrical): produces a growth deformity from restriction of lateral growth and continued medial growth; distal subluxation of the radial head (associated with fragmented medial coronoid process*), proximal subluxation of the ulna, carpal valgus, dorsal subluxation of the radiocarpal joint Degenerative joint disease	Short radius, limb deformity unlikely, humeroradial subluxation, lateral displacement of the radial head, oblique angulation of radial joint surface Degenerative joint disease
Treatment of Immature Animals (< 6 to 8 months)			
	1. Normal elbow joint a. Partial distal ulna ostectomy with free fat graft in the bone defect b. Postoperative bandage/splint support 2. Humeroulnar malarticulation a. Proximal ulna osteotomy to allow dynamic improvement of elbow incongruency through triceps muscle pull b. Bone realignment with single intramedullary pin c. Postoperative bandage/splint support	1. Complete closure a. Midshaft radial osteotomy and distraction with external fixator† b. Partial, distal ulnar ostectomy to correct humeroradial malarticulation c. Multiple midshaft radial osteotomies, distractions, and bone plating to maintain limb length 2. Incomplete closure a. Resection of closed physis with interposition of free fat graft b. Radial osteotomy and distraction with external fixator† c. Dome osteotomy of distal radius and external coaptation‡	1. Transverse radial osteotomy and distraction with external fixator 2. Multiple radial osteotomies and bone plate fixation 3. Partial distal ulna ostectomy and fat interposition 4. Proximal ulna ostectomy with intramedullary pinning for mild radial shortening

*Macpherson GC, Lewis DD, Johnson KA: Fragmented coronoid process associated with premature distal radial physeal closure in four dogs. Vet Comp Orthop Traumatol 5:93, 1992.

†Boudrieau RJ: Fractures of the radius and ulna. p. 1953. In Slatter D (ed): Textbook of Small Animal Surgery. 3rd Ed. Saunders, Philadelphia, 2003.

‡MacDonald JM, Matthiesen D: Treatment of forelimb growth deformity in 11 dogs by radial dome osteotomy and external coaptation. Vet Surg 20:402, 1991.

TABLE 81-1

Frequency, Effects, and Treatment of Radius and Ulna Growth Deformities—*cont'd*

DISTAL ULNAR PHYSEAL CLOSURE	DISTAL RADIAL PHYSEAL CLOSURE	PROXIMAL RADIAL PHYSEAL CLOSURE
Treatment of Mature Animals (> 8 to 10 months)		
1. Oblique or dome radial and transverse ulnar osteotomies using internal or external fixation[§] 2. Proximal dynamic ulnar osteotomy to correct humeroulnar malarticulation 3. Proximal ulnar osteotomy and intramedullary pinning to correct mild elbow incongruency	1. Oblique or dome osteotomy with internal or external fixation 2. Transverse osteotomy with distraction and internal or external fixation 3. Proximal ulnar osteotomy and intramedullary pinning to correct mild elbow incongruency	1. Oblique or dome osteotomy with internal or external fixation 2. Transverse osteotomy with distraction and internal or external fixation

[§]Lewis DD, Radasch RM, Beale BS: Initial clinical experience with the IMEX circular external skeletal fixation system. Vet Comp Orthop Traumatol 12:118, 1999; Balfour RJ, Boudrieau RJ, Gores BR: T-plate fixation of distal radial closing wedge osteotomies for treatment of angular limb deformities in 18 dogs. Vet Surg 29:207, 2000.

VIII. When hematogenous osteomyelitis is suspected, obtain serial blood cultures.
IX. See Chapter 111 for diagnosis of fungal infections.

Differential Diagnosis

I. Implant failure and unstable fracture
II. Neoplasia

Treatment

I. Acute osteomyelitis
  A. Prepare the owner for long-term antibiotic treatment (4 to 6 weeks) based on bacterial culture and sensitivity testing, and preferably using minimal inhibitory concentration values.
  B. If bacterial cultures are negative, select antibiotics that have superior penetration of bone.
  C. Common antibiotic options include the following:
    1. Cephalexin 30 mg/kg PO BID
    2. Cefazolin 20 mg/kg IV, IM, SC QID
    3. Amoxicillin/clavulanic acid 22 mg/kg PO TID
    4. Clindamycin 11 mg/kg IV, IM, PO BID to TID
    5. Enrofloxacin 15 mg/kg PO BID (dogs)
    6. Metronidazole 15 mg/kg IV, PO BID
    7. Gentamicin 6 mg/kg IV, IM, SC SID
  D. See Chapter 111 for treatment of specific fungal diseases.
  E. Surgical procedures may be indicated in certain situations.
    1. Debridement, lavage, and drainage
    2. Delayed wound closure
    3. Ensuring fracture stability and removal of loose implants
II. Chronic osteomyelitis
  A. Antibiotic options are similar to those for acute osteomyelitis.
  B. Surgical removal of necrotic debris and dead bone may be warranted.
    1. Sequestrectomy followed by curettage and packing, with an autogenous cancellous bone graft to stimulate healing
    2. Removal of original implants
    3. Stabilizing fractures if necessary
  C. Antibiotic-impregnated polymethylmethacrylate beads or other biodegradable polymers can be used to deliver local, high levels of antibiotics, especially aminoglycosides (Dernell, 1999).
  D. Myocutaneous grafts can enhance local blood supply and soft tissue coverage of an extensive wound (Pavletic, 1999).
  E. In severe infections, limb amputation may be considered.

Monitoring of Animal

I. Physical examinations to evaluate wound healing and limb function are performed every 1 to 2 weeks, depending on the severity of the infection.
II. Serial radiographic evaluations are performed every 4 to 6 weeks until soft tissue and bone healing is complete.
III. Surgical debridement and appropriate antibiotic therapy can result in response rates in dogs approaching 90% (Budsberg and Kemp, 1990; Braden 1991).

IDIOPATHIC DISORDERS

Bone Cysts

Definition and Causes

I. Three main types of bone cysts exist.
  A. Subchondral: located in the epiphysis and adjacent to the joint
  B. Solitary: located in the metaphysis of juvenile long bones
  C. Aneurysmal: locally destructive, tumorlike lesions

II. Cysts can be single (monostotic) or multiple (polystotic).
III. Cause is usually unknown, although trauma can produce cysts that result from hematomas in subperiosteal locations.

Pathophysiology

I. Subchondral bone cysts are lined with a synovial membrane and filled with fibrous, myxoid, or serosanguineous fluid.
II. Solitary bone cysts are lined with fibrous connective tissue and filled with serosanguineous fluid.
III. Aneurysmal bone cysts are filled with vascular sinusoids (Montgomery, 2003).

Clinical Signs

I. Pain on palpation of affected bone
II. Lameness from the expansile nature of the cyst or pathologic fracture
III. Possibly asymptomatic

Diagnosis

I. Diagnosis is based on radiography, aspiration for bacteriological and cytological evaluation, and biopsy.
II. On plain radiographs, cysts may appear as expansile, radiolucent defects with thinning of cortical bone, and they may appear mottled from trabecular bone.
III. Aspirates are negative for bacteria and contain noninflammatory, acellular serosanguineous fluid or blood.
IV. Biopsy of the cyst wall reveals fibrous connective tissue, hemosiderin-laden macrophages, and mononuclear inflammatory cells (Halliwell, 1993).
V. Aneurysmal bone cysts have larger numbers of multinucleate cells and spicules of osteoid on histopathology.

Differential Diagnosis

I. Neoplasia
II. Trauma
III. Infection

Treatment

I. If clinically significant, solitary cysts can be drained, curetted, and packed with autogenous cancellous bone graft.
II. Weakened bone may require internal or external fixation until osteogenesis of the defect is complete.
III. Steroid injections into the cyst (Miura et al., 2003) and the use of bone cement to fill the defect (Sarierler et al., 2004) have been described.
IV. Aneurysmal bone cysts might be better treated by complete excision of the lesion whenever possible, because of the possibility of malignant transformation (Barnhart, 2002).

Monitoring of Animal

I. In asymptomatic animals, schedule periodic physical and radiographic evaluations.
II. Serial clinical and radiographic evaluations after cyst surgery are conducted every 6 weeks until bone healing is complete.
III. Most solitary cysts have a favorable prognosis.

Hypertrophic Osteopathy

Definitions and Causes

I. Hypertrophic osteopathy is a proliferative periosteal reaction in the distal extremities of long bones of dogs and, rarely, of cats (de Melo Ocarino et al., 2006).
II. Increased peripheral periosteal blood flow occurs secondary to a mass (neoplastic or infectious) in the thorax or abdomen and produces a periosteal reaction.

Pathophysiology

I. The mechanism by which a thoracic or abdominal mass increases peripheral blood flow is unknown, although an autonomic neurovascular reflex may be involved (Halliwell, 1993).
II. Increased peripheral blood flow may cause periosteal congestion and new bone formation in the distal extremities.

Clinical Signs

I. Acute or chronic, bilaterally symmetrical limb swelling, more noticeable in the forelimbs
II. Lethargy, with low-grade lameness
III. Incidental finding secondary to a thoracic or abdominal mass

Diagnosis

I. Physical examination findings of bilaterally symmetrical swelling of the extremities and lameness in mature animals are suggestive of the condition.
II. Complete blood count, serum biochemistry profile, and urinalysis are usually unremarkable or reveal changes related to the underlying thoracic or abdominal mass.
III. Radiographs of the extremities reveal palisades of periosteal new bone on the phalanges, metacarpi, metatarsi, tibia, fibula, radius, and ulna.
IV. Presence of a thoracic or abdominal mass is demonstrated on radiography or ultrasonography.

Differential Diagnosis

I. Primary or secondary bony neoplasia
II. Osteomyelitis: bacterial or fungal
III. Trauma
IV. Hypervitaminosis A (cats)

Treatment

I. Biopsy or definitive surgical resection of the underlying thoracic or abdominal mass is indicated.
II. NSAIDs are used to reduce limb swelling and discomfort.
   A. Carprofen 2.2 mg/kg PO BID
   B. Meloxicam 0.1 mg/kg PO SID
   C. Deracoxib 1 to 2 mg/kg PO SID
III. In cats, no NSAID is currently licensed for long-term use, although meloxicam 0.1 mg PO SID appears to be well tolerated (Robertson and Taylor, 2004).

Monitoring of Animal

I. Owners must be warned that clinical signs may persist for several weeks after treatment of the primary disease.

II. Bony lesions can take months to remodel, and complete resolution is unlikely.
III. Prognosis depends on whether the underlying thoracic or abdominal disease can be successfully treated.

NUTRITIONAL AND METABOLIC DISORDERS

Renal Secondary Hyperparathyroidism

Definition and Causes

I. Renal failure initiates secondary hyperparathyroidism through homeostatic mechanisms.
II. Renal insufficiency leads to hypocalcemia, hyperphosphatemia, parathyroid gland hyperplasia, elevated parathyroid hormone (PTH) levels, and bone resorption (Barber and Elliot, 1998).
III. Impaired renal function results in decreased conversion of inactive vitamin D_3 to its active form, which leads to decreased gastrointestinal absorption of calcium, decreased osteoclastic activity, and eventual osteomalacia (Cavanagh and Kosovsky, 1993).

Clinical Signs

I. Signs are predominantly associated with renal failure.
   A. Polydipsia, polyuria
   B. Dehydration, lethargy
   C. Vomiting, diarrhea
   D. Inappetence, weight loss
II. See Table 81-2 for other clinical features.

Diagnosis

I. Diagnosis is based on history, clinical signs, laboratory findings (see Table 81-2), and radiography.
II. Radiography reveals decreased bone density and loss of alveolar septa and lamina dura of the teeth, which gives them a floating appearance.

Differential Diagnosis

I. Nutritional secondary hyperparathyroidism
II. Hypovitaminosis D
III. Primary hyperparathyroidism (see Chapter 43)

Treatment and Monitoring

I. Address the underlying renal failure (see Chapter 48).
II. Parathyroidectomy is rarely considered for cases refractory to treatment of the renal disease.
III. Prognosis depends on the underlying cause of renal failure.

Nutritional Secondary Hyperparathyroidism

Definition and Causes

I. Diets low in calcium and high in phosphorus cause nutritional secondary hyperparathyroidism, which leads to elevation in PTH and metabolic disturbances.
II. Disease is rare but occurs in young animals fed an all-meat or all-grain diet (Kawaguchi et al., 1993; Tomsa et al., 1999).

Pathophysiology

I. It is most often associated with diets low in elemental calcium or having an inappropriately balanced calcium: phosphorus ratio (1:20 to 1:50).
II. Low-circulating vitamin D may originate from the diet or occur secondary to intestinal malabsorption.
III. Elevated PTH increases calcium resorption in the distal convoluted tubules of the kidneys and causes increased skeletal bone resorption.

Clinical Signs and Diagnosis

I. See Table 81-2 for clinical features.
II. Diagnosis is based on dietary history, clinical signs, laboratory findings (see Table 81-2), and radiography.
III. Generalized osteopenia is seen on survey skeletal radiographs and may be accompanied by pathologic or folding fractures.

TABLE 81-2

Clinical Features of Nutritional and Metabolic Diseases Causing Osteopenia

CLINICAL FEATURE	RENAL SECONDARY HYPERPARATHYROIDISM	NUTRITIONAL SECONDARY HYPERPARATHYROIDISM	HYPOVITAMINOSIS D
Lameness	Uncommon	Yes (especially young animals)	Yes
Bony deformities	Yes	Yes	Yes
Loose teeth ("rubber jaw")	Yes	No	No
Problems with mastication	Yes	No	No
Pathologic fractures	No	Yes (long bones or vertebrae)	Yes
Soft tissue calcification	Yes (lungs, kidney, heart, stomach)	No	No
Serum calcium	Decreased	Normal or decreased	Decreased
Serum phosphorus	Increased	Normal or increased	Increased
Parathormone level	Increased	Increased	Increased
Serum alkaline phosphatase	Normal or increased	Normal or increased	Normal or increased

Differential Diagnosis

I. Renal secondary hyperparathyroidism
II. Congenital bone defects
III. Disuse atrophy secondary to surgical implants, coaptation devices, or spinal paralysis
IV. Endocrine disorders: hyperthyroidism, diabetes mellitus, hyperadrenocorticism
V. Paraneoplastic hypercalcemia (see Chapter 73)

Treatment

I. Feed an appropriate diet and supplement calcium to achieve a 2:1 calcium:phosphorus ratio during the healing phase.
II. Restrict exercise to prevent further skeletal damage.
III. External coaptation may be necessary to prevent pathologic fractures.

Monitoring of Animal

I. Evaluate serum calcium, phosphorus, alkaline phosphatase, PTH, and radiographs of affected sites every 6 to 12 weeks.
II. In the absence of severe bony abnormalities, the prognosis is good.
III. Fractures may heal as a delayed union, taking >3 months.
IV. Spinal fractures may result in permanent paresis or paralysis despite healing.

Hypovitaminosis D

Definition and Causes

I. Hypovitaminosis D occurs secondary to inadequate ingestion and absorption of vitamin D in the diet or lack of sunlight, because ultraviolet radiation is necessary for the formation of active vitamin D_3.
II. Decreased vitamin D leads to decreased calcium absorption from the intestines, a compensatory increase in PTH, and calcium resorption from the skeleton.
III. Young animals develop abnormal endochondral ossification (rickets); mature animals develop osteomalacia.

Clinical Signs and Diagnosis

I. Diagnosis is based on history (diet and lifestyle), clinical signs, laboratory findings (see Table 81-2), and radiography.
II. Radiographs reveal a wider physis, metaphyseal flaring, and osteopenia in the long bones of young animals, and more generalized bone resorption in mature animals.

Differential Diagnosis

I. Nutritional secondary hyperparathyroidism
II. Renal secondary hyperparathyroidism
III. Hypertrophic osteodystrophy

Treatment

I. Provide a balanced diet with correct formulation of calcium, phosphorus, and vitamin D.
II. Surgical correction of angular limb deformities may be necessary in mature animals.

Monitoring of Animal

I. Evaluate serum calcium, phosphorus, alkaline phosphatase, PTH, and radiographs of affected sites every 6 to 12 weeks.
II. In the absence of severe bony abnormalities, the prognosis is good.
III. Fractures may heal as a delayed union, taking >3 months.

Hypervitaminosis A

Definition and Causes

I. Hypervitaminosis A is a metabolic disease caused by prolonged excessive intake of vitamin A through supplements or diet (e.g., raw liver, milk).
II. Hypervitaminosis A causes metaphyseal flaring, retards longitudinal growth of bone, and depresses periosteal osteoblastic activity (Herron, 1993).
III. Osteophytes and exostoses occur on the occipital bone and cervical and thoracic vertebrae, and they have been associated with sternebrae, ribs, and periarticular regions of lone bones.

Clinical Signs

I. Depression and reluctance to groom
II. Neck pain, ventriflexion
III. Lameness or paresis of one or both thoracic limbs

Diagnosis

I. Diagnosis is based on dietary history, clinical signs, laboratory findings, and radiography.
II. Serum vitamin A is usually elevated (normal range, 50 to 200 μg/dL) (Polizopoulou, 2005).
III. Radiographs reveal exostoses, cervical scoliosis, and ankylosis.

Differential Diagnosis

I. Mucopolysaccharidosis
II. Cervical disk disease
III. Osteochondromatosis

Treatment

I. Provide an appropriate, balanced diet from an elevated position to reduce cervical motion.
II. Meloxicam 0.2 mg/kg SC, PO once or 0.1 mg/kg PO SID for 3 to 4 days may provide temporary analgesia (Mathews, 2000).

Monitoring of Animal

I. Bony changes cease after the diet is corrected.
II. Some remodeling may occur over the long term, but epiphyseal damage and ankylosis are irreversible.
III. Periodic physical and radiographic evaluations are performed to monitor disease resolution.

Mucopolysaccharidosis Type VI

Definition and Causes

I. Mucopolysaccharidosis VI is an autosomal recessive, lysosomal storage disease of Siamese cats.

II. The enzyme responsible for the breakdown of glycosaminoglycans—an important component of cartilage and bone—is functionally impaired, which leads to skeletal abnormalities (Crawley et al., 2003).
III. Excessive amounts of glycosaminoglycans are excreted in the urine.

Clinical Signs

I. Signs in Siamese cats by 6 to 8 weeks of age
II. Smaller than littermates
III. Facial dysmorphia: broad face, short nose, small ears, enlarged head
IV. Progressive difficulty walking, with pelvic limb paresis or paralysis secondary to compressive exostoses affecting the spinal cord
V. Progressive degenerative joint disease

Diagnosis

I. Diagnosis is suggested by signalment, clinical signs, laboratory findings, and radiography.
II. Glycosaminoglycans are detected on urinalysis.
III. Cytological examination of blood smears reveals abnormal cytoplasmic granules within neutrophils.
IV. Radiography reveals generalized osteopenia, exostoses, vertebral fusion, and widespread degenerative joint disease.

Differential Diagnosis

I. Hypervitaminosis A
II. Osteochondromatosis

Treatment and Monitoring

I. No definitive treatment exists.
II. Bone marrow transplantation has been described (Beekman, 1993; Dial et al., 1997).
III. Affected cats may live for several years with supportive care; however, the disease is progressive and overall prognosis is poor.

NEOPLASIA

Definition

I. Bone tumors can be primary or secondary.
II. Secondary tumors include distant metastases or local extension of soft tissue tumors invading adjacent bone.
III. Most bone tumors are primary and malignant (Chun, 2005).

Causes and Classification

I. Primary bone tumors
  A. Osteosarcoma
    1. It is the most common bone tumor in dogs (90%) and cats (>70%) (Chun, 2005).
    2. In dogs, the most common appendicular locations include the distal radius, proximal humerus, distal femur, and proximal tibia.
    3. In dogs, the most common axial sites are the mandible and the maxilla.
    4. Osteosarcoma in small dogs tends to affect the axial skeleton most often (Chun and de Lorimer, 2003).
    5. Appendicular and axial lesions are evenly distributed in the cat.
  B. Chondrosarcoma
    1. Second most common bone tumor in dogs (approximately 10%)
    2. Rare in cats
    3. Flat bones more frequently affected than long bones
  C. Fibrosarcoma: uncommon in cats and dogs
  D. Hemangiosarcoma
    1. Rare in cats and dogs
    2. Usually a locally invasive muscular disease
  E. Multilobular tumor of bone (multilobular osteochondrosarcoma)
    1. Uncommon in dogs and rare in cats
    2. Locally invasive tumor
    3. Arises from the flat bones of the skull in middle-aged and older dogs
  F. Multiple myeloma
    1. Uncommon in dogs and rare in cats
    2. Systemic plasma cell malignancy (see Chapter 77)
II. Metastatic bone tumors
  A. Rare in cats and dogs
  B. More likely to involve the diaphysis than a primary bone tumor
  C. Most common: mammary gland carcinoma, transitional cell carcinoma, prostate carcinoma

Clinical Signs

I. Lameness in an affected limb can vary from mild to severe.
II. The potential exists for a pathologic fracture with minimal trauma.
III. Pain, palpable swelling, or a mass may be detected at tumor location.
IV. Paresis, paralysis, and pain may be associated with extradural or nerve root compression from spinal neoplasia.
V. Cachexia is possible.
VI. Dyspnea may arise secondary to metastatic disease.

Diagnosis

I. Signalment is suggestive for some tumors; for example, osteosarcoma typically occurs in mature, large- and giant-breed dogs.
II. Radiographic changes include cortical destruction, periosteal new bone formation, osteolysis, osteoproliferation, soft tissue swelling, and pathologic fractures.
III. No radiographic changes are pathognomonic.
IV. Three radiographic views of the thorax may reveal metastatic lung lesions.
V. Elevated levels of serum alkaline phosphatase at the time of diagnosis are a negative prognostic factor (Ehrhart et al., 1998; Garzotto et al., 2000).
VI. Definitive diagnosis is based on histopathologic evaluation of a bone biopsy.
  A. Obtain sample using a Michel bone trephine or Jamshidi bone biopsy needle (Straw, 1996).

B. Submit samples for bacterial culture and antibiotic sensitivity testing to rule out fungal or bacterial osteomyelitis.
C. Definitive tumor diagnosis using this combined technique occurs in >90% of cases (Waters, 1993).

VII. Skeletal nuclear scintigraphy is a sensitive tool to identify concurrent or early bony metastasis.

Differential Diagnosis

I. Osteomyelitis
II. Trauma
III. Bone infarcts (emboli)
IV. Benign cystic lesions

Treatment

I. Palliative therapy may include medical management with NSAIDs alone or in combination with narcotics.
A. Transdermal fentanyl patches (3 to 5 μg/kg) provide analgesia for 3 to 4.5 days.
B. Tramadol may be given at 1 to 4 mg/kg PO BID to TID.

II. Bisphosphonates may provide palliation in dogs with osteosarcoma (Tomlin et al., 2000; Milner et al., 2004).
III. Chemotherapy alone is ineffective in the face of gross disease (Ogilvie et al., 1993).
IV. See Tables 81-3 and 81-4 for chemotherapeutic and surgical options for osteosarcoma and other bone tumors.

Monitoring of Animal

I. Dogs treated palliatively are usually euthanized because of local recurrence or lack of pain control.
II. Because most animals with osteosarcoma succumb to diffuse pulmonary metastasis, three views of thoracic radiographs are performed every 3 to 6 months.
III. Animals undergoing chemotherapy require frequent complete blood counts, platelet counts, and serum biochemistry panels.

TABLE 81-3

Overview of Appendicular Osteosarcoma Therapy over the Past 15 Years

SURGERY AND CHEMOTHERAPY PROTOCOL	REFERENCE	MEDIAN SURVIVAL (1-YEAR AND 2-YEAR SURVIVAL)
Amp alone (n = 19)	Mauldin et al., 1988	175 days (21%, 0%)
Amp + DOX 30 mg/m^2 dL + cDDP 60 mg/m^2 day 21 × 2 doses (n = 19; 36 appendicular, 2 axial)	Mauldin et al., 1998	300 days (37%, 26%)
Amp + cDDP 50 mg/m^2 every 28 days × 2-6 doses (n = 19)	Shapiro et al., 1988	301 days (unknown, unknown)
Amp + cDDP 50 mg/m^2 every 28 days × 6 doses or until metastasis noted (n = 16)	Kraegel et al., 1991	413 days (62%, ≥18%)
Amp alone (n = 17)	Straw et al., 1991	119 days (11%, 4%)
Amp + cDDP 70 mg/m^2 every 21 days × 2 doses (n = 19)	Straw et al., 1991	262 days (38%, 18%)
Amp + cDDP 70 mg/m^2, 21 days preop and immediately postop (n = 35)	Straw et al., 1991	282 days (43%, 16%)
Amp alone (n = 15)	Thompson and Fugent, 1992	168 days (20%, unknown)
Amp + cDDP 60 mg/m^2 × 2 doses at 2 and 7 weeks postop (n = 15)	Thompson and Fugent, 1992	290 days (33%, unknown)
Amp alone (n = 162)	Spodnick et al., 1992 ,	134 days (11.5%, 2%)
Amp/limb sparing + cDDP 60 mg/m^2 every 21 days × 1-6 doses (n = 22; 17 = amp, 5 = limb sparing); survival data not divided for surgery types	Berg et al., 1992	325 days (45.5%, 20.9%)
Amp/limb sparing + DOX 30 mg/m^2 every 2 weeks × 5 doses (n = 35; 33 = amp, 2 = limb sparing); because 2-3 doses were given adjunctive to surgery, only patients with minimal clinical signs were included; survival date not divided for surgery types	Berg et al., 1995	366 days (50.5%, 9.7%)
Amp + carbo 300 mg/m^2 every 21 days × up to 4 doses (n = 48)	Bergman et al., 1996	321 days (35.4%, unknown)
Amp + DOX 15-20 mg/m^2 (1-2 hours before cDDP) + cDDP 60 mg/m^2 × 3 doses starting 2 (n = 53) or 10 (n = 49) days postop; twelve dogs died after first cycle	Berg et al., 1997	2 days postop group: 345 days (48%, 28.3%, 3 years: 15.3%) 10 days postop group: 330 days (46.2%, 27.5%, 3 years: 18%)
Amp + cDDP 50 mg/m^2 dL + DOX 15 mg/m^2 day 2 × 4 (n = 16) Also treated with empty liposomes	Chun et al., 2000	540 days (68.7%, 25%)

Modified from Chun R, de Lorimer LP: Update on the biology and management of canine osteosarcoma. Vet Clin North Am Small Anim Pract 33:491, 2003; with permission.

Amp, Amputation; *DOX,* doxorubicin; *cDDP,* cisplatin; *postop,* postoperative; *preop,* preoperative; *carbo,* carboplatin.

TABLE 81-4

Treatment Options for Bone Neoplasia

OSTEOSARCOMA	CHONDROSARCOMA	FIBROSARCOMA	HEMANGIOSARCOMA	MULTILOBULAR TUMOR	METASTATIC BONE TUMORS
Limb amputation: median survival of 5 months in dogs (Spodnik et al., 1992); mean survival of 17 months in cats (Heldmann et al., 2000) Radiotherapy alone: pain relief for 2-4 months (Green et al., 2002) Limb amputation and chemotherapy: see Table 81-3; 1-year survival rates of 35%-60%; median survival rate of 10-18 months in dogs (Chun et al., 2000) Limb-sparing surgery ± chemotherapy, radiotherapy: aims to maintain a functional limb without negative effect on survival Best sites: proximal scapula (Trout et al., 1995), distal radius (La Rue et al., 1989; Farese et al., 2004; Liptak et al., 2004), and distal tibia (Rovesti et al., 2002)	Limb amputation or aggressive surgical resection Benefits of adjunctive chemotherapy and radiotherapy uncertain	Limb amputation or aggressive surgical resection Adjunctive chemotherapy for high-grade disease (Dernell et al., 1998b) Adjunctive chemotherapy and radiotherapy for unresectable masses (Forrest et al., 2000)	Limb amputation ± chemotherapy	Aggressive surgical resection: median survival 630-797 days (Straw et al., 1989; Dernell et al., 1998a)	Surgical treatment unrewarding Palliative radiation Metastectomy to remove lung masses: possibly useful in dogs with <3 nodules in one lung and if >300 days after diagnosis (O'Brien et al., 1993)

TRAUMATIC DISORDERS

Fractures

Definition and Causes

I. A bone fracture is a disruption of the normal architecture of bone.
II. Fractures can be defined by the following:
  A. Location
  B. Direction
  C. Number of fracture lines
  D. Reducible or nonreducible
  E. Open or closed

Pathophysiology

I. Fractures occur when excessive or abnormal forces are applied to a bone.
  A. Axial compressive forces tend to produce oblique fractures.
  B. Tensile forces tend to produce transverse fractures, particularly avulsion fractures when a tendon or ligament is attached to the bone (e.g., greater trochanter, olecranon, tibial crest).
  C. Shear forces lead to fractures along lines of maximal shear stress (e.g., Salter-Harris type IV fracture of the lateral condyle in an immature animal) (Schwarz, 1991).
  D. Bending forces lead to compression on the concave surface of a long bone and tension on the convex surface, which typically leads to a transverse or short oblique fracture.
  E. Torsional forces lead to spiral fractures.
II. Most fractures result from a combination of disruptive forces.
III. Velocity of force affects fracture pattern.
  A. Low-velocity forces tend to produce single fractures and minimal soft tissue trauma.
  B. High-velocity forces tend to produce comminuted fractures and significant damage to the surrounding soft tissues.

Clinical Signs

I. Acute weight-bearing or non–weight-bearing lameness in appendicular bone fractures
II. Soft tissue swelling, pain on palpation, crepitation, abnormal limb posture or position
III. External skin trauma, puncture, laceration, shearing wounds that may communicate with the fractured bone
IV. Concurrent injury of vital systems secondary to the trauma (e.g., pulmonary contusions, ruptured bladder)
V. Compromised neurological integrity with spinal fractures or peripheral nerve trauma associated with a long bone fracture

Diagnosis

I. Diagnosis is based on history, clinical signs, physical examination findings, and radiographic changes.
II. Careful palpation helps the clinician avoid missing multiple fractures in an affected limb.
III. Radiography of the affected limb is performed under sedation or anesthesia, with a minimum of two divergent views.
IV. Computerized tomography, when available, can be useful for evaluating fractures of the axial skeleton.

Differential Diagnosis

I. Pathologic fracture from neoplasia
II. Metabolic bone disease
III. Joint luxation

Treatment

I. Address and stabilize life-threatening injuries in the traumatized animal.
II. Pain relief before and after fracture management is provided using a variety of analgesic agents.
  A. Epidural narcotics
    1. Preoperative administration reduces anesthetic requirements and provides immediate postoperative analgesia.
    2. In dogs, options include the following:
      a. Morphine (preservative free) 0.05 mg/kg plus 0.5% bupivacaine 1 mL/15 kg (pelvic limb fractures)
      b. Morphine (preservative free) 0.05 mg/kg plus 0.5% bupivacaine 1 mL/20 kg plus 0.9% saline 1 mL/20 kg (thoracic limb fractures)
    3. In cats, preservative-free morphine is used alone.
      a. Pelvic limb: 0.07 mg/kg
      b. Thoracic limb: 0.1 mg/kg in 0.1 mL/kg 0.9 % saline
    4. Local anesthetics are not used in cats because of the proximity of the cat's spinal canal to the epidural space.
  B. Selective and regional blockage of the brachial plexus
    1. Lidocaine 2% or bupivacaine 0.5% are preferred.
    2. A 22-gauge, 1- to 1.5-inch needle is inserted into the axillary space at the level of the shoulder before forelimb surgery.
  C. Systemic narcotics
    1. Morphine
      a. Dogs: 0.25 to 0.5 mg/kg IM, SC
      b. Cats: 0.05 to 0.1 mg/kg IM, SC
    2. Oxymorphone
      a. Dogs: 0.025 to 0.1 mg/kg IV, IM, SC
      b. Cats: 0.025 to 0.05 mg/kg IM, SC
    3. Butorphanol 0.1 to 0.2 mg/kg IM, SC
    4. Buprenorphine
      a. Dogs: 0.005 to 0.02 mg/kg SC, IM, IV
      b. Cats: 0.005 to 0.01 mg/kg SC, IM, IV
    5. Hydromorphone
      a. Dogs: 0.1 to 0.2 mg/kg IV
      b. Cats: 0.02 to 0.1 mg/kg IV
    6. Fentanyl patch 3 to 5 μg/kg
      a. Applied 18 to 24 hours before surgery
      b. Provides analgesia for 3 days
III. If necessary, fractures are temporarily stabilized to increase the animal's comfort.

A. Distal to the elbow or stifle, use a Robert Jones bandage, with or without a splint (metal or fiberglass).
B. Proximal to the elbow or stifle, use cage confinement.

IV. Animals with closed fractures are given perioperative antibiotics at the time of anesthetic induction.
A. Cephalosporin 22 mg/kg IV every 2 hours
B. Oxacillin 22 mg/kg IV every 2 hours

V. Animals with open, contaminated fractures are given broad-spectrum antibiotics or combinations of antibiotics (see Treatment of osteomyelitis) while awaiting the results of bacterial culture and antimicrobial sensitivity testing.

VI. Some fractures are amenable to cage rest, such as rib fractures, ulnar fractures with an intact radius, or a fibula fracture with intact tibia.

VII. Techniques for fracture repair include external splints or casts, internal implants, and external fixators (Table 81-5).

VIII. Autogenous bone grafts can provide live osteoblasts, are osteoinductive and osteoconductive, and serve as a scaffold for mechanical support.
A. Bone grafts can be obtained from the greater tubercle of the humerus, distal condyle of the femur, and the wing of the ilium.
B. They are packed into fracture gaps to promote healing.

TABLE 81-5

Fixation Devices for Fractures

DEVICES AND TECHNIQUES	USES
External coaptation	Closed fractures distal to the elbow or stifle
IM pin (single)	Never
IM pin with full cerclage	Long oblique or spiral fractures
IM pin with external fixator	Many diaphyseal and metaphyseal fractures
Rush pin technique	Metaphyseal, physeal, and epiphyseal fractures
Tension band fixation	Avulsion or iatrogenic fractures of bony prominences
Interlocking IM nail	Most diaphyseal fracture configurations
External fixators	Most diaphyseal and metaphyseal fractures
Circular fixators	Most fractures (experience needed)
Bone plate (anatomic)	Most fracture configurations because of varied plate design
Bone plate and rod	Buttressed fracture repairs
Ancillary devices Full cerclage wires Hemicerclage wires K-wires/crossed K-wires Lag screws	

From Roush JK: Management of fractures in small animals. Vet Clin North Am Small Anim Pract 35:1137, 2005; with permission.

IM, Intramedullary.

Monitoring of Animal

I. Postoperative radiographs are taken to assess fracture repair and provide comparisons for follow-up radiographs.

II. Confinement and/or cage rest are essential for periods of time, depending on the specific fracture, and are combined with early physical therapy to enhance limb function (see Chapter 83).

III. Animals are given NSAIDs during the first 7 to 10 days after surgery (see Treatment of Panosteitis).

IV. Adequate nutrition must be ensured; feeding may have to be supplemented via nasoesophageal or esophagostomy feeding tubes or by using IV parenteral nutrition.

V. Soft tissue injuries associated with fractures may require open wound management and closure as a separate surgical procedure.

VI. Certain fracture repair techniques (e.g., casts, splints, external and circular fixators) require regular physical examinations to monitor for repair-related complications (e.g., pressure sores, soft-tissue swelling, discharge at the skin–pin interface).

VII. Radiographic rechecks are performed around 4 weeks in young animals and 6 weeks in mature animals, then every 4 to 8 weeks until fracture healing is complete.

VIII. Prognosis for fracture healing is generally good; however, some predictably problematic cases occur.
A. Open fractures and comminuted fractures have a higher incidence of osteomyelitis, delayed union, malunion, and nonunion.
B. Distal radial fractures in small-breed dogs require internal or external fixation and should not be splinted or casted for definitive repair.
C. Compressive fractures of growth plates in immature animals may not be appreciated on initial radiographs, but can lead to premature closure of the physis with the potential for subsequent angular limb deformities.
D. Distal femoral fractures in immature dogs can produce excessive callus, causing adhesions to the quadriceps muscle group (leading to ankylosis and stifle hyperextension).

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CHAPTER 82

Diseases of Muscle and Tendons

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CONGENITAL AND INHERITED DISORDERS

See Table 82-1.

DEGENERATIVE DISORDERS

Myositis Ossificans

Definition

I. Myositis ossificans is heterotrophic, nonneoplastic bone formation in the collagenous tissues of skeletal muscles.
II. Name is misleading because connective tissue (not muscle) is ossified, and evidence of inflammation is not always present.
III. It can be localized or generalized.
  A. Localized myositis ossificans
    1. Bone formation occurs in a single muscle or group of muscles.
    2. It is most common in large-breed, middle-aged, active dogs.
    3. It may be a separate entity in the Doberman pinscher, arising secondary to von Willebrand disease (Dueland et al., 1990).
  B. Progressive or generalized myositis ossificans
    1. Excessive fibrous connective tissue develops throughout skeletal muscles leading to muscle degeneration, dystrophic calcification, and ossification.
    2. It occurs in young to middle-aged cats and has rarely been reported in dogs (Guilliard, 2001; Asano et al., 2006).
    3. It is also known as *progressive ossifying fibrodysplasia* (Norris et al., 1980).

Causes and Pathophysiology

I. Cause is unknown.
II. Localized forms may be associated with one of the following:
  A. Acute or repetitive trauma
    1. Ossification of hematoma
    2. Tearing of periosteum, releasing osteoblasts
    3. Metaplasia of muscle and connective tissue to cartilage and bone
  B. Localized infection
  C. Microvascular bleeding from von Willebrand disease: Doberman pinschers
  D. Possible breed predisposition: German shepherd dogs
III. The progressive or generalized form may have a hereditary component and arise from a fibroblast defect in collagenous connective tissue, with secondary degeneration of muscle.

Clinical Signs

I. Localized form
  A. Palpable mass in affected muscle
  B. Exercise-induced muscle pain
  C. Lameness and stiffness: often in one limb
  D. Focal muscle atrophy
II. Progressive ossifying fibrodysplasia
  A. Lameness and stiffness is seen in one or more limbs, with pelvic limbs commonly affected.
  B. It may progress to decreased joint mobility and difficulty ambulating.
  C. Palpable, painful, firm nodules are seen, especially on the neck and back.
  D. It can progress over weeks to months to severe debilitation.

Diagnosis

I. Localized ossifying myositis
  A. Radiography can reveal the following:
    1. Stippled mineralized density in soft tissue (3 to 6 weeks), with mature bone detected 2 to 6 months after an injury
    2. ± Radiolucent core
    3. Possible adjacent periosteal reaction
  B. Ultrasonography and bone scintigraphy may be helpful.
  C. Biopsy findings are definitive.
    1. Central zone of spindle cells and hemosiderin-laden macrophages
    2. Intermediate zone of osteoid and immature bone
    3. Peripheral zone of mature bone, with resorption and remodeling that does not invade surrounding soft tissue
  D. Possible laboratory findings include the following:
    1. Elevated serum alkaline phosphatase
    2. Decreased von Willebrand factor, prolonged buccal bleeding times
II. Progressive ossifying fibrodysplasia

Text continued on p. 799.

TABLE 82-1

Congenital Myopathies

DISORDER AND DEFINITION	BREEDS AFFECTED	CAUSE AND INHERITANCE	CLINICAL SIGNS	DIAGNOSIS	DIFFERENTIAL DIAGNOSIS	TREATMENT AND PROGNOSIS	REFERENCES
Type II muscle fiber deficiency: predominance of type I and deficiency of type II muscle fibers, causing gait disturbance	Labrador retriever	Cause unknown Simple autosomal recessive	< 5 mo of age Initial gait abnormality progresses to generalized weakness, inability to hold head up. Exacerbated by exercise Marked skeletal muscle atrophy Stunted growth Progressive signs until maturity, then signs stabilize Megaesophagus Neurological examination normal or diminished tendon reflexes	Suspicious clinical signs in a Labrador Creatinuria* up to 30× normal; CK† less than normal Muscle biopsy: variable fiber diameter with increased endo- and perimysial connective tissue Deficiency of ATPase-staining type II fibers EMG may reveal myotonic discharges	Myasthenia gravis: older dogs; response to edrophonium chloride, EMG showing decremental response Nutritional myodegeneration: history of abnormal diet, progressive Congenital myotonia	None Diphenylhydantoin PO ineffective Diazepam PO may alleviate some signs Poor prognosis because lack of available treatment, but normal life span possible	Sharp et al. (1989) Gortel et al. (1996)
Muscular dystrophies, inherited myopathies	Alaskan malamute Golden retriever Groenendaeler shepherd Irish terrier Samoyed	Inability to produce dystrophin (cytoskeletal protein of muscle fibers) X-linked inheritance	*Dogs*: Onset at 6-8 wk of age Rapid progression of signs Difficulty swallowing and drooling	Compatible clinical signs in reported breeds Increased CK, aldolase, AST, ALT, and LDH	Congenital myotonia: myotonic dimple Hypokalemic myopathy of cats: elevated serum potassium	None Disease is progressive, but less rapidly after 6 mo of age (dogs)	Malik (1993) Robinson (1999) van Ham et al. (1993) Vos et al. (1986) Wetterman et al. (2000)

Modified from Davidson JR, Hosgood G: Disease of muscles and tendons. p. 806. In Morgan RV, Bright RM, Swartout MS (eds): Handbook of Small Animal Practice. 4th Ed. WB Saunders, Philadelphia, 2003; with permission.

CK, Creatine kinase; *EMG,* electromyography; *AST,* aspartate transaminase; *ALT,* alanine transaminase; *LDH,* lactate dehydrogenase.

*Normal = 0.1 to 1.6 mg/mL.

†Normal = 45 to 125 IU/dL.

Continued

TABLE 82-1

Congenital Myopathies—*cont'd*

DISORDER AND DEFINITION	BREEDS AFFECTED	CAUSE AND INHERITANCE	CLINICAL SIGNS	DIAGNOSIS	DIFFERENTIAL DIAGNOSIS	TREATMENT AND PROGNOSIS	REFERENCES
Muscular dystrophies—*cont'd*	Rottweiler Miniature schnauzer Welsh corgi Male cats	Males exhibit clinical signs Carrier females may have mild elevations in muscle enzymes without clinical signs Condition in golden retrievers is similar to Duchenne-type muscular dystrophy in humans	Stiff gait, rigid neck, adduction of hocks, abduction of elbows, tarsal flexor contraction, carpal hyperextension Hypertrophy of tongue and caudal thigh muscles Atrophy of other muscles, particularly truncal and temporal muscles Lumbar kyphosis Aspiration pneumonia from pharyngeal/esophageal dysfunction Exercise intolerance Normal neurological examination initially, with later proprioceptive deficits and hyporeflexia Dilated cardiomyopathy *Cats*: Onset at 12 mo of age Slow progression of signs Stiff, rigid neck Adduction of hocks Symmetrical muscular hypertrophy Lumbar kyphosis Reduced cardiac contractility and biventricular enlargement	Muscle biopsy variable: fiber necrosis and regeneration, hypertrophy (cat), fiber loss and fibrosis (dog), myofiber mineralization (both), and lack of dystrophia on immunostaining EMG: bizarre high-frequency discharges (golden retriever); diffuse, continuous myotonic discharge (Irish terrier) Normal nerve conduction velocity	Inherited myopathy of Devon rex cats: normal CK, AST, characteristic head and neck ventriflexion, megaesophagus, generalized muscle weakness and fatigue Immune-mediated polymyositis: characteristic cellular infiltrate in histological specimens	Poor prognosis	Bergman et al. (2002)

TABLE 82-1

Congenital Myopathies—*cont'd*

DISORDER AND DEFINITION	BREEDS AFFECTED	CAUSE AND INHERITANCE	CLINICAL SIGNS	DIAGNOSIS	DIFFERENTIAL DIAGNOSIS	TREATMENT AND PROGNOSIS	REFERENCES
Congenital myotonia: involuntary contraction of a muscle that persists after a voluntary effort or stimulation	Chow chow Cocker spaniel Labrador retriever Samoyed Staffordshire bull terrier West Highland white terrier Cats	Cause unknown Low membrane chloride conductance and accumulation of potassium in the tubular system may cause postexcitement depolarization of the muscle membrane and continued contraction of the muscle Autosomal recessive inheritance in the chow chow, but may have multifactorial etiology Thought to be heritable in cats	Abnormal stiff gait at 2-3 mo of age, lessens with exercise Abduction of forelimbs "Bunny hop" Arched back Muscle hypertrophy of all skeletal muscles, especially proximal appendicular muscles, tongue, and anal sphincter Normal muscle tone at rest Characteristic myotonic dimple persists for 30-40 sec after direct muscle stimulation (tongue or shaved limb) Dysphagia often observed	Typical clinical signs in a reported breed with myotonic dimple EMG: high-frequency myotonic a discharges with continuous insertional activity and possible decremental response Normal nerve conduction velocity CK may be elevated Muscle biopsy variable: hypertrophy, atrophy, and degeneration	Nutritional myodegeneration Cerebellar dysmyelinogenesis: also reported in young chow chows Animals with cerebellar disease can potentially recover, are not stiff, and have a continuous tremor of the head, neck, and trunk; they typically "bounce" repetitively on the hind limbs Inherited (X-linked) myopathy in cats	None Disease is not progressive Procainamide and quinidine may lessen initial weakness Diphenylhydantoin has no benefit Avoid prolonged exercise Fair to guarded prognosis Treatment not reported in cats because of potential drug side effects	Hickford et al. (1998) Toll et al. (1998) Hill et al. (1995)
Nemaline myopathy	Cats Border collie Schipperke	Cause unknown Thought to be inherited Only one report of several cats	Onset at 6-18 mo of age in cats and 6-24 mo in dogs Adult onset described in a dog Weakness, crouched, hypermetric gait Depressed patellar reflexes Progressive muscle atrophy	Muscle biopsy: nemaline rods in skeletal muscle fibers EMG: mild to moderate diffuse spontaneous activity		None Poor prognosis	Cooper et al. (1986) Delauche et al. (1998) Kube et al. (2006)

Continued

TABLE 82-1

Congenital Myopathies—*cont'd*

DISORDER AND DEFINITION	BREEDS AFFECTED	CAUSE AND INHERITANCE	CLINICAL SIGNS	DIAGNOSIS	DIFFERENTIAL DIAGNOSIS	TREATMENT AND PROGNOSIS	REFERENCES
Inherited myopathy of Great Danes	Great Dane	Cause unknown	Onset 6-19 mo of age No sex prediction Generalized tremors and collapse precipitated by exercise or excitement Generalized muscle atrophy, kyphosis, stiff pelvic gait Stunted Tucked position of pelvic limbs Progresses over 6-12 mo	EMG: fibrillation potentials and sharp waves Muscle biopsy: 50% of fibers contain a central core, fiber diameter variation, disruption of myofibrillar elements		None reported to be effective	Newsholme and Gaskell (1987) Targett et al. (1994) Feliu-Pasual et al. (2006)
Mitochondrial myopathy	Clumber spaniel Sussex spaniel German shepard dog Jack Russell terrier	Cause unknown Thought to be inherited Muscle mitochondria are unable to oxidize pyruvate	Onset 3-9 mo of age Collapse in sternal recumbency for 10-15 min with panting and tachycardia Progressive exerase intolerance Stilted gait	Metabolic acidosis after exercise CK possibly elevated		Correct lactic acidosis Prognosis is guarded	Breitschwerdt et al. (1992) Olby et al. (1997) Paciello et al. (2003)

A. Presence on plain radiographs of multiple mineralized densities distributed throughout muscles
B. Elevated serum creatine kinase (CK)
C. Biopsy findings in affected muscle
   1. Increased connective tissue between muscle fibers
   2. Mononuclear infiltration
   3. Muscle atrophy and degeneration

Differential Diagnosis

I. Neoplasia of bone or joints, including extraskeletal osteosarcoma
II. Dystrophic calcification, calcinosis circumscripta
III. Cartilaginous exostoses
IV. Callus formation secondary to bone healing
V. Radiopaque foreign body: teeth or bone fragments after bite wounds

Treatment and Monitoring

I. Localized ossifying myositis
   A. Treatment is indicated only for clinically significant lesions.
   B. Nonsteroidal antiinflammatory drugs may be helpful but must be avoided in dogs with bleeding tendencies.
      1. Carprofen 2.2 mg/kg PO BID
      2. Meloxicam 0.1 mg/kg PO SID
      3. Deracoxib 1 to 2 mg/kg PO SID
   C. Removal is recommended if the lesion is painful, if it restricts joint motion, or to obtain an excisional biopsy.
   D. Postoperative physical therapy is beneficial.
II. Progressive ossifying fibrodysplasia
   A. No specific, effective treatment is available.
   B. Corticosteroids, bisphosphonates, etretinate, and dietary changes have not alleviated the clinical signs or prevented disease progression.
   C. Prognosis is poor to guarded.

Fibrotic Myopathy

Definition and Causes

I. It is a chronic, progressive disorder of severe muscle contracture and fibrosis.
II. The exact cause is usually unknown.
III. Fibrotic myopathy may result from acute trauma, chronic repetitive trauma, autoimmune disease, drug reactions, infections, neurogenic disorders, and vascular abnormalities.
IV. Ischemia secondary to trauma may also lead to fibrosis.
V. Severely damaged muscle undergoes necrosis followed by fibrosis and contracture.
VI. Histologically, muscle is replaced by dense, collagenous connective tissue.

Clinical Signs

I. Muscles most often affected are the infraspinatus (infraspinatus contracture), quadriceps (quadriceps contracture), gracilis, and semitendinosus.
II. Signs are specific to the muscle or group of muscles affected.
   A. Quadriceps (Table 82-2)
   B. Gracilis, semimembranosus, semitendinosus
      1. Often affects active, mature, large-breed dogs, with German shepherd dogs overrepresented
      2. Short stride with a rapid medial rotation of the paw, external rotation of the hock, and internal rotation of the stifle during the middle to late phase of the stride.
      3. Possible reduction in passive movement of the thoracic limb and limb abduction
   C. Infraspinatus
      1. Usually a unilateral lesion, primarily in hunting or working breeds of dogs (Harasen, 2005; Devor and Sorby, 2006)
      2. Acute shoulder pain associated with exercise
      3. Progresses to a mechanical lameness 2 to 4 weeks after the initial injury, with adduction of the elbow, abduction of the thoracic limb, and external rotation of the antebrachium and carpus
      4. Lateral circumduction of the limb during each stride, with paw flipping forward

Diagnosis

I. Diagnosis is based on the history, clinical signs, physical examination findings, and diagnostic imaging.
II. The affected muscle may be palpably taut, hard, and usually nonpainful.
III. Diagnostic imaging may be helpful.
   A. Radiological findings may include the following:
      1. Patella lies more proximally than normal in cases of quadriceps contracture.
      2. Congenital stifle contracture produces stifle hyperextension, with both the distal femur and proximal tibia bending backwards (genu recurvatum).
      3. Occasionally streaks of mineralization may be seen in affected muscle groups.
   B. Ultrasonography may be able to differentiate other soft tissue abnormalities.
IV. Laboratory findings may include elevated levels of muscle enzymes in the early stages.

Differential Diagnosis

I. Neurological diseases
II. Hip dysplasia
III. Cranial cruciate ligament disease
IV. Lumbosacral disease

Treatment and Monitoring

I. Medical management is generally ineffective but may be acceptable for dogs with nondebilitating lameness.
II. Surgery aims to release the fibrous band(s) within the affected muscle.
   A. Quadriceps muscle: see Table 82-2
   B. Gracilis muscle: myotomy or myectomy of the affected muscle invariably leads to recurrence of clinical signs within 3 to 4 months
   C. Infraspinatus muscle: tenotomy results in immediate improvement in range of motion

III. Restrict activity for 2 weeks postoperatively.
IV. Prognosis depends on the affected muscle group.
  A. Quadriceps: guarded, considered a successful outcome if 50% to 75% use of affected limb returns
  B. Gracilis: guarded for recurrence, but affected animal makes an acceptable pet
  C. Infraspinatus: excellent for full recovery

INFECTIOUS DISORDERS

Protozoal Myositis

Definition and Causes

I. *Toxoplasma gondii* is the most common infectious cause of polymyositis.
  A. It may occur as part of a multisystemic infection in cats.
  B. In the dog, three clinical forms may occur.
    1. Generalized form that occurs in conjunction with canine distemper virus and may affect both the muscles and the central nervous system (CNS)
    2. Severe acute necrotizing myositis of adult dogs
    3. Polyradiculitis and polymyositis of young dogs (usually 3 to 6 months of age)
II. *Neospora caninum* can cause myositis and has been discovered in many dogs that were previously thought to have toxoplasmosis.

Clinical Signs

I. Severity of clinical signs is worse in very young (from 5 weeks of age) and immunosuppressed animals.
II. Several puppies in the same litter may be affected.
III. Gait abnormalities include hopping; progressive pelvic limb paresis; and acute, severe muscle pain (focal or generalized).
IV. *T. gondii* can produce a spastic hyperextension of the pelvic limbs, with severe muscle atrophy in dogs.
V. CNS and ocular signs include chorioretinitis, seizures, and stupor.
VI. Other clinical signs are cervical weakness; icterus, anorexia, and lethargy from liver dysfunction; dysphagia; and death.
VII. *N. caninum* is not usually associated with concurrent infections and more commonly produces a progressive ascending paralysis.

Diagnosis

I. Clinical signs compatible with polymyositis
II. Elevation of serum CK
III. Rising serum antibody titers to protozoal organisms (see Chapters 2 and 116)
IV. Mixed pleocytosis and a high protein count in cerebrospinal fluid (CSF) of animals with CNS signs
V. Histopathologic findings of muscle fiber atrophy, myonecrosis, and free or encysted organisms
VI. Tests to differentiate *T. gondii* from *N. caninum*
  A. Indirect fluorescent antibody tests on CSF, serum, or tissue
  B. Electron microscopy and immunohistochemical staining for *N. caninum*
  C. Polymerase chain reaction (PCR) assays

Differential Diagnosis

I. *Leptospira icterohaemorrhagiae*
II. Congenital myopathies
III. Nutritional myopathies
IV. Immune-mediated polymyositis
V. Hepatozoonosis (see Chapter 116)
VI. Sarcocystosis
  A. Pathogenic primarily in immunosuppressed animals
  B. Animals possibly seropositive for toxoplasmosis
  C. Specialized testing required for diagnosis (Vashisht et al., 2005)

Treatment and Monitoring

I. Antibiotic therapy is instituted, similar to that used for systemic toxoplasmosis.
  A. Clindamycin 10 to 20 mg/kg PO, IM BID to TID
  B. Trimethoprim-sulfadiazine 30 mg/kg PO BID, with pyrimethamine 0.25 to 0.5 mg/kg PO SID for 2 to 4 weeks in dogs or for 7 to 10 days in cats
II. Prognosis is guarded to poor because of concurrent diseases, immunosuppression, and CNS involvement.

Bacterial Myositis

Definition

I. Focal myositis may arise from direct infection of traumatized and devitalized muscle.
  A. Often associated with contamination of a wound
  B. May result from injection of bacteria into muscle (bite wounds)
II. Myositis may develop from hematogenous infections.

Causes

I. *Staphylococci* spp. and *Streptococci* spp.: most common in dogs
II. *Pasteurella multocida:* most common in cats
III. Other causes: *Clostridium tetani*, *Leptospira* spp. (especially *L. icterohaemorrhagiae*), *Corynebacterium* spp., gram-negative and anaerobic bacteria

Clinical Signs

I. Focal infection: localized muscle pain and swelling, lameness, ± fever
II. Diffuse myositis
  A. Generalized muscle pain, lethargy, malaise, fever
  B. Evidence of bacteremia and septicemia: injected mucous membranes, heart murmur, coagulopathies
  C. Death (possible in 24 hours)

Diagnosis

I. Diagnosis is suspected from compatible clinical signs, especially after muscle trauma.

II. Laboratory tests may be normal with focal disease; leukocytosis and elevated CK may be detected with diffuse disease.
III. Definitive diagnosis is based on identification of bacteria from affected tissue via aerobic or anaerobic culture or histopathology.

Differential Diagnosis

I. Focal myositis
  A. Subcutaneous abscess
  B. Muscle contusion or avulsion
  C. Parasitic myositis: *Dirofilaria immitis*
II. Diffuse myositis
  A. Toxoplasmosis, neosporosis, sarcocystosis (rare), trichinellosis (rare)
  B. Septicemia
  C. Streptococcal group G fasciitis (Naidoo et al., 2005)
  D. Other causes of fever, muscle and subcutaneous pain

Treatment and Monitoring

I. Localized myositis
  A. Wounds are surgically drained and lavaged.
  B. Warm, wet compresses TID to QID may be helpful.
  C. Broad-spectrum antibiotics are started and may be modified based on culture and sensitivity results.
  D. Prognosis is good, with resolution of signs within 7 to 10 days.
II. Diffuse myositis
  A. Parenteral antibiotics are indicated (see Chapter 113).
  B. Pain management and supportive care are instituted as needed.
  C. Prognosis is variable, depending on the degree of subcutaneous and systemic involvement, as well as the responsiveness of the causative bacteria to antibiotics.

METABOLIC MYOPATHIES

Feline Hypokalemic Polymyopathy

Definition and Causes

I. Chronic potassium depletion in cats produces a myopathy that causes acute onset of generalized weakness.
II. In many cats the cause is a total body depletion of potassium, usually from a combination of low dietary intake of potassium and increased urinary potassium loss (potassium-losing nephropathy).
III. Primary hyperaldosteronism associated with adrenocortical neoplasia may also cause persistent hypokalemia (Ash et al., 2005).
IV. A familial, inherited syndrome has been reported in Burmese cats.

Pathophysiology

I. Hypokalemia produces several effects on muscle cell membranes.
  A. Muscle cell hyperpolarization leads to increased sodium permeability of the sarcolemma and subsequent hypopolarization.
  B. Muscle cell hypopolarization causes muscle weakness.
  C. Hypokalemia may also affect muscle blood flow and lead to ischemic necrosis.
II. Depletion of potassium may occur for months before onset of clinical signs.

Clinical Signs

I. Acute onset of generalized weakness
II. Muscle pain, atrophy
III. Ventriflexion of the neck
IV. Stiff gait
V. Anorexia, weight loss
VI. Evidence of hypertension with primary aldosteronism

Diagnosis

I. Compatible clinical signs, with a normal neurological examination
II. Low serum potassium concentration (<3.5 mEq/L) and elevated CK (500 to 10,000 IU/L)
III. Low urine specific gravity and increased fractional urinary excretion of potassium with a nephropathy
IV. Elevated blood pressures with hyperaldosteronism
V. Electromyographic (EMG) abnormalities
  A. Increased positive sharp waves
  B. Fibrillation potentials
  C. Normal nerve conduction velocities
VI. Normal muscle histopathology on biopsy

Differential Diagnosis

I. Polymyositis
II. Polyneuropathies: diabetic neuropathy, vincristine-related neuropathy
III. Neuromuscular junction diseases: myasthenia gravis, certain toxicities
IV. Ethylene glycol toxicity
V. Severe anemia, other causes of weakness
VI. Thyrotoxicosis
VII. Thiamine deficiency
VIII. Hypernatremic myopathy
IX. Nemaline myopathy

Treatment and Monitoring

I. Potassium supplementation usually relieves the clinical signs.
  A. Potassium gluconate (more palatable and nonacidifying than potassium chloride [KCl]) is started at 5 to 8 mEq PO divided BID for cats with serum potassium <3 mEq/L.
  B. KCl in lactated Ringer's solution is administered IV at 0.4 mEq/kg/hr to severely hypokalemic cats.
    1. Measure serum potassium every 3 to 6 hours, and reduce infusion rates once potassium is >3.5 mEq/L.
    2. Monitor the electrocardiogram for arrhythmias and any catheterized veins for phlebitis.
    3. Monitor closely for potassium-related respiratory paralysis.

II. Dopamine (0.5 μg/kg/min IV) can induce a transient increase in serum potassium during life-threatening situations.
III. Monitor serum potassium SID until it returns to normal, then weekly.
IV. Once serum potassium stabilizes, a maintenance dose of potassium gluconate (2 to 6 mEq PO SID-BID) is usually effective.
V. A diet with adequate potassium (>0.6%) is also instituted.
VI. Prognosis for cats with hypokalemic myopathy is excellent with prompt diagnosis and treatment.

Exertional Myopathy in Greyhounds

Definition and Causes

I. Exertional myopathy is muscle damage that occurs primarily in greyhounds or working dogs after racing or exertion.
II. It is caused by acute muscle ischemia.
III. Exercise-induced muscle ischemia and lactic acidosis lead to lysis of muscle cell walls and release of myoglobin.
IV. Predisposing factors include the following:
   A. Lack of fitness
   B. Hot, humid conditions
   C. Overexcitement or exertion
   D. Excessive racing
V. Exertional myopathy may rarely develop secondary to prolonged seizure activity.

Clinical Signs

I. Mild cases have generalized muscle pain and swelling after strenuous exercise.
II. Signs in severe cases include the following:
   A. Distress, tachypnea
   B. Hard, painful swelling of affected muscles, especially of the trunk and limbs
   C. Myoglobinuria, possible hyperthermia
   D. Acute collapse, death within 48 hours from renal failure associated myoglobinuria

Diagnosis

I. Diagnosis is based on signalment, history, and clinical signs.
II. Myoglobinuria is a supportive finding.
III. Serum elevations of potassium, phosphorus, and muscles enzymes are common.
IV. Elevations of serum creatinine and blood urea nitrogen (BUN) occur with renal damage.
V. Postmortem histopathologic examination of muscles demonstrates multifocal hemorrhages and myonecrosis.

Differential Diagnosis

I. Heat stroke
II. Malignant hyperthermia
III. Certain toxicoses

Treatment and Monitoring

I. Intravenous fluids are started to prevent hypovolemia and promote renal excretion of myoglobin.
II. Sodium bicarbonate may be administered to combat muscle acidosis.
III. Enforced rest and cooling measures (see Chapter 135) are started.
IV. Diazepam is given at 0.5 mg/kg IV as a muscle relaxant.
V. Renal function and urine output are monitored.
VI. Prognosis is guarded for severe cases.

Malignant Hyperthermia

Definition and Causes

I. Malignant hyperthermia is severe elevation of the core body temperature from an abnormal physiological response to exercise or to certain drugs that produce peracute skeletal muscle hypercatabolism and contracture (Brunson and Hogan, 2004).
II. Drugs that may induce the condition in susceptible individuals include inhaled halothane and enflurane as well as injectable succinylcholine and lidocaine.
III. An autosomal dominant mutation in the gene encoding the skeletal muscle calcium release channel has been documented in mixed breed dogs (Roberts et al., 2001).
IV. A malignant, hyperthermia-like condition can occur in dogs after ingestion of hops (Duncan et al., 1997).

Pathophysiology

I. Malignant hyperthermia is associated with a hypersensitivity of calcium channels that allows the re-release of calcium in the sarcoplasmic reticulum.
II. Hypermetabolism of muscle depletes glycogen stores and generates heat, hypoxia, lactic acid, and carbon dioxide.

Clinical Signs

I. The condition is more common in males and heavily muscled dogs.
II. Mixed breed dogs, as well as the Labrador retriever, greyhound, and collie may be more commonly affected.
III. Initially tachycardia and tachypnea may be noted, followed by pyrexia.
IV. Muscle cramping and generalized rigidity ensue.
V. Occasionally contracture develops only of the masseter muscles.
VI. Respiratory distress from pulmonary edema and cardiovascular collapse may occur.
VII. Myoglobinuria and renal failure are often terminal events.

Diagnosis

I. Diagnosis is suggested from the clinical signs.
II. Laboratory findings include elevated serum levels of muscle enzymes, lactate, potassium, chloride, BUN, creatinine, and total protein, as well as decreased levels of calcium and bicarbonate.
III. Postmortem changes include the following:
   A. Immediate, generalized muscle rigidity
   B. Pale, soft, exudative musculature
   C. Variable muscle fiber size (hypertrophy common), increased numbers of internal nuclei on histopathology

Treatment

I. Discontinue all inciting drugs, stop anesthesia, and administer high flow rates of 100% oxygen.
II. Institute supportive therapy.
  A. Cooled 0.9% saline at 90 mL/kg/hr IV
  B. Sodium bicarbonate to correct acidosis
  C. Total body cooling (see Chapter 135)
  D. Shock doses of short-acting corticosteroids (see Chapter 132)
III. Dantrolene (skeletal muscle relaxant) is administered at 2 to 5 mg/kg IV.

Monitoring of Animal

I. Monitor renal function, urine output, and development of myoglobinuria.
II. Monitor electrolytes and acid-base status.
III. Monitor for cardiac arrhythmias.
IV. Prognosis is usually poor to guarded for dogs with the genetically mediated condition but may be good in dogs that are treated promptly for ingestion of hops.

Endocrine Myopathies

See Chapters 42 and 45.

IMMUNE-MEDIATED DISORDERS

Masticatory Myositis

Definition

I. Masticatory myositis is acute or chronic inflammation of the masticatory muscles that may lead to severe atrophy and difficulty opening the mouth.
II. It is the most common noninfectious, inflammatory myopathy of dogs.
III. It usually affects large-breed dogs.
IV. It is also referred to as *eosinophilic myositis, atrophic myositis,* and *cranial myodegeneration*.

Causes and Pathophysiology

I. Evidence indicates that autoantibodies to myosin cause the disease (Shelton and Paciello, 2006).
II. Masticatory muscles have a different embryologic origin (branchial arch) and are antigenically different (contain type 2M myofibers) from other skeletal muscle fibers.
III. Autoantibodies may be produced against these specific antigens.

Clinical Signs

I. Acute form
  A. Usually symmetrical swelling and pain of the muscles of mastication (temporalis, masseter)
  B. Difficulty opening the mouth (trismus)
  C. Anorexia from reluctance to open mouth
  D. Pyrexia
  E. Possible regional lymphadenopathy
  F. Exophthalmos from swelling of affected muscles, with secondary optic nerve stretching and blindness
II. Chronic form
  A. Progressive fibrosis and atrophy of muscles of mastication with inability to voluntarily or manually open the mouth (trismus)
  B. Difficulty with prehension, chewing and swallowing food, and weight loss
  C. Enophthalmos from atrophy of affected musculature

Diagnosis

I. Diagnostic findings include masticatory muscle swelling and pain or atrophy on physical examination, often with decreased ability to open the mouth.
II. Routine laboratory tests are often unrewarding but may reveal eosinophilia, as well as elevated serum globulin and muscle enzymes.
III. Serological testing for type 2M antibodies is the definitive test, but is not always positive.
IV. EMG findings may include the following:
  A. Positive sharp waves
  B. Fibrillation potentials
  C. Polyphasic motor unit potentials
  D. Electrical silence in areas of fibrosis
V. Histopathologic findings in muscle biopsies are helpful to identify both acute and chronic changes.
  A. Acute form: myofiber necrosis, diffuse and predominantly mononuclear cell infiltrates
  B. Chronic form: increased connective tissue and fibrosis, myofiber necrosis
VI. Radiographs of the temporomandibular joint help rule out other bony or joint diseases.
VII. Assays for autoantibodies against 2M fiber proteins may also be performed on frozen muscle specimens.

Differential Diagnosis

I. Polymyositis
II. Infectious myositis
III. Dermatomyositis
IV. Trigeminal neuropathy
V. Temporomandibular joint disease
VI. Retrobulbar inflammation
VII. Extraocular myositis (see Chapter 103)

Treatment and Monitoring

I. Immunosuppressive therapy is the treatment of choice.
  A. Prednisone is given at 1 to 2 mg/kg PO BID for 3 to 4 weeks, then tapered over 2 to 6 months.
  B. If the response to prednisone is poor, side effects are intolerable, or the drug cannot be tapered without relapses, then the following can be added:
    1. Azathioprine 2 mg/kg PO SID (dogs only), tapered once in remission
    2. Cyclophosphamide 1 to 2 mg/kg PO SID for 4 days on, 3 days off, for up to 3 weeks
  C. Continuously monitor the ability to open the jaw while on therapy.
  D. Relapses are common with premature tapering or withdrawal, and some dogs require prolonged therapy.
II. Insertion of a feeding tube may be considered in animals unable to eat.

III. Forced, manual opening of the jaw may be required in dogs when fibrosis and atrophy prohibits normal eating.
   A. Rib spreaders may be used to slowly tear the fibrosed muscles and open the jaw.
   B. An opening distance of 2 inches may be adequate in most animals.
   C. Excessive force may result in fractures of the teeth or jaw and must be avoided.
IV. Prognosis is most favorable when the diagnosis is made early in the course, before excessive fibrosis occurs.

Polymyositis

Definition and Causes

I. Polymyositis is a generalized inflammatory disease affecting one or more skeletal muscle groups.
II. Although the precipitating cause is unknown, the disease is a T cell–mediated immunological disease that results in muscle and fiber destruction and production of antimyosin autoantibodies (Neumann and Bilzer, 2006; Shelton and Paciello, 2006).
III. The condition can be seen in association with systemic lupus erythematosus (SLE) (Krum et al., 1977) and myasthenia gravis.
IV. Masticatory myositis may be a variant of polymyositis.

Clinical Signs

I. The disease may be acute and episodic or chronic and progressive.
II. It occurs in adult dogs of either sex and is characterized by the following:
   A. Weakness
   B. Anorexia, weight loss
   C. Stiff gait, reluctance to walk
   D. Muscle pain, pyrexia
   E. Dysphagia, dysphonia
   F. Regurgitation from megaesophagus
III. The muscles affected most commonly are those of the thoracic limbs, neck, esophagus, and pelvic limbs.

Diagnosis

I. Suspicion of polymyositis is initially based on clinical signs and a normal neurological examination.
II. Elevated serum CK is an inconsistent finding.
III. EMG may demonstrate generalized spontaneous electrical activity in affected muscles; however, if the disease is diffuse, it may be hard to localize testing sites.
IV. Muscle biopsy can be guided by EMG studies and usually reveals characteristic changes.
   A. Myofiber necrosis and phagocytosis
   B. Vacuolization and hyalinization
   C. Mononuclear infiltrates: lymphocytes, plasma cells
V. Serological testing for antimyosin antibodies is the definitive test, but is not positive in all cases.
VI. Antinuclear antibody assays and lupus erythematosus (LE) cell preparations may be positive, especially in cases with SLE.

Differential Diagnosis

I. Other immune-mediated disorders
   A. SLE
   B. Myasthenia gravis
   C. Polyarthritis
   D. Polyarteritis
II. Masticatory myositis
III. Polyneuropathies
IV. Infectious myopathies
V. Dermatomyositis
VI. Leptospirosis

Treatment and Monitoring

I. Immunosuppressive treatment is indicated.
   A. Prednisone is started at 1 to 2 mg/kg PO BID for 3 to 4 weeks, then tapered over 2 to 3 months.
   B. If the response to prednisone is poor, side effects are intolerable, or the drug cannot be tapered without relapses, then the following can be added:
      1. Azathioprine 2 mg/kg PO SID (dogs only), tapered once in remission
      2. Cyclophosphamide 1 to 2 mg/kg PO SID for 4 days on, 3 days off, for up to 3 weeks
II. Relapses are common with premature tapering or withdrawal, and some dogs require prolonged therapy.
III. Despite marked inflammation of muscles, regeneration, recovery, and reversal of fibrotic changes are possible in some dogs (Salvadori et al., 2005).
IV. Prognosis is guarded in cases with megaesophagus and SLE.

Dermatomyositis

Definition and Cause

I. It is an immune-mediated disease of dogs that causes inflammation of both skin and muscles.
II. The condition is familial in the Shetland sheepdog and collie, and may be an autosomal dominate trait with variable expressivity.
III. The disease also occurs in the Beauceron shepherd dog and possibly the Welsh corgi.

Clinical Signs

I. Onset is usually <6 months of age.
II. Alopecia, erythema, and scaling occur over areas of mechanical trauma, such as the muzzle, lips, tip of tail, around the eyes, pinnae, carpi, tarsi, and feet.
III. Pruritus of skin lesions is variable and may be related to secondary infections.
IV. Myositis may result in difficulty swallowing and chewing, a stiff gait, and reluctance to walk.
V. Regurgitation from megaesophagus may be noted.
VI. Severity of signs is variable, and signs may wax and wane.

Diagnosis

I. A combination of dermatological and myological signs, in a predisposed breed, is highly suggestive of the condition.

II. A serum biochemistry profile may reveal hyperglobulinemia and elevated CK.
III. Skin biopsy reveals the following:
  A. Follicular atrophy and perifollicular fibrosis
  B. Hydropic degeneration, apoptosis of basal cells
  C. Intrabasilar or subepidermal clefting
  D. Vasculitis
IV. Muscle fiber necrosis, atrophy, and inflammation are demonstrated on histopathology.
V. EMG shows positive sharp waves and fibrillation potentials in affected muscles of the head and limbs.
VI. Markers for the affected gene have been identified, making future genetic screening a possibility (Clark et al., 2005).

Differential Diagnosis

I. Other immune-mediated skin diseases: pemphigus complex, discoid lupus, vasculitis
II. Other immune-mediated myopathies: polymyositis, masticatory myositis

Treatment and Monitoring

I. Spontaneous resolution is possible in mildly affected dogs.
II. Minimize ultraviolet light exposure and trauma to affected areas.
III. Symptomatic therapy with topical sun blockers may be helpful.
IV. Pentoxifylline 25 mg/kg PO BID has induced partial and complete responses in some dogs (Rees and Boothe, 2003).
V. Vitamin E 200 to 800 IU PO BID to TID may be given for 2 to 3 months.
VI. Prednisone at 1 to 2 mg/kg PO SID may be tried for severe or unresponsive cases.
VII. Secondary skin infections are treated with appropriate antibiotics.
VIII. Prognosis is highly variable and related to the severity of the clinical signs.

NUTRITIONAL DISORDERS

Nutritional Myodegeneration

Definition and Causes

I. Nutritional myodegeneration resembles white muscle disease of large animals and is occasionally seen in dogs.
II. It has been produced experimentally by feeding selenium and vitamin E–deficient diets.

Clinical Signs

I. Generalized weakness
II. Difficulty rising, stiff gait
III. Swollen muscles
IV. Paraparesis
V. Dysphagia, dysphonia
VI. Sudden death in puppies with myocardial lesions

Diagnosis

I. History of abnormal diet
II. Elevated serum muscle enzymes
III. Abnormal findings on EMG
  A. Myopathic potentials
  B. Positive waves
  C. Fibrillation potentials
  D. Bizarre, high-frequency discharges
IV. Histopathologic abnormalities
  A. Pale muscles, with chalky longitudinal striations
  B. Myonecrosis, calcification of fibers, fiber regeneration and inflammation

Treatment and Monitoring

I. Supplement with selenium and vitamin E at 100 to 400 IU PO BID until the dog is clinically normal.
II. Correct the dietary abnormality.
III. Prognosis is usually poor if cardiac, diaphragmatic, and intercostals muscle are involved.

NEOPLASIA

Definition and Causes

I. Primary tumors of striated muscle
  A. Rhabdomyoma (Clercx et al., 1998; O'Hara et al., 2001)
  B. Rhabdomyosarcoma (Ginel et al., 2002)
  C. Primary skeletal muscle lymphoma (Harkin et al., 2000; Bennett et al., 2005)
  D. Common sites: appendicular muscles, larynx, muscles of head, heart
II. Metastatic (secondary) spread of tumors from distant sites
  A. Lymphoma
  B. Adenocarcinomas
  C. Hemangiosarcoma
  D. Malignant melanoma
III. Invasion of tumors in adjacent tissues
  A. Fibrosarcoma
  B. Osteosarcoma
  C. Mast cell tumor
  D. Hemangiopericytoma

Clinical Signs

I. Variable age of onset
II. Nonpainful swelling in affected muscle group
III. Lameness common when appendicular muscles affected

Diagnosis

I. Biopsy and histopathology are required for a definitive diagnosis.
II. Thoracic radiography and local lymph node biopsy are performed to stage the disease.

Treatment and Monitoring

I. For primary tumors, wide surgical excision is attempted to obtain clean surgical margins.
  A. Wide excision is often difficult.

Text continued on p. 814.

TABLE 82-2

Traumatic Muscle Injuries

INJURY	CAUSES AND PATHOPHYSIOLOGY	CLINICAL SIGNS	DIAGNOSIS	TREATMENT AND PROGNOSIS	REFERENCES
Thoracic Limb					
Rupture of the serratus ventralis	Acute trauma, although also presented as chronic injury Reported in the dog and cat	Upward displacement of the scapula with forelimb lameness Usually unilateral	Clinical signs and history	Acute injuries are treated conservatively with a shoulder sling or other non–weight-bearing bandage for 3-4 wk Chronic injuries may require surgical repair of the muscle or fixation of the scapula to the ribs using wire Very good prognosis	Bloomberg (1995)
Disruption of the tendon of origin of the biceps brachii	Avulsion: acute trauma Avulsion of tendon of origin from the supraglenoid tubercle in young large-breed dogs (4-8 mo of age) Displacement: repetitive injury Medial displacement of the tendon of origin from the intertubercular groove in the racing greyhound; also reported in the miniature poodle and border collie	Weight-bearing lameness: acute for avulsion, chronic for displacement Pain on flexion and extension of the shoulder	Clinical signs and radiographs Avulsion: avulsed segment of bone (supraglenoid tubercle) may be seen on radiographs Displacement: palpation of medial displacement of the tendon during flexion of the shoulder or during extension of the elbow with the shoulder held in partial flexion	Avulsion: surgical reattachment of the tendon (pin and tension band or screw) associated with a good prognosis Displacement in athletic animals: surgical reconstruction of the intertubercular ligament using screws and figure-of-eight suture across the tendon as it sits in the groove Displacement in sedentary animals: rest and administration of anti-inflammatory drugs possibly successful Displacement with surgical stabilization has a good prognosis for return to function and fair prognosis for return to racing	Boemo and Eaton-Wells (1995)

Modified from Davidson JR, Hosgood G: Disease of muscles and tendons. p. 806. In Morgan RV, Bright RM, Swartout MS (eds): Handbook of Small Animal Practice. 4th Ed. WB Saunders, Philadelphia, 2003; with permission.

Traumatic Muscle Injuries—*cont'd*

INJURY	CAUSES AND PATHOPHYSIOLOGY	CLINICAL SIGNS	DIAGNOSIS	TREATMENT AND PROGNOSIS	REFERENCES
Tenosynovitis of the biceps brachii tendon	Unknown, but likely secondary to trauma, overuse, and repetitive injury Middle-aged or older medium- and large-breed dogs No breed or sex predilection	Usually unilateral, but may be bilateral Intermittent, chronic, or progressive weight-bearing forelimb lameness that worsens after exercise and improves with rest Resistance to flexion and extension of the shoulder	History, clinical signs, and physical examination findings Acute pain elicited when pressure is applied directly to the bicipital tendon during flexion and extension of the shoulder Atrophy of the infraspinatus and supraspinatus muscles Radiographs (including craniodistal-cranioproximal flexed view) may identify dystrophic calcification of the tendon, osteophytes in the intertubercular groove, or a mineralized joint mouse within the tendon sheath Contrast arthrography may demonstrate filling defects along the tendon, adhesions between the tendon sheath and tendon, or joint mice No radiographic changes may be apparent in acute cases Cytological evaluation of synovial fluid consistent with DJD, but may be normal Diagnosis confirmed by exploratory arthrotomy and microscopic examination of biopsied tissue	Acute cases: nonsteroidal antiinflammatory medication with limited activity for 4-6 wk Severe or chronic cases: intrasynovial injection of 10-40 mg methylprednisolone acetate no more than every 2 wk; do not exceed 2 injections; rest for at least 2 wk after injection Arthroscopic tevotomy indicated for refractory cases (dogs that do not improve after 1 or 2 injections of corticosteroids) or for removal of joint mice if identified Prognosis for return to function is generally good	Kramer et al. (2001) Stobie et al. (1995) Wall and Taylor (2002) Esterline et al. (2005)

DJD, Degenerative joint disease.

Continued

TABLE 82-2

Traumatic Muscle Injuries—*cont'd*

INJURY	CAUSES AND PATHOPHYSIOLOGY	CLINICAL SIGNS	DIAGNOSIS	TREATMENT AND PROGNOSIS	REFERENCES
Mineralization of the supraspinatus tendon	Cause unknown May be initiated by hypoxia of the tendon Mineralization deep in the tendon may cause mechanical irritation of the biceps tendon sheath	Role in causing lameness is unclear May have forelimb lameness or may be asymptomatic Must rule out all other causes of forelimb lameness (OCD, DJD, bicipital tendonitis, elbow pathology, etc.)	Mineralization seen on radiographs—often bilateral Contrast arthrography or arthrocentesis may rule out other causes of shoulder lameness Ultrasonography or nuclear scintigraphy may help differentiate between an actively inflamed tendon and asymptomatic mineralization	Conservative management with rest and nonsteriodal antiinflammatory drugs or local injection of methylprednisolone acetate If no response to conservative management, surgical removal of mineralization may resolve the lameness Mineralization may recur after surgery, but signs do not necessarily recur Therapeutic ultrasound	Kriegleder (1995) Laitinen and Flo (2000)
Rupture of the origin of the long head of the triceps	Typically racing greyhounds Avulsion of the origin from the posterior edge of the scapula	A hollow depressed area posterior and distal to the scapula	Based on clinical signs and history	Conservative management with rest may be sufficient Surgical reattachment of the muscle to the caudal scapula may be required Prognosis for return to racing is fair; same level of racing may not be attained owing to decreased range of motion of the shoulder	
Avulsion of the triceps tendon	Associated with trauma, local corticosteroid injection, or spontaneous avulsion Detachment of the triceps tendon occurs from its point of insertion on the olecranon Immature animals may have avulsion of the proximal epiphysis of the olecranon	Acute injury or chronic lameness Acute non–weight-bearing lameness with pain and reduced range of motion on flexion and extension of the elbow Chronic disruption associated with thickening and fibrosis over olecranon, muscle atrophy of affected forelimb	Based on clinical signs and radiographs Avulsed fragment of bone proximal to the olecranon may be seen on radiographs	Surgical repair of tendon using tension-relieving tendon sutures or reattachment of the olecranon epiphysis using a pin and tension band or screw is indicated Coaptation of the limb for 2 wk with physiotherapy and restricted exercise is advised for a further 3-4 wk Prognosis after acute injury is good, but joint motion may be restricted Prognosis after chronic injury is fair	Anson and Betts (1989) Davies and Clayton-Jones (1982) Gilmore (1984) Liehmann and Lorinson (2006)

OCD, Osteochondritis dissecans.

TABLE 82-2

Traumatic Muscle Injuries—*cont'd*

INJURY	CAUSES AND PATHOPHYSIOLOGY	CLINICAL SIGNS	DIAGNOSIS	TREATMENT AND PROGNOSIS	REFERENCES
Injury of the flexor carpi ulnaris	Chronic, repetitive injury in racing greyhounds Transverse tears may occur through the tendon of the humeral head The insertion of the ulnar head and a bony fragment may avulse from the accessory carpal bone ("bowed tendon")	Poor performance Mild lameness After repeated injury, swelling and bruising are observed over the accessory carpal bone	Based on clinical signs and history	Transverse tears and avulsions should be surgically repaired Postoperative coaptation is required Prognosis for return to racing after transverse tears of the humeral head is good Prognosis for avulsion of the ulnar head is poor	
Injury to the digital flexor and extensor tendons	Lacerations above or below the metacarpal and metatarsal pads Digital extensor tendon injury is less critical owing to the many anastomoses of the tendon after they branch from the main tendon	Laceration may be accompanied by profuse hemorrhage Postural changes: superficial digital flexor injury alone may result in little change; deep digital flexor tendon injury results in flattening of one or more digits Chronic injury may result in excoriation of the metacarpal or metatarsal pads owing to prolonged postural changes	Based on clinical signs and surgical exploration of the laceration site Pressure, using the palm of the hand, on the bottom of the pads may allow detection of any postural change in the digits	Surgical repair is required if there are postural changes Coaptation is indicated if there are no postural changes Prognosis for acute injuries is good Prognosis for chronic injuries is poor owing to fibrosis and the inability to anastomose the tendon if there are extensive deficits	Williams et al. (1997)
Carpal laxity syndrome	Cause is unknown May be discrepancy in rate of growth between extensor and flexor muscle groups Reported in German shepherd dogs, boxers, Great Danes	Unilateral or bilateral carpal hyperflexion or hyperextension in puppies (<16 wk old)	Based on signalment and clinical signs	Exercise on grass Avoid use of splints Condition usually improves in 2-6 wk	Alexander and Early (1983) Shires et al. (1985)
Pelvic Limb					
Injury to the tensor fascia lata	Injury of racing greyhounds Tearing of the musculotendinous junction Most often the left rear leg of dogs racing in the United States	Weight-bearing lameness Palpable and visible depression in the proximal cranial area of the thigh	Based on clinical signs and palpation of thigh depression	Surgical repair is indicated Prognosis for return to racing after primary repair is good	

Continued

TABLE 82-2

Traumatic Muscle Injuries—*cont'd*

INJURY	CAUSES AND PATHOPHYSIOLOGY	CLINICAL SIGNS	DIAGNOSIS	TREATMENT AND PROGNOSIS	REFERENCES
Rupture of the gracilis muscle	Injury of the racing greyhound, but also seen in working dogs Exact cause is unknown; sudden exercise in an unfit animal may predispose to injury Substantial hemorrhage can occur Unilateral injury is more common	Ventral displacement of the origin (or dorsal displacement of the insertion) is observed and palpated on the inside of the thigh Significant bruising over the inside of the thigh Pelvic limb lameness and difficulty rising, particularly 12-24 hr after the injury	Based on clinical signs and palpation of the muscle avulsion	Surgical repair or reattachment of the avulsed tendon to the bone may be indicated if return to racing is desired Prognosis for return to racing is fair Fibrosis at the surgical site may restrict motion	Eaton-Wells (1992)
Quadriceps contracture	Associated with inadequate fracture repair, osteomyelitis, severe trauma, or overzealous tissue handling Adhesions form between the quadriceps muscle and the femur Usually occurs in young animals Prolonged immobilization of the hind leg in extension or failure to bear weight soon after internal fixation may also be factors Also reported as a congenital disorder and in association with toxoplasmosis Disuse osteoporosis, irreversible DJD of the stifle, and growth disturbances can occur (hip luxation, bone hypoplasia, increased femoral torsion, medial patellar luxation, and limb shortening)	Pelvic leg held with the stifle and hock stiff in extension May be non–weight-bearing or use the leg as a peg leg The affected leg is held cranial with respect to the other hind leg Later clinical signs, if left untreated, include atrophy of the thigh muscles, bending of the stifle caudally in genu recurvatum with the hock extended, proximal positioning or medial luxation of the patella, and subluxation of the hip	Based on history and clinical signs In chronic cases, radiographs may reveal changes consistent with DJD of the stifle, hip luxation, or disuse osteoporosis of the long bones	Surgery is indicated to attempt to restore stifle joint mobility; adhesions between the quadriceps muscles and the femur are broken down and the stifle is flexed carefully to release any remaining fibrous tissue (excessive force could result in a Salter fracture of the distal femur or proximal tibia) Sliding myoplasty or Z-myoplasty of the quadriceps may be indicated Postoperative maintenance of stifle flexion using a 90-90 flexion sling, a Robinson sling, or an external pin splint for 4-5 days is indicated Physical therapy is also required Results are unpredictable; surgery may result in 50%-75% restoration of limb use If surgery is unsuccessful or there is advanced osteoarthritis of the stifle joint, stifle arthrodesis or amputation may be required	Bardet and Hohn (1984) Liptak and Simpson (2000)

TABLE 82-2

Traumatic Muscle Injuries—*cont'd*

INJURY	CAUSES AND PATHOPHYSIOLOGY	CLINICAL SIGNS	DIAGNOSIS	TREATMENT AND PROGNOSIS	REFERENCES
Quadriceps contracture—*cont'd*				Prevention of this condition is preferable; femoral fracture repairs in young animals should be stable and allow early return to function Animals exhibiting signs of hyperextension following femoral fracture repair should have a flexion sling or dynamic flexion apparatus applied	
Disruption of the tendon of origin of the long digital extensor	Traumatic avulsion of the tendon of origin occurs in immature, large-breed dogs Displacement of the tendon occurs in young dogs	Avulsion causes mild weight-bearing lameness and pain on manipulation of the affected stifle Lateral soft tissue swelling may be present Displacement causes chronic, mild, weight-bearing lameness	Based on clinical signs and radiographs Radiographs may show avulsed bone and cartilage near the extensor fossa of the lateral femoral condyle, best observed on the lateral projection In a very young dog, the portion of bone may consist primarily of cartilage and not be visible on radiographs Diagnosis is confirmed by advanced imaging or exploratory arthrotomy Displacement can be palpated during extension and flexion of the stifle, which allows detection of the tendon moving in and out of the muscular groove	Surgical reattachment of the avulsed segment using bone screws is the treatment of choice Prognosis for return to function after acute injuries is good to excellent For displacement, surgical stabilization of the tendon by reconstruction of the supporting retinacular tissue, use of a staple to make a roof over the tendon, or tenotomy and transplantation of the tendon to the craniolateral aspect of the proximal tibia (as a last resort) is indicated Prognosis after surgery for displacement is variable	Fitch et al. (1997)

Continued

TABLE 82-2

Traumatic Muscle Injuries—*cont'd*

INJURY	CAUSES AND PATHOPHYSIOLOGY	CLINICAL SIGNS	DIAGNOSIS	TREATMENT AND PROGNOSIS	REFERENCES
Avulsion of the lateral or medial head of the gastrocnemius muscle	Trauma Reported in the fox terrier, German shepherd dog, Labrador retriever	Weight-bearing lameness and soft tissue swelling over the caudal aspect of the stifle are apparent Hyperflexion of the stifle and hock is present	Based on clinical signs and radiographs revealing caudal and distal displacement of the fabella	Surgical reattachment of the tendon Prognosis for acute injuries is good	Robinson (1999)
Avulsion of the tendon of the popliteal muscle	Trauma	Weight-bearing lameness and soft tissue swelling over the lateral aspect of the stifle	Based on clinical signs and radiographs, which reveal displacement of the popliteal sesamoid bone and possibly a bony fragment from the lateral femoral condyle, positioned caudal to the point of attachment of the popliteal tendon	Surgical reattachment of the tendon Prognosis for acute injuries is good	Tanno et al. (1996)
Disruption of the Achilles mechanism (common calcaneal tendon, composed of three major musculotendinous units: (1) gastrocnemius muscle, (2) superficial digital flexor and (3) common tendon of the biceps femoris, semitendinosus, and gracilis muscles)	Rupture occurs primarily in mature working or racing dogs Injury has also been reported in cats Result of an animal jumping and landing on its rear legs May be bilateral Rupture secondary to parasitic disease of the gastrocnemius muscle also reported Disruption of the connective tissue over the superficial digital flexor tendon causes displacement of the tendon during weight bearing	Tarsal hyperflexion (<90°) and stifle hyperextension owing to the inability to extend the tarsus Degree of tarsal hyperflexion depends on the completeness of Achilles mechanism disruption The animal walks on the plantar surface of the tarsus Displacement of the superficial digital flexor tendon is associated with a mild, chronic, weight-bearing lameness with the hock slightly hyperflexed, but not to the same degree as with complete calcaneal tendon disruption	Clinical signs of tarsal hyperflexion and palpable flaccidity of the calcaneal tendon If the superficial digital flexor tendon is intact, the digits will flex when the tarsus is flexed Standing or stress radiographs may aid diagnosis, particularly in partial ruptures, because the entire tendon must be disrupted before excessive tarsal hyperflexion is present Ultrasonography may help localize the site of injury	Acute damage requires tenorrhaphy, or apposition of the muscle–tendon or tendon–bone junction Chronic rupture or injury can be treated by shortening the calcaneal tendon to reestablish function Prognosis for acute rupture or severance of the Achilles mechanism in most animals is good Prognosis in very large dogs, or in racing dogs for return to racing, is poor Prognosis for chronic injuries with fibrosis is less favorable, although function may be improved after surgery	Mauterer et al. (1993) McNichols et al. (2000) Reinke et al. (1993) Rivers et al. (1997) Mughannam and Reinke (1994) Parker and Cardinet (1984) Kramer et al. (2001) Moores et al. (2004) Ridge and Owen (2005) Nielson and Pluhar (2006)

TABLE 82-2

Traumatic Muscle Injuries—*cont'd*

INJURY	CAUSES AND PATHOPHYSIOLOGY	CLINICAL SIGNS	DIAGNOSIS	TREATMENT AND PROGNOSIS	REFERENCES
Disruption of the Achilles mechanism—*cont'd*		Tissue thickening around the tuber calcanei may be apparent	Displacement of the superficial digital flexor tendon is diagnosed on clinical signs, and by palpation of the tendon and thickened tissue to one side of the tuber calcanei	Arthrodesis of the tibiotarsal joint may be required if surgical repair is unsuccessful Prognosis for normal function after surgical stabilization of the superficial digital flexor tendon is very good	
Compartment syndrome	Interstitial pressure is elevated within a closed fascial compartment Causes of increased pressure include increased compartment volume (hemorrhage), post-ischemic tissue swelling, or external pressure (tight bandage)	Nonresolving swelling, pain, tense muscle Occurs in the craniolateral crural, caudal crural, caudal anterbrachial, and femoral compartments	Measure compartmental pressure with a catheter Contrast arteriography	Surgical decompression by fasciotomy	de Haan and Beale (1993) Radke et al. (2006) Bar-Am et al. (2006)

B. Amputation may be required for appendicular neoplasia.

II. In cases of metastatic or locally invasive neoplasia, treatment depends on the primary tumor.

III. Prognosis is related to whether the tumor is primary or secondary, the feasibility of complete excision, and the tumor's responsiveness to adjunctive chemotherapy or radiation therapy.

MUSCLE AND TENDON TRAUMA

See Table 82-2.

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CHAPTER 83

Physical Therapy and Rehabilitation

Robert A. Taylor

GENERAL CONSIDERATIONS

Initial Assessment

I. Both the initial and subsequent physical assessments of the injured or affected body part are vital for developing physical therapy and rehabilitation plans and for providing an objective parameter to assess recovery and response.
II. Such parameters include weight-bearing status, limb circumference measurements, and determination of joint range of motion, in addition to a complete history and physical examination.

History

I. The nature of the injury, when it occurred, positive identification of the affected limb or body part, preexisting medical conditions
II. Methods of treatment already administered, including any surgical treatments
III. Response to previous conservative or surgical treatment
IV. Frequency of recurrence, any current supplements or nonprescription drug therapy

Physical Examination

I. A full orthopedic evaluation and a baseline neurological examination are conducted.
   A. Physical findings should match the diagnosis.
   B. For example, a dog with a 6-week-old, cranial cruciate ligament (CCL) injury typically has partial weight-bearing lameness, evidence of synovial effusion, medial buttressing, and instability.
   C. If the dog has non–weight-bearing lameness for 2 weeks, then other diagnostic considerations must be entertained.
II. The degree of muscle atrophy and decreased range of motion can help determine the chronicity of the injury and the length of time necessary for physical therapy and rehabilitation.
   A. In general, if an injury has been untreated with physical therapy for 6 weeks, then at least 12 weeks of therapy will be necessary.
   B. With an acute CCL injury, synovial and cartilage changes are evident by 3 to 4 weeks; muscle atrophy continues for at least 6 weeks.
III. Long-standing muscle atrophy, joint atrophy, and diminished weight bearing and range of motion result in the need for prolonged physical and rehabilitation therapy.
IV. Neurological and/or oncologic issues may mimic orthopedic problems, and they must be excluded during the diagnostic efforts.
V. See Table 83-1 for a list of common conditions to be ruled out by the clinician.

Monitoring of Progress

I. Response or lack of response to therapy is important.
II. Before beginning therapy, the clinician must have clearly delineated goals and measurable parameters of success.
   A. For example, goals that might be achievable when treating a postoperative case of CCL stabilization would include full range of motion, normal gait, full restoration of muscle mass, and return to function by 12 to 14 weeks.
   B. Achievable goals after physical therapy and rehabilitation for bilateral femoral head and neck osteotomy include pain-free range of motion and restoration of gluteal muscle strength.
III. If the animal's response to physical therapy and rehabilitation is inconsistent with expected results, then the clinician should reconsider the diagnosis.
   A. For example, a dog recovering from CCL stabilization should be ambulatory at a walking gait 4 weeks after surgery.
   B. By the sixth week of therapy, a persistent nonweight-bearing lameness and lack of progress regarding muscle mass restoration indicate the need for confirmation of diagnosis and evaluation of the lack of response to the physical therapy.

TYPES OF PHYSICAL THERAPY

Heat Therapy

Definition

I. Heat therapy is the application of a heat source to a body part.
II. Heat may be applied via direct transfer from a hot-water bottle, warmed fluid packs, ultrasound techniques, and diathermy.

TABLE 83-1

Common Conditions of the Pelvic Limbs That May Benefit from Physical Therapy

BODY LOCATION	COMMON CONDITIONS
Digits, pads, feet	Paronychia Lacerations of the interdigital skin or foot pads Luxations of the interphalangeal joints Luxations of the tarsometatarsal joint Fractures of the metatarsal bones Fractures of the phalanges Fractures of the sesamoid bones
Tarsus	Osteochondritis dissecans of the talus Fracture of the calcaneus Fracture of the central tarsal bone Fracture of the third or fourth tarsal bones Luxations of the tarsus with damage to the short or long tarsocrural ligaments Osteoarthritis Disruption of the common calcaneal tendon Rupture of the plantar ligaments
Tibia and fibula	Fractures of the tibia and fibula Panosteitis Traumatic periostitis Osteosarcoma
Stifle	Cranial cruciate ligament rupture Osteochondritis dissecans of the femoral condyles Injuries to the medial/lateral collateral ligaments Medial/lateral patellar luxation Medial/lateral meniscal damage Fractures Congenital absence of the patella Caudal cruciate ligament disruption Osteoarthritis
Femur	Fracture of the femur Panosteitis Osteosarcoma
Coxofemoral joint	Hip dysplasia Fracture of the acetabulum Fractures of the femoral head or neck Fracture/separation of the proximal capital femoral physis Legg-Calvé-Perthes disease Traumatic luxation of the coxofemoral joint Osteoarthritis

Reprinted with permission from Taylor RA: Orthopedic and neurologic evaluation. p. 185. In Millis DL, Levine D, Taylor RA (eds): Canine Rehabilitation and Physical Therapy. Elsevier Saunders, St. Louis, 2004.

Effects

I. Increases regional blood flow
II. Elevates pain threshold
III. Accelerates resolution of inflammation
IV. Causes vasodilation from stimulation of cutaneous thermoreceptors and the release of vasoactive peptides
V. Accelerates the rate of biochemical reactions
VI. Increases extensibility of collagenous tissues

Indications

I. Heat therapy is recommended after resolution of acute inflammation.
   A. In most orthopedic cases, heat therapy is used 2 weeks after surgery (after suture removal).
   B. Heat application is used after femoral head and neck excision, beginning the third postoperative week.
II. Application of heat to a body part or limb can enhance vasodilation as well as venous and lymphatic drainage.
III. Heat can be used after joint surgery to increase the extensibility of collagenous tissues and help regain joint range of motion.

Application Recommendations

I. Heat is usually applied during the second or third week after surgery or trauma.
II. Periincisional heat may be applied QID for 10 minutes.
III. When using heated water, care must be taken to avoid excessive temperatures (>42.2° C [108° F]).
IV. To avoid burns, do not use heat that is uncomfortable when placed on a human forearm.

Cautions and Contraindications

I. Superficial (or deeper) burns are easy to create with overaggressive use of heat.
II. Hot packs must be checked for leaks or thermal hot spots to avoid burning the animal, especially if heat is used while the animal is anesthetized, sedated, or has diminished nociception.
III. Avoid heat in the early phases of inflammation, because it may exacerbate edema and increase periincisional pain.
IV. Contraindications include use of heat on limbs or body parts with decreased sensation, during the first postoperative week, and when the animal does not tolerate the heat.

Cryotherapy

Definition

I. Cryotherapy is the application of cooling agents to regional areas of the body.
II. Cooling of tissues can be achieved by the local use of ice or ice packs, certain types of cryogens, or circulation of a coolant agent in a blanket or booty placed on the extremity.

Effects

I. Decreases blood flow via vasoconstriction
II. Decreases nerve conduction velocity of nociception fibers and can provide analgesia
III. Decreases pain and inflammation

IV. Increases tissue viscosity and stiffness
V. Effects mediated through decreased metabolism and local vasoconstriction

Indications

I. It may be used within the first 10 to 14 days of an injury or surgery to combat acute inflammation.
   A. Periincisional cooling for 7 to 10 days after surgery
   B. Regional cooling after joint manipulation
   C. Regional application over tendons and ligaments during physical therapy and rehabilitation
II. It can be used in emergency care for burns (see Chapter 134).
III. Cryotherapy provides postoperative analgesia and is used to reduce pain after joint mobilization procedures.

Application Recommendations

I. Ice packs are applied to periincisional tissues for 10 minutes QID for the first postoperative week.
II. A neoprene booty that cools via a refrigerant pumped through a network of tubes can reduce the need for postoperative analgesia after stifle surgery.

Cautions and Contraindications

I. Avoid excessive cryotherapy in regions of decreased sensation
II. Limit duration of cryotherapy to 20 minutes; thermal washout and reflex vasodilation will rewarm peripheral tissue within 20 minutes.

Passive Range-of-Motion Exercise

Definition

I. Exercise is often the mainstay of physical therapy.
   A. Exercise may involve active or passive activities.
   B. In most instances, the application of active "open-chain" activities, such as cycling, to animals is difficult, so most active therapeutic exercise involves "closed-chain" activities.
   C. Closed-chain activities usually revolve around normal canine activities such as sitting, standing, walking, trotting, or swimming.
II. Passive range of motion is an exercise activity that passively moves a joint through its normal arc of motion.
   A. In many acute or chronic problems, the range of motion is limited.
   B. After surgery of the extremities, passive range-of-motion exercises are a vital part of the immediate postoperative care.
   C. Such exercises are performed without active muscle contractions and are done to the limit of the animal's tolerance for motion.

Effects

I. Helps reduce loss of range of motion after extremity surgery
II. Helps mobilize tissue edema
III. Stretches ligaments, tendons, and joint capsules at the beginning and end of the available range of motion
IV. Decreases postoperative pain

Indications

I. Dogs recovering from CCL surgery receive 10 to 15 minutes of passive range-of-motion exercises three to four times daily.
II. Dogs recovering from cubital joint arthroscopy for fragmented coronoid removal receive passive range-of-motion exercises 10 to 15 minutes four to six times daily.
III. Early attention to passive range of motion minimizes the risk of joint contracture.

Application Recommendations

I. Passive range-of-motion exercises are done for 10 minutes QID, beginning the first day after joint or extremity surgery.
II. The affected limb is gently grasped while the dog is in a comfortable position.
   A. The joint is either flexed or extended, unless the joint is resistant or painful.
   B. The extremity is held in this position for 30 seconds and then moved in the opposite direction.
   C. At no time are vigorous manipulations done that create pain or discomfort for the dog.

Cautions and Contraindications

I. Passive range-of-motion exercises are contraindicated after unstable fixation of fractures, immediately after total joint replacement surgery, and after certain skin-grafting procedures.
II. Avoid overzealous motion after total elbow replacement, extensive skin-grafting procedures, or when extensive tension-relieving sutures are used for wound closure.

Therapeutic Exercise

Definition

I. Therapeutic exercise is active, participatory exercise done to improve muscle health and redevelopment, extend the range of motion of joints, and improve tissue atrophy.
II. The method and application of therapeutic exercise is customized based on the animal's needs and the resources of the hospital and staff members.
III. Treadmill walking involves the use of conventional treadmills for rehabilitation and physical therapy.
IV. Aquatic therapy involves the use of water as a medium for physical therapy.
   A. Its physical nature provides buoyancy of the animal's body, resistance to movement, and compression to body soft tissues.
   B. These properties can be exploited to provide earlier therapeutic exercise.
   C. Its resistance and viscosity provide resistance to motion and can be used to stimulate muscle contractions.

Effects

I. Treadmills are useful for patterning gait and to encourage early, postoperative weight bearing.
   A. The movement of the belt encourages the dog to walk.
   B. Activity may be awkward at first, but most dogs quickly acclimatize to its motion.

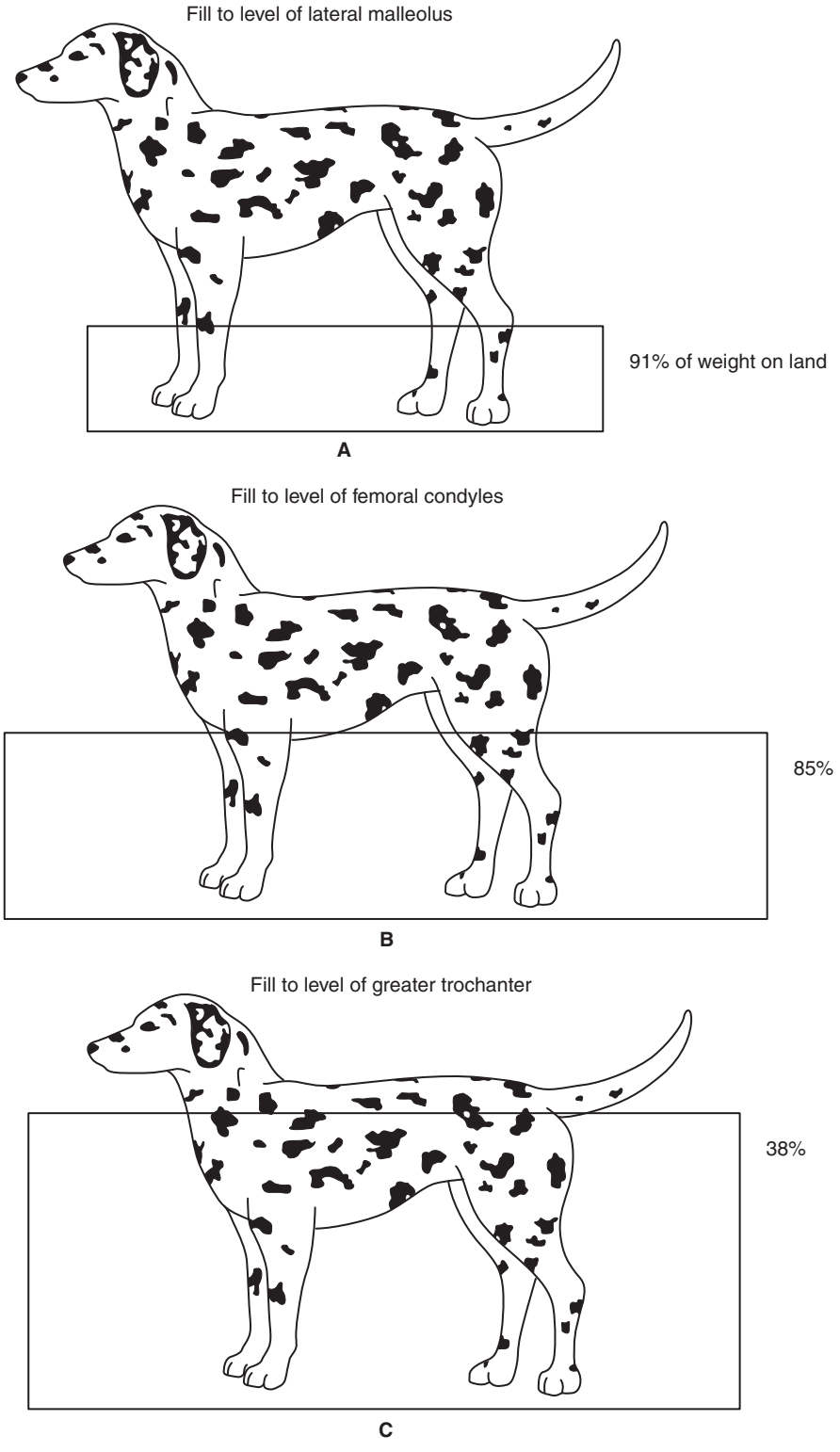

FIGURE 83-1 Dogs in water to the level of the lateral malleolus (**A**), lateral epicondyle (**B**), and greater trochanter (**C**), illustrating the amount (percent) of weight displacement that occurs with different levels of water. *Reprinted with permission from Taylor RA: Aquatic therapy. p. 265. In Millis DL, Levine D, Taylor RA (eds): Canine Rehabilitation and Physical Therapy. Elsevier Saunders, St. Louis, 2004.*

II. Aquatic therapy involves the use of water as a medium for physical therapy.
   A. Its physical nature provides buoyancy of the animal's body, resistance to movement, and compression to body soft tissues (Figure 83-1).
   B. These properties can be exploited to provide earlier therapeutic exercise.
   C. Water provides resistance to motion and can be used to stimulate muscle contractions.

Indications

I. Indications for treadmill exercise
   A. Treadmill exercise is used to restore muscle mass and full range of motion after most types of orthopedic procedures.
   B. It can be more effective than leash walking because the grade and speed of the treadmill can be adjusted to the animal.
   C. Specific indications include the following:
      1. Extremity surgery: cruciate surgery, total joint replacement
      2. Neurological and orthopedic surgery: intervertebral disc disease
      3. Fitness and agility training
      4. To provide strengthening in certain types of neuromuscular or orthopedic diseases

II. Indications for aquatic exercise
   A. Aquatic therapy increases strength and endurance, improves range of motion of joints, enhances the well-being of the animal, improves agility, and can reduce pain.
   B. Using the natural buoyancy of water allows for earlier weight bearing after trauma or surgery.
   C. Specific indications include the following:
      1. Certain orthopedic conditions: fracture repair, repair of CCL rupture, total hip replacement, treatment of tendonitis
      2. Certain neurological conditions: fibrocartilaginous emboli, intervertebral disc disease, polymyopathy, polyneuropathy, after repair of vertebral fractures or luxation

Application Recommendations

I. Beginning 3 to 6 weeks after CCL stabilization, level-grade treadmill walking is started at a speed of 1.5 miles per hour for 15 minutes and is gradually increased over the next 4 to 6 weeks.
II. Free swimming may be started after shoulder surgery for osteochondrosis.
III. Underwater treadmill therapy is useful after total hip replacement and CCL stabilization surgery.

Cautions and Contraindications

I. Treadmill exercise: unstable extremity fractures, fractious or unruly animals
II. Aquatic exercise: fear of water, open wounds, presence of external fixators, concurrent cardiovascular diseases, unstable diabetes mellitus

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CHAPTER 84

Introduction

Rosanna Marsella

ORGANIZATION

I. This section is designed with a problem-based approach in mind.
II. The most common primary lesions, clinical presentations, and pertinent differential diagnoses are discussed.
III. When overlap exists between clinical disorders (i.e., the same disease may have multiple types of lesions), the reader is referred to another chapter for additional information.

HISTORY

I. Many lesions in dermatology are nonspecific (e.g., alopecia secondary to pruritus, scaling), so a through history is necessary to appropriately rank differential diagnoses.
II. It is important to note the age of onset and whether the disease has changed over time.
   A. Sudden-onset pruritus in a geriatric animal raises the concern for diseases other than allergies (e.g., cutaneous lymphoma), because allergies are more likely to develop in younger animals.
   B. Sudden-onset, intense pruritus in a very young animal raises the suspicion of diseases such as scabies, food allergy, and flea allergy, because they can affect animals at a very young age.
III. Seasonality of the condition also helps to rule in or rule out diseases.
   A. Animals that are pruritic only on a seasonal basis are more likely to suffer from flea allergic dermatitis or atopic dermatitis secondary to pollens.
   B. Contact allergy from plants that are only present on a seasonal basis is also possible.
IV. It is important to record whether pruritic diseases started with pruritus alone or whether lesions were present before the onset of the pruritus.
V. As the disease progresses, skin lesions commonly change; therefore it is important to know what lesions were present at the beginning of the disease.

DERMATOLOGIC EXAMINATION

I. It is important to examine all areas of the skin including ears, footpads, nails, and mucocutaneous junctions.
II. Attention is focused on the presence and type of primary lesions; often they provide a clue to the underlying disease.
   A. A macule is a circumscribed flat area of color change, and most are either erythematous or hyperpigmented.
   B. A papule is a small elevation of the skin ≤1 cm in diameter.
   C. Plaque is formed when multiple papules coalesce together.
   D. A pustule is a small elevation of the skin that contains purulent material.
   E. A nodule is a small solid elevation of the skin >1 cm that extends in to the deeper layers of the skin.
   F. A vesicle is an elevation of the epidermis that is filled with clear fluid.
   G. A bulla is a vesicle that is >1 cm in diameter.
   H. Secondary lesions evolve from primary lesions; in more chronic cases they may be the only lesions detectable.
   I. Epidermal collarettes are the remnants of pustules and present as a circular rim of scaling.
   J. Crusts are formed when exudate, serum, and/or blood become dried.
   K. Ulcers and erosions develop after the rupture of bullae and vesicles.
   L. Comedones result from plugging of hair follicles with keratin.
   M. Alopecia is often secondary to self-inflicted trauma.

N. Hyperpigmentation is frequently secondary to inflammation and indicates that the acute phase of the inflammatory process has resolved.

III. Distribution of lesions is also important when ranking differential diagnoses.
   A. Patchy hair loss on the trunk is more suggestive of types of folliculitis, such as superficial pyoderma, whereas patchy hair loss on the head and extremities is more suggestive of dermatophytosis and demodicosis.
   B. Pustular eruption primarily affecting the face (periocular region, pinnae, bridge of the nose) is highly suggestive of autoimmune diseases such as pemphigus foliaceous, whereas the same eruption affecting the ventral abdomen is more suggestive of a superficial pyoderma.

IV. Most dogs with skin problems develop secondary infections that may mask the underlying disease.
   A. In many cases the secondary infection must be addressed before the underlying disease can be diagnosed because infections may alter the clinical presentation and changes seen on histopathology.
   B. Once all the lesions have been recorded make a list of differential diagnoses, ranking them accordingly to the index of suspicion.
   C. Proceed with diagnostic tests.
   D. A minimum data base for an animal with skin problems includes a deep skin scraping to rule out demodicosis, cytological examination to investigate the presence of secondary infections and the types of inflammatory cells present, and a dermatophyte culture to rule out dermatophytosis.

CHAPTER 85

Pruritic Skin Diseases

Lisa Akucewich | Nicola Williamson

IMMUNE-MEDIATED DISORDERS

Flea Allergic Dermatitis

Definition and Causes

I. Pruritic, papular dermatitis arising from sensitization to the allergens produced by fleas (Scott et al., 2001c)
II. Follows exposure to fleas
III. No breed or sex predilection
IV. Age of onset: 6 months to 5 years
V. Most often seasonal, but nonseasonal in subtropical or tropical areas

Pathophysiology

I. Flea saliva and whole flea extract contain antigenic substances, including polypeptides, amino acids, aromatic compounds, and fluorescent materials (Scott et al., 2001c).
II. Flea allergic dermatitis arises from an adverse immunological response to the flea saliva (Moriello and Mason, 1995b).
III. It may be both an immediate and a late-phase Type I immunoglobulin (Ig) E mediated hypersensitivity response to flea saliva (Wilkerson et al., 2004).
IV. Type IV hypersensitivity has also been suggested.

Clinical Signs

I. Moderate to severe pruritus
II. Papules, erythema, self-inflicted trauma
III. Most common lesion locations in dogs: tail head, caudal thighs, antebrachial area of forelimbs
IV. Hair loss, excoriation, hyperpigmentation, scaling
V. Signs specific to cats
   A. Head and neck pruritus
   B. Eosinophilic granulomas complex
   C. Miliary dermatitis (Scott et al., 2001c)
VI. Flea feces and fleas: often not evident in cats because of excessive grooming behavior

Diagnosis

I. Suggestive history and physical examination findings, especially lesion distribution
II. Response to flea control
III. Intradermal skin testing with flea extract: false negatives common (Scott et al., 2001c)
IV. Presence of fleas and flea dirt, especially with use of flea comb

Differential Diagnosis

I. Other hypersensitivity reactions: adverse food reactions, atopic dermatitis
II. Drug reactions
III. Infectious diseases: *Malassezia* spp. dermatitis, bacterial folliculitis, dermatophytosis
IV. Parasitic disorders: demodicosis, scabies, cheyletiellosis, pediculosis

Treatment

I. Environmental flea control involves the following:
   A. Adulticides: synthetic pyrethrins (permethrin)
      1. Short-acting, with quick knockdown effect
      2. Toxic to cats in concentrations >0.5%
      3. Can be used indoors and outdoors
      4. Example: indoor room and area foggers
   B. Juvenile hormone analogue (ovicidal and larvicidal)
      1. Methoprene: insect growth regulator
         a. Sensitive to ultraviolet (UV) light, so used only indoors
         b. Example: *Precor 2000 Plus Premise Spray*
      2. Pyripoxyfen: insect growth regulator
         a. UV-light resistant
         b. Used indoors and outdoors
         c. Average duration of efficacy: 4 months
         d. Example: Virbac *Knockout Room* and *Area Fogger*
      3. Fenoxycarb
         a. Stable indoors for up to 40 weeks
         b. Used indoors and outdoors
         c. UV-light resistant
         d. Examples: *Insegan, Logic, Torus, Varikill*
   C. Miscellaneous ovicidal and larvicidal treatments
      1. *Steinernema carpocapsae* nematodes
         a. Biopesticides for outdoor flea control
         b. Flea larvae and pupae killed in grass and soil
         c. Replacement needed every few weeks; do not reproduce or move
         d. Need continuous moisture and shade
         e. Example: *Interrupt* (Veterinary Product Laboratories, Phoenix, Ariz.)

2. Sodium borate
   a. Nontoxic and applied to carpets
   b. Ovicidal and larvicidal by dehydration
   c. Professionally applied product guaranteed for up to 1 year

II. Numerous agents are available for individual flea control.
   A. Adulticides
      1. Fipronil
         a. Applied every 2 to 3 weeks, waiting 24 to 48 hours after bathing or swimming
         b. Examples: *Frontline Plus* (fipronil and methoprene), *Frontline Spray*
      2. Imidacloprid
         a. Applied every 2 to 3 weeks, waiting 24 to 48 hours after bathing or swimming
         b. Examples: Advantage, Advantix (imidacloprid and permethrin)
      3. Permethrin
         a. Applied every 2 to 3 weeks, waiting 24 to 48 hours after bathing
         b. Contains 45% to 60% permethrin
         c. Contraindicated in cats (high permethrin concentration)
         d. Cat and dog contact avoided until product completely dry
         e. Examples: *Bio-spot, Advantix*
      4. Selamectin
         a. Semisynthetic avermectin applied to skin for control of fleas, heartworm, ticks, certain intestinal and surface parasites
         b. Example: *Revolution*
      5. Permethrin 2%: adulticide, repellant
         a. Applied one to two times weekly, applied to a dry hair coat
         b. Used alone or in combination with spot-on treatments
         c. Used cautiously on dogs if cats in same household
         d. Contraindicated in cats (high permethrin concentration)
         e. Example: Virbac *Knockout Pet Spray*
      6. Neonicotinoid insecticides
         a. Act at the nicotinic acetylcholine receptor
         b. Rapidly acting, eliminated after oral administration
         c. Efficacy for 24 to 48 hours
         d. Example: *Capstar*
   B. Insect growth inhibitor: lufenuron
      1. Given monthly
      2. Several months are needed to obtain full benefit
      3. Examples: *Program, Sentinel*

III. Corticosteroids are recommended for short-term use only, in the absence of secondary infections.
   A. Prednisone 1 mg/kg PO SID for 5 days, then reduced to 0.5 mg/kg QOD
   B. Combination of prednisolone 2 mg and trimeprazine 5 mg *(Temaril-P)* (Plumb, 1999)
      1. Capsules given PO SID, and tablets given PO BID.
         a. Dog <5 kg: 1 capsule or 0.5 tablet
         b. Dog ≥5 to 10 kg: 2 capsules or 1 tablet
         c. Dog ≥10 to 20 kg: 4 capsules or 2 tablets
         d. Dog ≥20 kg: 6 capsules or 3 tablets
      2. After 4 days, dose reduced by 50% and adjusted as necessary.

IV. Topical glucocorticoids may be helpful.
   A. Triamcinolone 0.0125% *(Genesis Spray)* is applied SID for 7 days, then QOD and eventually discontinued.
   B. Hydrocortisone 1% *(ResiCORT Conditioner)* is applied one to two times weekly after bathing and not rinsed.
   C. Potential side effects with long-term use include cutaneous atrophy, comedones, demodicosis, calcinosis cutis (Hengge et al., 2006).

V. Weekly lime sulfur dips (4 oz lime dip/gal water) may decrease the pruritus.

VI. Secondary bacterial (see Chapter 86) and *Malassezia* spp. infections are treated accordingly (see Malassezia Dermatitis).

Monitoring of Animal

I. Environmental and individual flea treatments help control the disease, but it cannot be cured.

II. Prognosis is good to excellent with appropriate flea control.

Atopic Dermatitis

Definition and Causes

I. Atopy is a genetically inherited, recurrent, pruritic skin disease that is associated most commonly with IgE antibodies to environmental allergens.

II. Average age of onset is 1 to 3 years (Scott et al., 2001c).

III. Predisposed breeds include the boxer, Chihuahua, Gordon setter, Yorkshire terrier, Cairn terrier, Boston terrier, Chinese shar-pei, Labrador retriever, golden retriever, West Highland white terrier, English setter, Irish setter, English bulldog, American cocker spaniel, pug, Dalmatian, Scottish terrier, Wirehaired fox terrier, miniature schnauzer, Belgian tervuren, Shiba Inu, and Beauceron.

IV. No sex predilection exists.

V. No breed or sex predilection has been demonstrated in cats.

Pathophysiology

I. Type I hypersensitivity develops against environmental allergens.

II. Genetically predisposed dogs percutaneously absorb, inhale, or possibly ingest various allergens that provoke allergen-specific IgE or IgG production (Olivry and Hill, 2001).

Clinical Signs

I. Mild to severe pruritus of ears, face, axilla, feet, ventrum of body

II. Pruritus often generalized

III. Otitis externa common

IV. Secondary pyoderma and *Malassezia* spp. dermatitis common

V. Seasonal to perennial

Diagnosis

I. Diagnosis is often based on history, clinical signs, and the exclusion of other pruritic skin diseases.
II. Positive results on allergy testing are considered supportive.
III. Intradermal skin testing is the preferred method for diagnosis (Scott et al., 2001c), but certain medications must be withdrawn or they interfere with the test.
  A. Antihistamines: 10 to 14 days
  B. Oral and topical steroids: 30 to 45 days
  C. Injectable steroids: 60 days
  D. Oral fatty acids: 10 to 14 days
IV. Serum-based allergy tests have both false-positive and false-negative results.
  A. They are used when intradermal testing is unavailable, in animals in which withdrawal of medications cannot be done, and when sedation is risky.
  B. They are often performed in conjunction with intradermal testing.

Differential Diagnosis

I. Other allergic dermatoses: adverse food reactions, flea allergic dermatitis, contact allergy
II. Parasitic diseases: demodicosis, scabies
III. Infectious diseases: *Malassezia* spp. dermatitis, bacterial folliculitis, dermatophytosis
IV. Drug eruption

Treatment

I. Allergen-specific immunotherapy is preferred.
  A. Mechanism of hyposensitization is complex, several proposed hypotheses.
    1. Humoral desensitization: reduces levels of IgE
    2. Cellular desensitization: reduces reactivity of mast cells and basophils
    3. Immunization: induction of blocking antibody
    4. Generation of allergen-specific suppressor cells
  B. Allergen-specific vaccines are made based on results of the allergy test.
  C. Immunotherapy reduces pruritus, as well as skin and ear infections by 60% to 80%.
  D. It may take up to 1 year to see beneficial results.
II. Antihistamines can be used long term (Scott et al., 2001b).
  A. Diphenhydramine 2.2 mg/kg PO TID (dog)
  B. Chloropheniramine 0.4 mg/kg PO TID (dog) and 2 mg PO BID (cat)
  C. Hydroxyzine 2.2 mg/kg PO TID (dog) and 10 mg PO BID to TID (cat)
  D. Clemastine 0.05 to 0.1 mg/kg PO BID (dog) and 0.67 mg PO BID (cat)
III. Omega-3 fatty acids (docosahexanoic acid 240 mg and eicosapentaenoic acid 360 mg) are given at 1 capsule per 10 kg PO SID in both dogs and cats.
  A. Inhibition of arachidonic acid metabolism and generation of antiinflammatory mediators reduce pruritus.
  B. They are used in conjunction with other therapies.
IV. Antiinflammatory doses of prednisone (0.5 to 0.1 mg/kg PO QOD) are recommended for short-term therapy only, because of the potential cutaneous and systemic side effects.
V. Cyclosporine may control clinical signs in dogs at 5 mg/kg PO SID.
  A. Full effect may not be seen for 4 to 6 weeks.
  B. Pruritus can be controlled at QOD dosing in some dogs.
  C. Side effects include vomiting, diarrhea, gingival hyperplasia, papillomatosis, hirsutism, bacteriuria, nephropathy, bacterial skin infections, involuntary shaking, bone marrow suppression, and lymphoplasmacytoid dermatosis.
VI. Topical therapy for pruritus may also be tried.
  A. Triamcinolone 0.0125%
  B. Hydrocortisone conditioner 1%
  C. Lime sulfur dip
  D. Routine bathing to remove allergens every 7 days
VII. Secondary bacterial and *Malassezia* spp. infections are treated accordingly.
VIII. Individual and environmental flea control is instituted because 80% of atopic dogs also have flea allergic dermatitis (Scott et al., 2001c).

Monitoring of Animal

I. Atopy is a life-long disease and requires long-term management.
II. Control of secondary infections and exposure to fleas is important.
III. Recheck examinations are warranted to minimize flare-ups.

Contact Dermatitis

Definition and Causes

I. Contact dermatitis is an intensely pruritic, macular, papular dermatitis that usually affects sparsely haired skin after exposure to certain allergens.
II. Allergens include shampoos, soaps, topical medications (especially those containing antibiotics), insecticides, carpet, disinfects, and ants (Moriello and Mason, 1995).
III. In the southeastern United States (e.g., Florida), an allergic-contact dermatitis to plants of the Commelinaceae family is common in dogs (Marsella et al., 1996).
IV. No known sex or breed predilection exists.
V. Clinical signs generally occur in animals >6 months of age.
VI. Dogs are affected more often than cats.

Pathophysiology

I. Type IV hypersensitivity reaction is directed against small allergens (haptens) that are in contact with the skin (Marsella et al., 1996).
II. It involves two phases.
  A. Sensitization phase: initial exposure to the substance, without the development of an allergic reaction
  B. Elicitation phase: reexposure of sensitized the animal to the offending substance resulting in dermatitis

Clinical Signs

I. Intense pruritus occurs in areas of contact, especially the ventrum, face, pinnae, and feet (sparsely haired or bare areas).
II. Erythema and papular dermatitis of the ventrum, face, pinnae, and feet may also be noted.

Diagnosis

I. History and physical examination findings may be suggestive.
II. Clinical signs resolve if animal is confined away from the allergen.
III. Reexposure to the allergen leads to recurrence within 48 hours.
IV. Patch testing may be considered (Moriello and Mason, 1995b).
  A. Suspected allergens are applied directly to the skin.
  B. Test substance is suspended in petroleum jelly, applied to shaved skin, and covered with a bandage for 48 to 72 hours.
  C. Test sites are evaluated for erythema, induration, and vesication.
V. Obtain a biopsy of the lesion and submit it for dermatohistopathologic analysis.

Differential Diagnosis

I. Allergic dermatoses: adverse food reactions, flea allergic dermatitis
II. Parasitic diseases: demodicosis, scabies
III. Infectious diseases: *Malassezia* spp. dermatitis, bacterial folliculitis, dermatophytosis
IV. Systemic drug eruption

Treatment

I. Remove allergen from the environment and prevent access of affected animal to identified substances.
  A. Kennel or confine the animal to an uncarpeted room if carpet is suspected.
  B. Walk dogs only on dirt surfaces or paved roads if a contact allergy to *Commelinaceae* spp. is suggested.
II. Consider administering pentoxifylline at 15 to 20 mg/kg PO TID (Marsella et al., 1996).
  A. It is a methylxanthine derivative with immunomodulatory and rheologic effects.
  B. Side effects include gastrointestinal and central nervous system (dose related) signs.
III. Antiinflammatory doses of prednisone (0.5 to 0.1 mg/kg PO QOD) are recommended for short-term relief.
IV. Topical corticosteroid products (see previous discussion under Atopic Dermatitis) may be applied to affected areas.

Monitoring of Animal

I. Recheck animal in 10 to 14 days to evaluate resolution of lesions.
II. Avoid contact with offending allergen.
III. If exposure to allergen is difficult to avoid, continue regular bathing, topical corticosteroids for pruritus, and pentoxifylline 15 to 20 mg/kg PO BID to TID.
IV. Prognosis is excellent if the offending allergen can be avoided.

Adverse Food Reactions

Definition

I. Adverse food reaction (e.g., food allergy, food intolerance) is a nonseasonal, pruritic skin disorder of dogs and cats associated with ingestion of a substance found in the animal's diet (Rosser, 1993).
II. It can manifest as recurring, superficial bacterial infections and/or otitis externa and otitis media (Moriello and Mason, 1995a).
III. See also Chapter 122.

Causes and Pathophysiology

I. Beef, fish, chicken, eggs, and dairy products are the allergens to which dogs and cats most commonly develop adverse reactions.
II. No breed or sex predilection exists.
III. Reactions can occur at any age.
IV. Pathophysiology is unknown.

Clinical Signs

I. No pruritus to intense pruritus: nonseasonal
II. Macules, papules, pustules leading to alopecia, excoriation, scale, and crusts
III. Recurrent ear and skin infections: bacterial, yeast
IV. Gastrointestinal signs (10% to 15%): vomiting, diarrhea, increased frequency of bowel movements (Scott et al., 2001c)

Diagnosis

I. Perform a food trial by feeding a restricted, novel protein diet to which the animal has not been previously exposed (Rosser, 1993).
  A. Nutritionally balanced home-cooked diets are preferred for their lack of preservatives.
  B. Sources of proteins used include venison, rabbit, goat, beans, ostrich, and alligator.
  C. Many diets also contain white potato (see Chapter 122).
  D. Treat all secondary skin infections appropriately.
  E. Average length of food trial is 8 to 10 weeks.
  F. If infections (superficial pyoderma) recur, the diet trial time may require modification.
  G. For example, a 3-week relapse rate of superficial pyoderma may warrant antibacterials and extending the diet trial by approximately 5 weeks.
  H. Potato treats may be given.
II. Eliminate all other treats, including rawhide chew treats.
III. Heartworm prevention is changed from flavored tablets to unflavored tablets or topical selamectin.
IV. Clinical improvement is suggestive of the diagnosis; however, provocative challenge with the original diet is necessary to confirm the diagnosis (Rosser, 1993).

Differential Diagnosis

I. Allergic dermatoses: atopic dermatitis, flea allergic dermatitis, contact allergy
II. Parasitic diseases: demodicosis, scabies
III. Infectious diseases: *Malassezia* spp. dermatitis, bacterial folliculitis, dermatophytosis
IV. Drug eruption

Treatment and Monitoring

I. Avoid the offending food allergen or preservative.
II. Development of new food allergies is rare, but possible.
III. Outcome and prognosis are excellent if the offending allergen is identified and avoided.

INFECTIOUS DISORDERS

Acute Moist Dermatitis

Definition and Causes

I. Local irritation from a primary problem leads to self-trauma, which initiates an itch-scratch cycle (Moriello and Mason, 1995b).
II. No sex or age predilection exists.
III. It is common in animals with flea allergic dermatitis, otitis externa, and otitis media.
IV. Other underlying problems include other ectoparasites, atopic dermatitis, adverse food reactions, contact dermatitis, anal sac disease, and periocular diseases.
V. It is more common in hot and humid weather.
VI. Predisposed animals tend to have a dense undercoat, such as the golden retriever, Labrador retriever, German shepherd dog, and Saint Bernard (Scott et al., 2001a).

Clinical Signs

I. Highly pruritic to painful erosions of the skin surface develop rapidly and are associated with alopecia, exudation, and erythema.
II. Lesions typically affect the tail base area, lateral aspects of hind legs, trunk, neck, and face.
III. Lesions are often solitary, although multiple lesions can occur.
IV. Site affected may be related to the underlying cause.
   A. Lesions associated with flea allergic dermatitis often affect the dorsal rump and base of the tail area.
   B. Lesions associated with otitis externa occur on the neck and head.

Diagnosis

I. Diagnosis is based on history of acute onset and presence of a solitary intensely pruritic lesion.
II. Based on distribution of the lesion, look for the suggested cause.

Differential Diagnosis

I. Superficial pyoderma (bacterial folliculitis)
II. Dermatophytosis
III. Demodicosis

Treatment

I. Identify and treat the underlying cause.
II. Clip the area well, and remove all surface debris by gentle cleansing with dilute antimicrobial solutions (e.g. chlorhexidine, povidone-iodine).
III. Shampoo the area with topical benzoyl peroxide, which is left on for 10 to 15 minutes and then rinsed off; repeat the process two to three times weekly until lesions are resolved.
IV. Topical astringents (aluminum acetate 2% [*Domeboro* solution]) may be helpful.
V. Systemic glucocorticoids are used (see Atopic Dermatitis) to break the itch cycle.
VI. If evidence of folliculitis is noted at the periphery of the hot spot (papules), then systemic antibiotics are indicated for at least 3 weeks.
VII. Further trauma can be prevented by an Elizabethan collar.

Monitoring of Animal

I. Address predisposing factors to eliminate or modify self-trauma (e.g., flea allergic dermatitis, otitis externa).
II. Some dogs may have repeated episodes.
III. Pay attention to regular grooming, hygiene, flea control, and/or ear cleaning, especially during hot and humid weather conditions.
IV. If systemic antibiotic therapy is instituted, recheck the animal in 3 weeks.

Superficial Bacterial Folliculitis (Pyoderma)

See Chapters 86 and 88.

Bacterial Furunculosis

See Chapter 88.

Malassezia spp. Dermatitis

Definition

I. *Malassezia pachydermatis* is a commensal yeast that may overcolonize the skin of dogs.
II. Predisposition is reported in the basset hound, West Highland white terrier, dachshund, American cocker spaniel, English springer spaniel, and German shepherd dog, possibly because they have significantly more yeast on their skin (Matuosek and Campbell, 2002).

Causes

I. Antibiotic therapy may be a predisposing factor.
II. Other predisposing causes in dogs include the following (Matuosek and Campbell, 2002):
   A. Diseases of keratinization: primary seborrhea
   B. Immunosuppression: secretory IgA defects
   C. Endocrine diseases: hypothyroidism (especially Labrador retrievers), hyperadrenocorticism
   D. Possibly atopic dermatitis: role controversial
III. Generalized *Malassezia* spp. dermatitis in cats is usually associated with a systemic disease (e.g., metabolic disease, neoplasia) and is considered a serious finding.

IV. It is more common in the spring and summer, as well as in any months with high humidity.

Pathophysiology

I. For a commensal organism to become a primary pathogen, it must acquire virulence sufficient to overcome normal host defenses.
II. *Malassezia pachydermatis* has a symbiotic relation with commensal *Staphylococcus* spp.
   A. Both agents produce mutually beneficial growth factors.
   B. Growth of *Malassezia* spp. in vitro is enhanced by the presence of staphylococci.
   C. Inhibition of either agent does not inhibit the growth of the other.

Clinical Signs

I. Pruritus is a major and consistent sign.
II. Cats may have a waxy otitis, chin acne, or a generalized scaling dermatosis.
III. In dogs, dermatitis can be localized (external otitis, perianal, muzzle, periocular areas, feet) or generalized.
IV. Face rubbing, head shaking, foot licking, chewing, and scooting may occur.
V. Primary lesions (papules, pustules) are not usually seen unless a superficial folliculitis is also present.
VI. Erythema, lichenification, hyperpigmentation, alopecia, scaliness, and greasiness of the skin are common.
VII. A strong rancid odor (seborrhea-like odor) can occur, especially in dogs.
VIII. Folliculitis, furunculosis, and follicular sebaceous cysts (interdigital cysts) may also develop.

Diagnosis

I. Cytology is the most useful tool.
II. Acetate tape preparation cytology, swabs, or superficial skin scrapings are used to collect surface material.
   A. A glossy finish tape is recommended.
   B. After surface material is collected, the tape is stained with Diff-Quik.
   C. Tape is applied to a clean glass slide and examined under oil emersion.
   D. Yeast organisms stain purple and may appear oval, round, or peanut shaped.
III. Fungal culture on Sabouraud's agar may be used to diagnose *Malassezia* spp. but is not often necessary.
IV. Biopsy is not a reliable way to diagnose the disease.
   A. Yeast are evident only when present in large numbers and are easily lost with formalin fixation of the sample.
   B. Histopathological findings are characterized by the following:
      1. Superficial perivascular to interstitial dermatitis with irregular hyperplasia, diffuse spongiosis, and lymphocytic exocytosis of the epidermis and follicular infundibulum are typical.
      2. Parakeratosis is prominent.
      3. Lymphocytes, histiocytes, and plasma cells are the dominate dermal inflammatory cells.
      4. Yeast may be visualized in surface and/or infundibular keratin.

Differential Diagnosis

I. Allergic skin diseases: atopic dermatitis, food allergy, flea allergy, contact allergy
II. Drug eruption
III. Infectious diseases: superficial pyoderma, dermatophytosis
IV. Parasitic diseases: demodicosis, scabies
V. Neoplasia: mycosis fungoides

Treatment

I. Topical therapy
   A. Selenium sulfide 1% *(Selsun Blue)* is a keratolytic, antiseborrheic, degreasing agent (Scott et al., 2001b).
      1. It is recommended if the skin is greasy, waxy and scaly.
      2. It may be irritating in some animals and should not be used in cats.
      3. The frequency of use is dependent on severity of the condition (1 to 2 times weekly until resolution).
   B. Ketoconazole shampoo *(Nizoral, KetoChlor)* is effective in killing *Malassezia* spp.
      1. It is excellent for mild to moderate seborrhea oleosa.
      2. Use one to two times weekly until resolution.
      3. Ketoconazole shampoo is available over-the-counter.
   C. Chlorhexidine shampoo (3% to 4%) may be effective.
      1. Formulations can be drying and/or irritating.
      2. Chlorhexidine 2% in combination with miconazole 1% shampoo *(Malaseb)* is used one to two times weekly for yeast and bacteria.
   D. Enilconazole 0.2% rinse is also very effective (but not licensed for use in animals in the United States).
   E. Miconazole 1% *(Miconazole, ResiZOLE)* shampoo and conditioner may be applied one to two times weekly, depending on the severity of the condition.
   F. Vinegar-and-water (1:5 or 1:10) rinses are inexpensive and effective long-term treatments that help prevent relapses in some dogs (e.g., swimmers).
   G. Lime sulfur dip 2% can be used to relieve the itching and has mild antiyeast properties.
      1. The dip can be very drying to skin and hair coat.
      2. Use one to two times weekly.
II. Systemic therapy
   A. Ketoconazole 5 mg/kg PO BID is helpful in dogs.
      1. Side effects are nausea, vomiting, anorexia, and hepatotoxicity.
      2. It is avoided in cats because of nausea, vomiting, and anorexia.
      3. It is teratogenic in pregnant animals.
      4. Lightening of the hair coat may occur after 3 to 4 months of use but resolves after discontinuation.
   B. Itraconazole 5 mg/kg PO SID may be as effective but is more expensive.
      1. Side effects are nausea, vomiting, anorexia, and hepatotoxicity (lesser degree).

2. Vasculitis has been reported in doses at 10 mg/kg daily.

C. Fluconazole 2.5 mg/kg PO SID is used when concerns exist regarding liver toxicity.
1. Side effects are nausea, vomiting, abdominal discomfort, anorexia, and hepatotoxicity (lesser degree).
2. It does not suppress the adrenal corticotropic hormone axis.

D. Terbinafine 15 to 30 mg/kg PO SID may be considered.
1. Side effects are nausea, vomiting, abdominal discomfort, anorexia, and hepatotoxicity.
2. Neutropenia and pancytopenia have also been reported.

PARASITIC DISORDERS

Cheyletiellosis

Definition

I. It is an infection with a surface dwelling mite that results in variable pruritus.
II. It is also known as *walking dandruff*.

Causes

I. *Cheyletiella yasguri* is the species that affects dogs.
II. *Cheyletiella blakei* is the species that affects cats.

Pathophysiology

I. *Cheyletiella* spp. are obligate parasites.
II. Their 21-day life cycle is completed entirely on the host.
III. Ova are attached to hairs by fibrillar strands.
IV. Mites live in the keratin layer and create pseudotunnels in the epidermal debris.
V. Mites periodically attach to the epidermis and engorge themselves on fluid from the skin.

Clinical Signs

I. Highly contagious between dogs, cats, and humans.
II. Nonpruritic scale on the dorsum can progress to widespread scale and alopecia.
III. Pruritus may become severe.
IV. Cats may develop erythroderma and papular crusty eruptions.
V. Some cats only appear to overgroom the dorsum and have mild or no skin lesions.

Diagnosis

I. Identification of eggs (oval shaped, 200 μm) or mites (350 to 500 μm, four pairs of legs with combs and accessory mouth parts that look like hooks) is done by using superficial skin scrapings, acetate tape preparations, scale and hair collected with a flea comb, and sometimes fecal flotation.
II. Mites may be seen without magnification (appear as walking dandruff).

Differential Diagnosis

I. Cats: causes of seborrhea and military dermatitis, including liver disease and diabetes mellitus
II. Dogs
A. Bacterial pyoderma
B. Primary or secondary seborrhea
C. Demodicosis
D. Nutritional deficiency dermatoses
E. Intestinal parasitism
F. Hypersensitivity disorders: atopy, food allergy, flea allergy
G. Sarcoptic or otodectic mange
H. Pediculosis

Treatment

I. Treat all dogs, cats, and rabbits in contact with the infected animal.
II. Apply lime sulfur dips weekly for 6 weeks.
III. Apply a topical parasitical powder, dip, shampoo or spray weekly for 4 weeks.
IV. Consider administering ivermectin at 0.2 to 0.3 mg/kg SC, PO every 2 weeks for 3 doses (except in sensitive breeds of dogs).
V. Fipronil spot-on or spray (6 mg/kg) may be applied monthly for two treatments.
VI. Apply selamectin 6 to 15 mg/kg topically every 30 days; response may be improved by dosing every 2 weeks for three treatments.
VII. Treat the environment with an insecticide spray or fogger that is effective against fleas.

Monitoring of Animal

I. Prognosis is good; however, the mite is highly contagious among dogs, cats, rabbits, and humans.
II. Recheck the animal 3 to 4 weeks after starting treatment.

Notoedric Mange

Definition and Cause

I. *Notoedres cati* is a highly contagious mite that primarily infects cats, but dogs, foxes, and rabbits can also be infected.
II. *N. cati* is a surface-dwelling mite that causes papules, lichenification, thickening of the skin, and tightly adherent yellow-gray crusts.
III. The disease is also called *feline scabies*.
IV. The mite is zoonotic.

Clinical Signs

I. Lesions first appear on the medial, proximal margin of the pinnae.
II. Lesions rapidly spread to the rest of the ear, face, eyelids, and neck.
III. Feet and perineum may be affected, and lesions can become widespread.
IV. Lesions consist of thickened, wrinkled skin with tightly adherent gray to yellow crusts.
V. Intense pruritus may lead to self-mutilation and secondary bacterial infections.
VI. Peripheral lymphadenopathy may be present.

Diagnosis

I. Demonstration of the mite on skin scraping
II. Biopsy
  A. Thickened epidermis
  B. Focal, parakeratotic, hyperkeratosis and superficial perivascular dermatitis
  C. Mite segments seen in the stratum corneum

Differential Diagnosis

I. Otodectic mange, cheyletiellosis
II. Food allergy, atopy
III. Pemphigus complex
IV. Systemic lupus erythematosus

Treatment

I. All cats in the household are treated.
II. Crusts and debris are removed with a mild shampoo, then lime sulfur (2% to 3%) dip is applied weekly for six to eight treatments.
III. Ivermectin may also be given 0.2 to 0.3 mg/kg PO, SC every 2 weeks for three treatments.
IV. Selamectin can be applied topically for two applications, 4 weeks apart.

Monitoring of Animal

I. If no response to treatment is seen, then evaluate the animal for recurrence.
II. If recurrence has occurred, the animal may be reinfested from the environment or from untreated dogs, cats, or rabbits.

Sarcoptic Mange

Definition and Causes

I. Sarcoptic mange is a pruritic disease of dogs and foxes that is caused by the superficial burrowing mite, *Sarcoptes scabiei* var. *canis*.
II. Sarcoptic mites can transiently infect humans and cats.

Pathophysiology

I. Mites live in the stratum corneum and create burrows in which they lay eggs.
II. Pruritus is the result of a hypersensitivity reaction to the mite.
III. Life cycle is completed on the host.
IV. Mites can survive off the host for a minimum of 6 to 21 days.

Clinical Signs

I. Scabies is characterized by a nonseasonal intense pruritus.
II. Alopecia, erythema, papules, scales, and crusts are common.
III. Lesions are commonly found on the ear margins, elbows, hocks, and ventrum.
IV. With chronic infections, lesions become widespread, but the dorsum is usually spared.
V. Humans in contact with infected dogs may develop a pruritic papular reaction.
VI. Well-groomed animals may have intense pruritus, with minimal to no skin lesions.
VII. Generalized lymphadenopathy may be present.
VIII. Weight loss and lethargy may occur secondary to chronic pruritus and discomfort.

Diagnosis

I. High suspicion based on intense pruritus
II. Demonstration of mites, mite eggs, or fecal material on skin scrapings
  A. Multiple skin scrapings are best obtained from the elbows, hocks, lateral margin of the pinnae, and ventrum.
  B. Approximately 50% of infected dogs have negative skin scrapings.
III. Positive response to treatment for the mite
IV. Poor response to corticosteroids

Differential Diagnosis

I. Hypersensitivity disorders: atopy, food allergy, flea allergic dermatitis
II. Secondary bacterial or *Malassezia* spp. infections

Treatment and Monitoring

I. All dogs in contact with the infected dog must be treated.
II. Apply selamectin topically every 2 weeks for three treatments.
III. Fipronil spray may be applied every 2 weeks for three treatments.
IV. Ivermectin may be given 0.2 to 0.3 mg/kg PO, SC every 2 weeks for three treatments, except in ivermectin-sensitive breeds (e.g., collies, Shetland sheepdog, Old English sheep dog, Australian shepherd).
V. Milbemycin oxime may be administered 1.5 mg/kg PO every 2 weeks for three treatments.
VI. Lime sulfur dips may be done weekly for six treatments.
VII. In severe cases the environment must also be treated with parasiticide sprays.
VIII. Secondary infections must be appropriately treated.
IX. If the animal's pruritus has not decreased after 21 days of treatment, then perform further diagnostic tests and reevaluate treatments.

Otodectic Mange

Definition and Cause

I. Otitis and dermatitis in the dog and cat are caused by *Otodectes cyanotis*.
II. *Otodectes* spp. primarily infest the ear canal, but can live on adjacent skin.
III. The mite is spread between animals by direct contact or via fomites.
IV. Mites cause irritation and a hypersensitivity reaction.

Clinical Signs

I. Copious cerumen production usually occurs in both ears but can be unilateral.
II. Pruritus is common.

III. Alopecia and/or a papular crusting dermatitis can occur on the pinnae; around the ear, face, and neck; and on the dorsolumbar area.
IV. Some animals may be asymptomatic carriers.

Diagnosis

I. Direct visualization of the mite in the ear canal or in cerumen
II. Microscopic identification of mites in cerumen to which mineral oil has been added
III. Examination of superficial skin scrapings

Differential Diagnosis

I. Atopy, food allergy
II. Notoedric, sarcoptic mange
III. Pediculosis, chiggers
IV. Pelodera dermatitis
V. Flea allergy dermatitis

Treatment

I. Prognosis is excellent as long as all animals in contact with the infected animal are treated.
II. Ears are cleaned with a ceruminolytic agent.
III. Treatment includes the following:
   A. Pyrethrin ear drops SID for 7 days; repeated in 7 days
   B. Thiabendazole *(Tresaderm)* SID for 7 days; repeated in 7 days
   C. Ivermectin 0.01% otic solution *(Acarexx)* 0.5 mL in each ear once; repeated in 2 weeks
   D. Selamectin applied to the skin for two treatments, 30 days apart
   E. Fipronil two to three drops in the ear; repeated in 7 and 30 days (not approved for this use)
   F. Ivermectin 1% solution 0.2 to 0.4 mg/kg PO, SC every 2 weeks for three treatments (not approved for this use)
   G. Treatment of secondary infections
   H. Possible whole-body treatment

NEOPLASIA

Epitheliotropic Lymphoma (Mycosis Fungoides)

See Chapter 91.

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CHAPTER 86

Disorders Causing Focal Alopecia

Robert A. Kennis

INFECTIOUS DISORDERS

Canine Demodicosis

Definition

I. Demodicosis is a folliculitis caused by proliferation of *Demodex canis* mites.
II. *D. canis* mites are passed from the mother to the offspring within the first few days of birth.
III. Dogs that develop clinical signs may have localized or generalized lesions.
IV. Adult-onset demodicosis is frequently associated with immunosuppression from an underlying cause.

Causes

I. Causative mite is *D. canis*, a follicular mite.
II. A long, slender mite has also been reported but is less common.

Pathophysiology

I. Pathogenesis of clinical demodicosis is poorly understood; however, stress may play a role.
II. Genetic predisposition exists in dogs that develop juvenile-onset generalized disease.
III. Dogs born by cesarean section and not allowed to nurse do not have mites.
IV. Dogs with no history of juvenile demodicosis may develop clinical signs at a later age.
    A. Possible underlying causes include the following:
        1. Hyperadrenocorticism
        2. Hypothyroidism
        3. Administration of immunosuppressive agents (corticosteroids)
        4. Neoplasia
    B. Some cases of adult-onset demodicosis are idiopathic.

Clinical Signs

I. Localized demodicosis
    A. Alopecia frequently occurs in a circumscribed pattern.
        1. Hair may epilate easily from the leading margin of the lesion.
        2. Broken hairs are not commonly associated with demodicosis.
    B. Comedones (plugged hair follicles) may be present.
    C. Pustules and papules may occur and indicate a secondary infection.
    D. Epidermal collarettes may be present.
    E. Dogs are rarely pruritic unless secondary infection is present.
    F. Feet and muzzle are frequently affected in juvenile-onset, localized demodicosis.
II. Generalized demodicosis
    A. Alopecia may be circumscribed, diffuse, locally or generally extensive, and possibly symmetrical.
    B. Hairs may epilate easily from the leading margins.
    C. Comedones may occur.
    D. Papules, pustules, hemorrhagic pustules, and draining tracts may be present.
    E. Development of crusting and scaling is variable.
    F. Pruritus is uncommon unless secondary infection is present.
    G. Odor from the skin surface may occur with secondary infection.

Diagnosis

I. Diagnosis is based on the observation of *D. canis* mites on skin biopsy, plucked-hair analysis (trichogram), or deep skin scraping from affected regions.
II. Deep skin scrapings are performed because the mite is located deep within the follicle.
    A. Pinching the skin may move mites to a more superficial location within the hair follicles.
    B. Skin is scraped with a scalpel blade or knife until hemorrhage is observed, indicating that the scraping is at the level of the dermis near the base of the hair follicle.
    C. Collected debris is mixed with mineral oil on a glass slide, and a coverslip is added to aid observation.
    D. Microscopic evaluation (×10) identifies mites.
    E. If mites are present, then the clinician documents whether they are alive or dead and determines the ratio of juvenile mites (egg, larvae, and nymph stages) to adult mites, which is beneficial for assessing response to treatment.
    F. Deep skin scrapings are the best way to diagnose demodicosis.
III. Plucked-hair analysis (trichogram) involves examining hairs from the leading margin of the lesion.

A. A hemostat or thumb forceps is used to grab the hairs near the skin surface.
B. Plucked hairs are placed on a glass slide containing a drop of mineral oil, with the hairs aligned for easier observation of the hair bulbs.
C. Microscopic evaluation (×10) reveals mites near the base of the hairs.
D. This diagnostic procedure is not as sensitive as deep skin scrapings.

IV. Biopsy and histopathology are useful for chronically inflamed skin and for demodicosis involving the feet.
A. Sedation and anesthesia may be needed if a local anesthesia of the sample site cannot be performed.
B. Skin is generally not aseptically prepared, but hair is clipped from the site to better access the selected lesion.
C. A 6-mm Baker biopsy punch can be used for collecting the sample, which should extend to the subcutaneous fat.
D. Collected samples are submitted in formalin, and special stains are not required to identify mites.

Differential Diagnosis

I. Localized demodicosis
A. Dermatophytosis
B. Bacterial folliculitis
C. Alopecia areata
D. Vaccination reaction
E. Pattern baldness

II. Generalized demodicosis
A. Dermatophytosis
B. Bacterial folliculitis
C. Alopecia areata
D. Pattern baldness
E. Cutaneous drug eruption
F. Anagen and telogen defluxion
G. Vasculitis
H. Neoplasia
1. Squamous cell carcinoma
2. Cutaneous lymphosarcoma
I. Sebaceous adenitis
J. Nutritional-related diseases
1. Zinc-responsive dermatosis
2. Vitamin A–responsive dermatosis
3. Hepatocutaneous syndrome
K. Autoimmune diseases
1. Pemphigus complex
2. Lupus and lupuslike reactions
L. Metabolic diseases
1. Hyperadrenocorticism
2. Hypothyroidism

Treatment and Monitoring

I. Localized demodicosis
A. Rotenone ointment (*Goodwinol;* containing botanical extract from orris root)
1. Apply SID to BID to the alopecic regions.
2. Warn the owner that the alopecic areas may become larger once treatment is started, from the mechanical epilation of hairs during application and the outward spreading of the mites.
B. Benzoyl peroxide gel (*Pyoben* gel, *Oxydex* gel)
1. Apply SID to the alopecic regions.
2. It does not kill or remove the mites from the follicles but helps to limit secondary infection, and unplugs hair follicles.
3. This product bleaches fabric; therefore it must be completely dry before animal is allowed on furniture and rugs.
4. Product has limited efficacy.
C. Observation only
1. Many cases of localized demodicosis are self-limiting, but secondary infection and underlying causes must be addressed.
2. Localized demodicosis may progress to a generalized form, so advise the owner to watch for new lesions or worsening of clinical signs.

II. Juvenile-onset generalized demodicosis
A. Treat all concurrent secondary bacterial and parasitic infections.
B. Correct any nutritional imbalances.
C. Spay or castrate dogs with generalized disease.
D. Treat the demodicosis with amitraz.
1. Amitraz *(Mitaban)* is the only licensed and approved product for the treatment of generalized demodicosis, and it can be used in dogs ≥12 weeks of age.
2. Remove all the hair to allow maximum skin contact with the dip.
3. Bathe the dog in a benzoyl peroxide–based shampoo and towel dry before dipping (may be done the day before).
4. Mix one bottle of the amitraz with 2 gallons of warm water.
5. Sponge the mixture onto the dog, making sure to wet all skin surfaces.
6. Allow the dog to air dry and keep it from getting wet between dips.
7. Continue dips every 2 weeks until two negative skin scrapings occur 2 weeks apart; follow with one more dip.
8. Sedation is a likely side effect.
9. Untoward side effects include bradycardia, hypothermia, seizures, coma, hyperexcitability, pruritus, vomiting, or diarrhea.
10. Small dogs are more susceptible to these side effects, probably because of their increased surface area:body weight ratio.
11. It is best to dip small dogs in the hospital and closely monitor them for 24 hours post-dipping.
12. Yohimbine may be used to reverse the adverse side effects associated with amitraz.
13. Tactik is an industrial-grade amitraz product that is not licensed or approved for use on dogs, so is not recommended.

III. Adult-onset generalized demodicosis
A. Treat all secondary infections, with the selection of antibiotics based on bacterial cultures for chronic cases.

1. Severe bacterial infections are treated to near-clinical remission before instituting amitraz dips.
2. Aggressive bathing and alternative miticide therapy can be considered during this time.

B. Treat any underlying cause, such as hypothyroidism, hyperadrenocorticism, and neoplasia.
C. Treat the demodicosis with amitraz as outlined previously.
   1. Dogs with demodicosis of the feet are allowed to stand in the solution for maximum contact.
   2. Refractory cases are sometimes treated with weekly dipping or dipping with double-strength solution (one bottle mixed with 1 gallon water) every 1 to 2 weeks.
D. Ivermectin 1% *(Ivomec)* is an alternative mitocide.
   1. Initial dosage is 0.1 mg/kg PO SID for 7 days, then increased to 0.2 mg/kg PO SID for 3 weeks if no side effects occur.
   2. Continue at the same dosage for 2 additional weeks if adequate improvement is seen.
   3. If live mites and juvenile stages are seen, increase to 0.3 mg/kg PO SID for another month, and reassess the animal.
   4. Doses can gradually be increased to 0.6 mg/kg PO SID if needed.
   5. Signs of toxicity include mydriasis, excessive salivation, lethargy, coma, and death.
   6. Ivermectin is contraindicated in the collie, Shetland sheepdog, Australian shepherd, border collie, and Old English sheepdog.
   7. Several precautions exist when using ivermectin for the treatment of demodicosis.
      a. Do not give to dogs <12 weeks old.
      b. Treatment may take months to achieve a clinical remission; therefore treatment should continue for 1 month beyond two negative skin scrapings taken 2 weeks apart.
      c. Relapses are common.
      d. Do not administer concurrently with amitraz.
      e. No reversal agent is available if ivermectin toxicity occurs—only supportive care.
      f. Idiosyncratic reactions have occurred in breeds other than those listed above, so obtain written consent from the owner before instituting this therapy.
E. Milbemycin *(Interceptor)* may also be tried.
   1. Dose is 1 to 2 mg/kg PO SID.
   2. It may be used in breeds for which ivermectin is contraindicated.
   3. If live mites and/or juvenile stages are seen after 1 month of therapy, then the dose may be doubled.
   4. Toxicities and side effects are uncommon, but the product may be cost-prohibitive for some clients.
   5. Complete remission may take many months.
   6. Treatment should continue for 2 months beyond two negative skin scrapings taken 2 weeks apart.
   7. Relapses are common.
   8. Milbemycin should not be used concurrently with either ivermectin or amitraz.

Dermatophytosis

Definition

I. Dermatophytosis is a fungal skin infection in dogs and cats that targets the growing anagen hairs and surface keratin of the skin.
II. The common name for this infection is *ringworm*.

Causes

I. The most common causes include the following:
   A. *Microsporum canis:* a zoophilic species
   B. *Microsporum gypsum:* a geophilic species
   C. *Trichophyton mentagrophytes:* a zoophilic species
II. Dermatophytosis of dogs and cats can be caused by other species found on food, zoo animals, and humans.
III. All dermatophytes are zoonotic.

Pathophysiology

I. Animals can develop dermatophytosis by coming into contact with active fungal spores from the environment, fomites, or an infected animal.
II. Dermatophytes only infect growing hairs, so when the hair stops growing or falls out, the infection resolves.
III. Host immunity (cell-mediated) is important for the prevention and resolution of dermatophyte infections.
IV. Drugs and diseases that suppress cell-mediated immunity increase the risk of dermatophytosis.
V. Trauma and skin maceration (e.g., bathing, grooming) may help establish dermatophyte infections.

Clinical Signs

I. Alopecia is variable, but is the classic lesion.
   A. Alopecia may be patchy to diffuse.
   B. Focal lesions may be well circumscribed as the infection spreads outward.
      1. Chronic lesions may have new hair growth in the center of an outward-spreading infection.
      2. Coalescing, circumscribed lesions may form a serpiginous leading margin.
   C. Affected hairs tend to break rather than epilate easily.
   D. Alopecia is usually asymmetrical.
II. Scaling is variable.
   A. Dry scaling areas (seborrhea sicca) may be associated with the alopecia.
   B. Epidermal collarettes may be present.
III. Primary lesions such as papules, pustules, or nodules may be seen.
IV. Secondary lesions may evolve from primary lesions or from trauma, and include scaling, excoriation, hyperpigmentation, crusts, collarettes, alopecia, and erythema.
V. Pruritus is variable.
VI. Because this disease is contagious, other pets and/or people within the same household may be affected.

Diagnosis

I. Definitive diagnosis is by fungal culture.
  A. Allows identification of the genus and species
  B. Allows for antifungal susceptibility testing
II. To obtain a fungal culture, do the following:
  A. Clean the affected areas with cotton soaked in alcohol to decrease bacterial contamination, and allow the area to air dry.
  B. Use a sterile hemostat or thumb forceps to grasp the hair near the skin surface.
    1. Select the leading margin of an active lesion.
    2. Place the hair, scale and crusts in a sterile Petri dish or sterile carrier for submission to a laboratory.
    3. Alternatively, place the collected hairs, scale and crust on the surface of a fungal culture plate or dermatophyte test media (DTM).
      a. Keep the sample in a dark, humid area at room temperature.
      b. Fungal growth is associated with a red color change in the DTM.
  C. A sterile tooth brush may also be used to collect the sample.
    1. Brush the entire animal and dispose of excess hair.
    2. Submit the toothbrush in a sealed bag to a reference laboratory.
    3. Alternatively, touch the tips of the brush to the DTM.
    4. Include any hair and scale that was collected.
    5. It is an excellent technique to use on animals with resolving lesions or on suspected asymptomatic carriers.
III. A trichogram may be helpful in identifying fungal infected hairs.
  A. Pluck hairs from the leading margin of the lesion.
  B. Place hairs on a glass slide with a drop of mineral oil and apply a cover slip.
    1. Potassium hydroxide solution may be used as a clearing agent instead of mineral oil to better visualize the fungal spores.
    2. Lactophenol blue may also be used to stain the slide.
  C. Observe under ×10 magnification with the light condenser turned down.
  D. Fungal-infected hairs appear fuzzy because of the damaged cuticle.
  E. Fungal spores may be seen on the hairs.
  F. A fungal culture is performed to identify the genus and species of the organism.
IV. Wood's lamp examination involves using a cobalt-blue light to identify dermatophytes that fluoresce.
  A. It only identifies some species of *Microsporum canis*.
  B. False negatives are common.
  C. False positives may occur from topical mediations.
  D. It does not identify an active infection because hairs may fluoresce that are no longer infectious.
  E. Best results are obtained if the lamp is allowed to warm for at least 10 minutes.
  F. It is only a screening tool and not a substitute for a fungal culture.

Differential Diagnosis

I. Bacterial folliculitis
II. Demodicosis
III. Alopecia areata
IV. Vaccine reaction
V. Pattern baldness
VI. Adverse drug reaction
VII. Vasculitis
VIII. Sebaceous adenitis
IX. Nutritional causes of alopecia and scaling
  A. Zinc-responsive dermatosis
  B. Vitamin A–responsive dermatosis
  C. Hepatocutaneous syndrome
X. Autoimmune disorders
  A. Pemphigus complex diseases
  B. Lupus and lupuslike reactions
XI. Ectoparasites
  A. *Cheyletiella* spp.
  B. Lice
  C. *Notoedres* spp.
  D. *Otodectes* spp.
  E. Fleas
XII. Metabolic disorders
  A. Hyperadrenocorticism
  B. Hypothyroidism
XIII. Neoplasia
  A. Squamous cell carcinoma
  B. Mast cell tumor
  C. Cutaneous lymphoma

Treatment and Monitoring

I. Lime sulfur dip
  A. Mechanism of action unknown
  B. Helps to decrease scale and pruritus
  C. May be used as a sole therapy or adjunctive therapy
  D. No age restrictions, but very young animals should be observed for hypothermia while the solution is drying
  E. Applied weekly until a negative fungal culture is achieved
  F. Precautions
    1. Do not allow cats to self-groom while the product is still wet.
    2. The product can tarnish jewelry and stain fabric.
    3. The strong sulfur odor is somewhat offensive, so owner compliance may be compromised.
II. Griseofulvin
  A. Dose for microsized product is 10 to 120 mg/kg PO SID or in divided doses.
    1. Initial dosage is 25 mg/kg PO BID.
    2. Decrease dose if the ultramicrosized formula is used.
  B. Continue for 2 weeks beyond a negative fungal culture.
  C. Precautions are numerous (Plumb, 1999).
III. Ketoconazole
  A. Dose range is 5 to 10 mg/kg PO SID to BID, with 10 mg/kg PO SID preferred in dogs.

B. Use with caution in cats.
C. Use for 2 weeks beyond a negative fungal culture.
D. Precautions are described under Treatment for Acute Moist Dermatitis in Chapter 85.

IV. Itraconazole
A. Dose range is 5 to 10 mg/kg PO SID to BID in both dogs and cats.
B. Use for 2 weeks beyond a negative fungal culture.

V. Fluconazole
A. Dose is 2.5 to 10 mg/kg PO SID to BID.
B. Use for 2 weeks beyond a negative fungal culture.

VI. Topical therapy for focal lesions
A. Topical medications with known efficacy include clotrimazole, ketoconazole, miconazole, enilconazole, and lime sulfur.
B. Topical medications with possible efficacy include thiabendazole, iodine products, and sodium hypochlorite (bleach).
C. Chlorhexidine and captan rinse are products with limited efficacy against dermatophytes.
D. Localized skin reactions may occur from these products.
E. When applying topical medications to cats, prevent oral ingestion.
F. Avoid products containing corticosteroids.
G. Efficacy of shampoo products is controversial.

Canine Superficial Bacterial Folliculitis

Definition

I. It is a bacterial skin infection leading to alopecia and inflammation of the hair follicles.
II. Follicular inflammation may predispose the follicle to bacterial infection.

Causes

I. Common associated bacteria include the following:
A. *Staphylococcus intermedius*
B. *Staphylococcus schleiferi*
C. *Staphylococcus epidermidis*
D. *Staphylococcus xylosis*
E. *Micrococcus* spp.
F. Gram-negative aerobes
G. *Streptococcus* spp.
H. *Bacillus* spp.
I. Various anaerobic species

II. Infections may arise from underlying cutaneous, metabolic, or immunological abnormalities.
III. Secondary infections are common and may be associated with the following:
A. Allergies
B. Seborrhea
C. Metabolic diseases: hyperadrenocorticism, hypothyroidism, diabetes mellitus
D. Iatrogenic causes: bathing, topical drugs or medications
E. Immunodeficiencies of immunoglobulin A, G, or M

Pathophysiology

I. Host factors allowing bacterial colonization
A. Changes in pH
B. Increased moisture
C. Altered cell turnover rate
D. Altered local cytokine production
E. Systemic illness

II. Predisposing causes of bacterial infection
A. Follicular inflammation
B. Follicular obstruction: seborrheic conditions, comedone formation
C. Follicular degeneration: endocrinopathy, corticosteroids
D. Other infections: dermatophytosis, demodicosis
E. Follicular damage from pruritus (allergy)

Clinical Signs

I. Alopecia
A. Circumscribed, outward spreading
B. Diffuse
C. Easy hair epilation owing to follicular inflammation

II. Papules, pustules
III. Epidermal collarettes, crusts
IV. Superficial moist dermatitis
V. Pyotraumatic folliculitis
VI. Chronic lesions: hyperpigmentation, lichenification
VII. Deep infections: nodules, hemorrhagic pustules, draining tracts

Diagnosis

I. Identification of increased/high numbers of bacteria on direct impression sample
A. A clean glass slide is applied to an affected lesion.
1. Pustules are gently ruptured.
2. Sample the leading margin of epidermal collarettes.
3. A cotton swab may be used to collect samples from highly exudative or draining lesions.

B. Stain the slide with a Modified Wright's stain.
C. A Gram stain may be helpful in identifying bacteria in highly exudative or hemorrhagic samples.
D. View with a ×100 oil immersion objective.
E. The presence of increased amounts of bacteria (both intra or extracellular) along with inflammatory debris or inflammatory cells is diagnostic.
F. NOTE: It is difficult to find bacteria on normal skin when direct impression samples are made.

II. Biopsy and histopathology
A. Local anesthesia with lidocaine is usually adequate.
B. A 6-mm Baker biopsy punch is recommended for primary lesions (papules or pustules).
C. Perform surgical excision with the long axis of the blade extending across the leading margin of the lesion.
D. Bacteria may be seen on histopathology but may require special stains.
E. Absence of bacteria does not rule out a bacterial cause of the problem.
F. The pattern of inflammation may help to elucidate the underlying cause of the infection.

G. Perifollicular dermatitis is suggestive of an underlying allergic cause, demodicosis, or a bacterial or dermatophyte infection.
H. In cases in which bacteria are present on cytology, consider treating the infection empirically before performing a biopsy.
I. A poor response to therapy indicates the need for a biopsy.

III. Bacterial culture and susceptibility testing
A. Primary lesions (pustules) are sampled directly.
1. The hair around the lesion is clipped away.
2. The pustule is ruptured with a sterile 25-gauge needle.
3. Pustule contents are collected on a sterile swab.
B. Secondary lesions (crusts, epidermal collarette) may also be cultured.
1. Gently lift the crust and scale with a sterile swab and culture the under side of the lesion.
2. Normal bacteria flora may be cultured with this technique, so it is important to correlate clinical findings and cytologic findings with culture results (false-positive results may occur).
C. Chronic and deep lesions are best cultured via biopsy and submitted for macerated tissue culture.
1. Aseptically prepare the skin and allow it to air dry before biopsy.
2. Place the biopsy sample in a culture medium or sterile Petri dish.
3. Request aerobic, anaerobic, and fungal cultures.
4. Submit a second sample for histopathologic analysis.
D. Antibiotics are withheld for at least 48 hours before sample collection.

Differential Diagnosis

I. Because most bacterial infections are secondary to an underlying problem, emphasis is placed on diagnosing the cause.
II. Clinical signs of bacterial folliculitis can resemble many diseases.
A. Dermatophytosis
B. Demodicosis
C. Primary or secondary seborrhea
D. Sebaceous adenitis
E. Endocrinopathies: hypothyroidism, hyperadrenocorticism, sex hormone imbalances
F. Vasculitis
G. Sterile panniculitis
H. Traumatic-induced dermatitis from pruritic causes (see Chapter 85)
I. Neoplasia

Treatment

I. Treat the underlying cause.
II. Institute topical and or systemic therapy.
A. Topical shampoos: benzoyl peroxide, chlorhexidine, ethyl lactate
B. Oral antibiotics (see Table 88-1)

Monitoring of Animal

I. Therapy is continued 1 week beyond clinical remission.
A. Three weeks is usually adequate for acute cases.
B. Bathing may speed resolution of the problem.
II. Poor response to therapy or intolerance of the selected medication requires additional steps.
A. Consider bacterial culture with susceptibility.
B. Consider biopsy with histopathology.
III. Recurrence after successful treatment is possible.
A. Treated for an inadequate time
B. Resistance to the selected antibiotic
IV. Seek the underlying cause of any recurrences.

INFLAMMATORY DISORDERS

Vaccine-Associated Vasculitis

Definition and Cause

I. Affected dogs develop an expanding focus of alopecia at the site of vaccination, especially a rabies vaccine.
II. Lesions may not develop for 2 to 4 months after vaccination.
III. The reaction leads to permanent, scarring alopecia.

Pathophysiology

I. Vasculitis develops at the injection site.
II. Ischemia of the hair follicles occurs.
III. Inflammation may or may not be visible during the acute phase.

Clinical Signs

I. Focal, complete alopecia is typical.
II. The lesion is usually circumscribed and erythematous.
III. The skin may become atrophic and/or hyperpigmented.
IV. Scaling is variable.
V. The lesion is usually nonpruritic.

Diagnosis

I. Diagnosis is made based on history and clinical findings.
II. Biopsy and histopathology may be helpful in ruling out other causes of alopecia.
III. Biopsy during the acute phase may indicate a vasculitis.
A. Lesions are usually not apparent: however, until alopecia develops and the vasculitis has subsided.
B. Other causes of vasculitis must be ruled out.

Differential Diagnosis

I. During the acute phase of the reaction
A. Spider bites
B. Systemic illness: ehrlichiosis, Rocky Mountain spotted fever
C. Adverse drug reaction
D. Neoplasia: lymphoma
E. Dermatomyositis
F. Burns: caustic or thermal
II. During the chronic phase of the lesion
A. Spider bite

B. Adverse drug reaction
C. Burns

III. Causes of epidermal collarettes
A. Bacterial folliculitis
B. Dermatophytosis
C. Demodicosis

Treatment and Monitoring

I. During the acute phase of the reaction, pentoxifylline may be used at 10 to 15 mg/kg PO BID.
II. If the lesion is cosmetically disfiguring, then it may be surgically excised.
III. Advantages and disadvantages of vaccination must be considered when future vaccinations are chosen, because reactions can worsen with repetitive use.
IV. Consider treatment with pentoxifylline at the time of injection and continue for several weeks afterward.

MISCELLANEOUS DISORDERS

Alopecia Areata

Definition and Causes

I. It is an uncommon disorder characterized by patchy to diffuse hair loss.
II. Skin is not grossly inflamed.
III. T lymphocytes and antifollicular antibodies may be present
IV. It may be multifactorial in origin.

Clinical Signs

I. Alopecia: focal to multifocal, diffuse to patchy, symmetrical or asymmetrical, sometimes well circumscribed
II. No clinical evidence of skin inflammation
III. Possible spontaneous hair regrowth

Diagnosis

I. Diagnosis is based on biopsy and histopathology.
II. Multiple biopsy samples are collected.
III. A trichogram may reveal dysplastic hairs.

Differential Diagnosis

I. Focal alopecia: vaccine reaction, follicular dysplasia, bacterial folliculitis, demodicosis, dermatophytosis
II. Symmetrical alopecia: endocrinopathies, pattern baldness, psychogenic alopecia in cats
III. Chronic oral or parenteral corticosteroid administration

Treatment and Monitoring

I. Affected animals may recover spontaneously.
II. No defined treatment exists.

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CHAPTER 87

Disorders Causing Symmetrical Alopecia

Rudayna M. Ghubash

CONGENITAL/DEVELOPMENTAL DISORDERS

Pattern Baldness

Definition and Causes

I. Tardive hypotrichosis is a condition in which animals are born with normal hair coats and develop alopecia as they mature.
II. It is also known as *acquired-pattern alopecia*, *canine pinnal alopecia*, and *dachshund pattern baldness*.
III. Four separate syndromes have been reported.
  A. Pinnal alopecia of dachshunds
    1. It is more common in males.
    2. Alopecia usually starts between 6 and 9 months of age.
  B. Ventral and caudal alopecia of Boston terriers and dachshunds
    1. Also reported in the Chihuahua, whippet, greyhound, Italian greyhound, and Manchester terrier.
    2. Condition occurs primarily in females.
    3. Alopecia typically begins around 6 months of age.
  C. Bald thigh syndrome of greyhounds
  D. Pattern alopecia of Portuguese water dogs and American water spaniels: begins around 6 months of age

Pathophysiology

I. It is probably genetic in origin.
II. Specific hair follicle pathophysiology is unknown.

Clinical Signs

I. In general, all these conditions develop symmetrical alopecia that tends to be restricted to certain areas of the body.
II. Some animals have a thin, fine hair coat in affected areas.
III. With pinnal alopecia of dachshunds, the alopecia is symmetrical and involves the dorsal haired surface of the pinna and the caudal auricular area.
IV. Boston terriers and dachshunds develop symmetrical alopecia that occurs on the ventrum, ventral neck, caudal auricular area, and the medial aspect of the hind legs.
V. In bald thigh syndrome of greyhounds, symmetrical alopecia occurs on the caudal aspect of the hind legs.
VI. Pattern alopecia of Portuguese water dogs and American water spaniels is characterized by symmetrical alopecia of the ventral neck, the medial aspect of the hind legs, and potentially the entire tail.

Diagnosis

I. Pattern baldness is often diagnosed based on age of onset, breed, clinical signs, and exclusion of other diseases.
  A. Skin scrapings are performed to rule out parasitic causes, such as demodectic mange.
  B. Dermatophyte cultures are used to rule out dermatophytosis.
  C. If the alopecia is occurring in a middle-aged or older animal, then endocrine testing is conducted to rule out hypothyroidism and hyperadrenocorticism.
II. Diagnosis can be supported by histopathology of skin biopsies of the alopecic areas.
  A. Normal epidermis and dermis
  B. Diminutive hair follicles
  C. Hair follicles not in growth arrest cycle
    1. Not primarily in telogen or catagen
    2. Key difference from endocrine alopecias

Differential Diagnosis

I. Sex hormone dermatoses
II. Hypothyroidism
III. Hyperadrenocorticism
IV. Follicular dysplasia
V. Demodicosis
VI. Dermatophytosis
VII. Ear margin seborrhea

Treatment and Monitoring

I. No successful treatment has been developed.
II. Melatonin has been useful in some affected animals at 3 mg PO SID to BID for dogs <10 kg and at 6 mg PO SID to BID for dogs >10 kg.
  A. Main side effect of melatonin is gastrointestinal upset.
  B. If no evidence of hair regrowth is seen after 6 months, then melatonin can be stopped.
III. No monitoring is required because this is a self-limiting, aesthetic disease.

IDIOPATHIC DISORDERS

Cyclical Flank Alopecia

Definition and Causes

I. The disorder is also known as *seasonal flank alopecia* and *canine recurrent flank alopecia*.
II. It is a localized follicular dysplasia on the trunk that is usually symmetrical in nature, seasonal, and associated with a noninflammatory hyperpigmentation of the skin.
III. The syndrome is most common in the English bulldog, French bulldog, boxer, and Airedale terrier.
IV. It has also been documented in the miniature schnauzer, miniature poodle, Doberman pinscher, Bouvier de Flandres, Scottish terrier, Staffordshire terrier, Griffon Korthal, and Affenpinscher.

Pathophysiology

I. Underlying pathogenesis of this condition is poorly understood.
II. Because of higher incidences in certain breeds, a genetic influence is suspected.
III. Because of seasonality and higher occurrence in certain regions of the world, photoperiod and variations in regional climates probably also influence the hair follicle cycle.

Clinical Signs

I. Typically a bilateral, symmetrical alopecia develops in the thoracolumbar region, with hyperpigmentation of the underlying skin.
II. It can be unilateral.
III. The alopecia usually has a well-demarcated border.
IV. Spontaneous regrowth of hair usually occurs within 3 to 8 months.
V. Alopecia usually occurs every year around the same time.
   A. Some animals (20%) have a one-time occurrence (Scott et al., 2001a).
   B. Sometimes the occurrence of alopecia skips a year.
   C. The extent of the alopecia can vary from year to year.

Diagnosis

I. Diagnosis is based on occurrence in a compatible breed, seasonal history, clinical signs, ruling out other differential diagnoses, and histopathology of the skin.
   A. Skin scrapings to rule out demodicosis
   B. Fungal cultures to rule out dermatophytosis
   C. Endocrine testing to rule out hypothyroidism and hyperadrenocorticism
II. It can be difficult to diagnose with histopathology, depending on the timing of the disease when the biopsy is performed.
III. Several histological characteristics predominate.
   A. Significant follicular hyperkeratosis is usually present.
   B. Dilated hyperkeratotic infundibulum atop abnormally truncated hair follicles results in a "witch's foot" appearance that is unique to this disease.

Differential Diagnosis

I. Hyperadrenocorticism
II. Hypothyroidism
III. Alopecia X
IV. Follicular dysplasia
V. Sex hormone dermatoses
VI. If alopecia is not symmetrical
   A. Demodicosis
   B. Dermatophytosis
   C. Follicular dysplasia
   D. Sebaceous adenitis

Treatment and Monitoring

I. Hair typically regrows spontaneously at the end of the season.
II. Because this is only a cosmetic condition, therapy may be unnecessary.
III. Melatonin therapy is effective in some dogs.
   A. Mechanism of action is unknown.
   B. Melatonin has been useful in some affected animals at 3 mg PO SID to BID for dogs <10 kg and at 6 mg PO SID to BID for dogs >10 kg.
      1. The primary side effect of melatonin is gastrointestinal (GI) upset.
      2. Response to melatonin therapy is expected within 6 months.
   C. Melatonin therapy can be started before the historical season for alopecia in an attempt to prevent the condition from developing.

ENDOCRINE AND METABOLIC DISORDERS

Alopecia X

Definition and Causes

I. Alopecia X is a bilaterally symmetrical alopecia of unknown cause, with a poorly understood pathophysiology.
II. A great deal of confusion exists regarding this disorder.
III. It is also called *adult-onset growth hormone deficiency (hyposomatotropism), growth-hormone responsive alopecia, castration-responsive alopecia, biopsy-responsive alopecia, congenital adrenal hyperplasia-like syndrome,* and *pseudo-Cushing's disease.*
IV. It is also known colloquially as *black skin disease* and *coat funk.*
V. It often occurs in the Pomeranian, chow chow, Keeshond, and miniature and toy poodles.
VI. It has been reported in the Airedale terrier, dachshund, German wirehaired pointer, Alaskan malamute, and Portuguese water dog.

Pathophysiology

I. Alopecia X is most likely a defect in the ability of the hair follicle to cycle properly.
II. In the 1980s it was initially thought to be a growth hormone deficiency, although several reports refuted this theory.

A. One third of dogs evaluated with this condition had normal growth hormone concentrations in response to xylazine or gonadotropin-releasing hormone (Lothrop, 1988).
B. Affected dogs lack other signs relating to a growth hormone deficiency.
C. Selective deficiency of growth hormone from the pituitary gland would be rare.
D. Normal dogs can grow hair in response to growth hormone injections, so response to treatment does not indicate a deficiency.

III. One study proposed that the disease resulted from an adrenal steroid hormone imbalance (Schmeitzel and Lothrop, 1990).
A. Researchers thought that partial deficiency of the 21-hydroxylase enzyme resulted in an increase in adrenal steroid intermediate products, which interfered with the normal hair follicle cycle.
B. However, no systemic signs are associated with this disease.
C. Another study found no abnormalities in the 21-hydroxylase gene of alopecic Pomeranians (Takada et al., 2002).
D. Not all animals with this syndrome have the classic hormonal abnormalities that are expected with a 21-hydroxylase deficiency.

IV. A recent abstract investigated the change in hair follicle estrogen receptors in dogs treated with melatonin for this disease (Frank, 2006).
A. Of the dogs that regrew hair, none showed any changes in follicular estrogen receptors before and after response to treatment.
B. Up-regulation of follicular estrogen receptors is probably not the cause of this syndrome, because down-regulation of receptors did not occur in animals responding to treatment.

Clinical Signs

I. Bilaterally symmetrical alopecia of the flanks, neck, caudal hind legs, and perineum
II. Hyperpigmentation of the underlying skin
III. Lack of systemic signs
IV. Loss of primary hairs and a "puppy coat" appearance

Diagnosis

I. Perform skin scrapings to rule out demodicosis.
II. Submit fungal cultures to rule out dermatophytosis.
III. Endocrine testing is used to eliminate the possibility of hypothyroidism or hyperadrenocorticism.
IV. University of Tennessee sex hormone panel is helpful in diagnosing animals with abnormalities in intermediate forms of sex hormones, even though the exact relationship to the disease is unknown.
V. Skin histopathology is consistent with an endocrine alopecia, after other endocrine diseases have been eliminated as possibilities
A. Prominent flame follicles
B. Arrest of the hair follicles in telogen and catagen

Differential Diagnosis

I. Hyperadrenocorticism
II. Hypothyroidism
III. Sex hormone dermatoses
IV. Cyclical flank alopecia

Treatment and Monitoring

I. Melatonin can cause hair regrowth in some animals.
A. The mechanism of action is unknown.
B. Melatonin has been useful in some affected animals at 3 mg PO SID to BID for dogs <10 kg and at 6 mg PO SID to BID for dogs >10 kg.
1. Main side effect of melatonin is gastrointestinal upset.
2. If response occurs, hair growth is expected within 6 months.

II. Intact animals often respond to neutering, but debate continues regarding whether the condition in these animals is truly alopecia X or a sex hormone problem.
III. Mitotane can cause hair regrowth in some cases.
A. Dose recommendations vary from 15 to 25 mg/kg/day PO.
B. Treatment is not recommended because it involves treating an aesthetic disease with a drug that has potentially serious side effects.

IV. Trilostane has been effective.
A. In one study, trilostane resulted in hair growth in three Alaskan malamutes with Alopecia X (Leone et al., 2005).
1. Dose ranged from of 3.0 to 3.6 mg/kg/day PO.
2. Monitoring consisted of a complete blood count (CBC), chemistry panel, and adrenocorticotropic hormone (ACTH) stimulation tests at 2 weeks, 4 weeks, 3 months, and 6 months after initiating therapy.
3. No abnormalities on CBCs and chemistry panels were noted in any dogs, and cortisol assays were normal, indicating that excessive adrenal suppression did not occur.

B. Another study treated 16 Pomeranians and eight miniature poodles with Alopecia X (Cerundolo et al., 2004).
1. Most of the Pomeranians (85%) and miniature poodles (100%) grew hair within 4 to 8 weeks when treated SID to BID, with a mean daily dose of 10.85 mg/kg/day PO.
2. No adverse effects were noted.

V. It is debatable whether mitotane and trilostane are better options than no treatment at all because this is an aesthetic disease.

Hypothyroidism

Definition

I. Hypothyroidism is characterized by a deficiency of thyroid hormones from either structural or functional abnormalities of the thyroid gland.
II. Animals are typically affected during middle age.

III. Increased incidence of the disease has been reported in the Airedale terrier, beagle, American cocker spaniel, Great Dane, golden retriever, Labrador retriever, Irish setter, and Old English sheepdog.
IV. No difference in incidence has been detected between the two sexes.

Causes and Pathophysiology

I. The most common cause of canine hypothyroidism is lymphocytical thyroiditis, a genetically linked, immune-mediated disease of the thyroid glands.
II. Idiopathic atrophy of the thyroid glands also leads to a decrease in production of thyroid hormones (see Chapter 42).

Clinical Signs

I. Dermatological signs occur in many hypothyroid dogs.
II. Dogs are nonpruritic, unless the condition is complicated by secondary infection.
III. Bilaterally symmetrical alopecia is usually confined to areas of wear, such as the lateral trunk, ventral thorax, and tail.
IV. Alopecia typically spares the head and extremities.
V. Hair coat is dull and of poor quality.
VI. Some dogs exhibit a poor ability to heal from wounds.
VII. Seborrhea sicca, seborrhea oleosa, and secondary bacterial and yeast infections are common.
VIII. Comedones and hyperpigmentation may be noted.
IX. If myxedema is present, then the skin can be puffy or thickened (especially on the head).

Diagnosis

I. Histopathologic examination may be used initially to determine whether the cause of the alopecia is endocrine or nonendocrine.
   A. Significant follicular atrophy
   B. Vacuolated, hypertrophied arrector pili muscles
   C. Increased level of dermal mucin
   D. Hair follicles in growth cycle arrest
II. Certain abnormalities on routine blood work are supportive but not diagnostic.
   A. Mild nonregenerative anemia
   B. Hypercholesterolemia
   C. Hypertriglyceridemia
III. Measurement of thyroid hormones is used to definitively diagnose the disease, but results can be difficult to interpret.
   A. Total serum thyroxine (T_4)
      1. Normal T_4 almost always excludes the diagnosis of hypothyroidism.
      2. Decreased T_4 levels should be interpreted in conjunction with other tests.
      3. Nonthyroidal illnesses, drug administration, and breed variations (greyhounds) can cause low T_4 levels.
      4. Diestrus and pregnancy can cause elevated T_4 levels.
      5. One study found an overlap in T_4 levels between normal dogs, hypothyroid dogs, and nonhypothyroid dogs with concurrent illness (Nelson and Ihle, 1991).
   B. Free T_4 by equilibrium dialysis
      1. It is the most accurate representation of thyroid function, as it is the form of the hormone that can actively enter cells and bind to receptors.
      2. Free T_4 is less affected by sickness, serum protein concentration, and other conditions compared with total T_4.
   C. Thyroid-stimulating hormone (TSH) (Peterson et al., 1997; Ramsey et al., 1997)
      1. Useful in conjunction with other tests (not by itself)
      2. Elevated in 66% to 75% of hypothyroid dogs
      3. Normal in 25% to 33% of hypothyroid dogs
      4. Elevated in about 10% of euthyroid dogs

Differential Diagnosis

I. Hyperadrenocorticism
II. Sex hormone dermatoses
III. Alopecia X
IV. Cyclical flank alopecia
V. Follicular dysplasia
VI. Postclipping alopecia
VII. Telogen effluvium

Treatment

I. Supplementation with a brand name thyroxine product is recommended.
   A. Generic thyroid supplements sometimes contain a lower hormone level than listed on the bottle and may not always be reliable.
   B. Beginning dose recommendation is 0.02 mg/kg PO BID.
   C. Once the animal is controlled on the BID regimen, the dose can sometimes to be decreased to SID, with the same level of control.
II. Initial lower dose (0.01 mg/kg PO BID) may be used in animals with preexisting cardiac disease and then gradually increased over time.

Monitoring of Animal

I. Check postpill total T_4 level 4 to 6 weeks after starting thyroid supplementation to make sure the animal is receiving the proper dose.
   A. If an animal is receiving supplementation BID, collect a blood sample 4 to 6 hours after the previous dose for a peak level.
   B. This level should be at the high end of the reference range or slightly above normal, because this is the peak level of the day.
II. If the dog is receiving supplementation SID, then a trough total T_4 is checked just before the scheduled time to receive the medication.
   A. Level should be at the low end of the reference range.
   B. This is the lowest thyroid level of the day.
III. If adjustments are made to the dose, then T_4 levels are checked again 4 to 6 weeks later.
IV. Once the maintenance dose has been established, postpill thyroid levels are checked twice yearly.

V. Measuring total T_4 is sufficient for evaluating postpill levels.
VI. Thyrotoxicosis caused by oversupplementation, or supplementation of a nonhypothyroid dog, is rare.
  A. Incidence of toxicity is low because of rapid metabolism and excretion of thyroid hormones in dogs.
  B. Clinical signs include polyuria, polydipsia, excessive weight loss, and tachycardia.

Spontaneous Hyperadrenocorticism

Definition

I. Hyperadrenocorticism is characterized by excessive production of glucocorticoids by the adrenal gland, as a result of pituitary gland or adrenal gland dysfunction.
II. It is most common in middle-aged to older dogs.
III. A higher incidence has been reported in female dogs.
IV. Breeds with a higher incidence include the miniature and toy poodle, dachshund, Boston terrier, boxer, and beagle.

Causes and Pathophysiology

I. Pituitary-dependent hyperadrenocorticism
  A. Most cases (85%) are caused by a pituitary tumor that leads to excessive secretion of adrenocorticotropic hormone (ACTH) (Scott et al., 2001c).
  B. This excess of ACTH causes a bilateral hypertrophy of the adrenal glands and leads to increased production of cortisol.
  C. Tumor can be a microadenoma or macroadenoma.
II. Adrenal-dependent hyperadrenocorticism
  A. About 15% to 20% of affected dogs have a functional adrenal tumor that produces excessive cortisol (Scott et al., 2001c).
  B. Tumor can be an adenocarcinoma or adenoma.

Clinical Signs

I. Bilaterally symmetrical alopecia, typically of the trunk
II. Hyperpigmentation
III. Calcinosis cutis
IV. Comedones
V. Thin, hypotonic skin
VI. Skin that is easily bruised
VII. Secondary bacterial pyoderma, *Malassezia* spp. dermatitis, demodicosis

Diagnosis

I. See Chapter 45 for an in-depth discussion on the diagnosis of spontaneous hyperadrenocorticism.
II. History and the ACTH stimulation test can be used to differentiate between spontaneous and iatrogenic hyperadrenocorticism.
  A. Chronic use of oral corticosteroids or injectable steroids can predispose an animal to iatrogenic hyperadrenocorticism.
  B. Animals with iatrogenic hyperadrenocorticism show a minimal response to exogenous ACTH (ACTH stimulation test) because the adrenocortical axis is suppressed.
III. Skin biopsies are consistent with an endocrinopathy.
  A. Epidermal, follicular and sebaceous gland atrophy
  B. Dilation and hyperkeratosis of the hair follicles
  C. Hair follicles in growth cycle arrest
  D. Calcinosis cutis highly suggestive

Differential Diagnosis

I. Hypothyroidism
II. Sex hormone dermatoses
III. Alopecia X
IV. Cyclical flank alopecia
V. Iatrogenic hyperadrenocorticism

Treatment and Monitoring

I. See Chapter 45 for an in-depth discussion on the treatment of hyperadrenocorticism, including doses and monitoring.
  A. Mitotane *(o,p'-DDD, Lysodren),* an adrenocorticolytic agent that results in selective necrosis and atrophy of the adrenal cortex, is the most commonly used treatment for canine hyperadrenocorticism.
  B. Trilostane, a competitive inhibitor of the 3β-hydroxysteroid dehydrogenase enzyme in the adrenal glands, inhibits the production of progesterone and its end products and is efficacious in the treatment of canine pituitary-dependent hyperadrenocorticism.
  C. Ketoconazole lowers cortisol levels by inhibiting enzymes involved in steroid biosynthesis but is not very efficacious.
  D. L-Deprenyl (selegiline hydrochloride, *Anipryl*), a selective and irreversible monoamine oxidase type B inhibitor that restores central dopamine concentrations, is effective in 20% of canine pituitary-dependent hyperadrenocorticism cases (Reusch et al., 1999).
II. It can take several months for hair to grow and skin to normalize, and new hair growth can differ from its previous color and quality.
III. If calcinosis cutis is present, then the time until hair regrowth can be prolonged.
  A. A thin film of topical dimethyl sulfoxide (DMSO) can be applied to areas of calcinosis cutis SID to break down calcium deposits.
  B. Gloves must always be worn when handling DMSO.
  C. Baseline serum calcium levels are checked and repeated monthly in severe cases to monitor for hypercalcemia.

Iatrogenic Hyperadrenocorticism

Definition and Causes

I. Iatrogenic hyperadrenocorticism arises from exogenous administration of glucocorticoids, and clinical symptoms are similar to spontaneous hyperadrenocorticism.
II. Long-term oral, injectable, and topical glucocorticoids have all been implicated in this disease.

Pathophysiology

I. Excessive amounts of exogenous glucocorticoids produce similar effects on organs as they do in spontaneous hyperadrenocorticism.

II. This results in suppression of ACTH output by the pituitary gland, which leads to suppression of cortisol production by the adrenal glands.

Clinical Signs

I. Bilateral, symmetrical alopecia of the trunk
II. Hyperpigmentation
III. Calcinosis cutis
IV. Comedones
V. Thin, hypotonic skin
VI. Skin that is easily bruised
VII. Secondary bacterial pyoderma, *Malassezia* spp. dermatitis, demodicosis

Diagnosis

I. History of exposure to exogenous glucocorticoids is usually obtained.
II. Affected animals have a minimal response to exogenous ACTH (ACTH stimulation test) because the adrenocortical axis is suppressed.
III. Liver enzymes are often elevated.
IV. The low-dose dexamethasone suppression test cannot be used to diagnose this disease.

Differential Diagnosis

I. Hypothyroidism
II. Sex hormone dermatoses
III. Alopecia X
IV. Cyclical flank alopecia
V. Spontaneous hyperadrenocorticism

Treatment

I. Discontinue all glucocorticoids.
II. If the glucocorticoids have been given orally or topically, they are slowly tapered over several weeks to allow the adrenal glands to recover from the suppression and start producing endogenous cortisol.
III. If calcinosis cutis is present, then a thin film of topical DMSO can be applied to areas of calcinosis cutis SID to break down calcium deposits.
   A. Gloves must always be worn when handling DMSO
   B. Baseline serum calcium levels are checked and repeated monthly in severe cases to monitor for hypercalcemia.

Monitoring of Animal

I. Serial ACTH stimulation tests can be done while the glucocorticoids are being tapered, and then every 3 to 4 weeks after discontinuation of the glucocorticoids, until the test result returns to normal.
II. If no permanent damage has been done to any internal organs, the prognosis is good.

Sex Hormone Dermatoses in the Male Dog

Definition

I. Sex hormone dermatoses are a poorly defined group of diseases characterized by dermatological symptoms secondary to an underlying dysfunction of the sex hormones.
II. They are often secondary to neoplastic conditions of the reproductive tract.
III. They are usually seen in middle-aged to older animals.
IV. Increased incidence is reported in the boxer, collie, Shetland sheepdog, and Weimaraner.

Causes and Pathophysiology

I. In male dogs, Sertoli's cell tumors, interstitial cell tumors, and seminomas may cause an endocrine alopecia, with Sertoli's cell tumors being the most common.
II. Skin disease and feminization occur from an abnormal ratio of sex hormones or from hyperestrogenism.

Clinical Signs

I. Bilaterally symmetrical alopecia
II. Hyperpigmentation of the skin
III. Linear preputial dermatoses on the ventral caudal abdomen
IV. Alterations in coat color
V. Behavioral changes
VI. Feminization: pendulous prepuce, gynecomastia, enlarged nipples
VII. Signs of bone marrow suppression secondary to hyperestrogenemia: anemia, thrombocytopenia, pancytopenia

Diagnosis

I. Palpation of an enlarged scrotal testes or an abdominal mass in a cryptorchid dog
II. Advanced imaging to locate a testicular tumor
III. Biopsy and histopathologic examination of the testicle to confirm the presence of a tumor
IV. Laboratory assays to document increased estrogen levels
V. Hematological examination and bone marrow aspirate to evaluate a hypoplastic bone marrow (nonregenerative anemia, thrombocytopenia, leukopenia) secondary to estrogen toxicity
VI. Histopathologic examination of the skin similar to other endocrinopathies, especially hypothyroidism
   A. Arrest of hair follicle cycle
   B. Atrophy of the hair follicles

Differential Diagnosis

I. Hypothyroidism
II. Hyperadrenocorticism
III. Alopecia X
IV. Cyclical flank alopecia
V. Follicular dysplasia

Treatment and Monitoring

I. Bilateral castration is indicated.
II. In one study, 8% of Sertoli's cell tumors and 11% of seminomas metastasized, but interstitial cell tumors were usually benign (Scott et al., 2001c).
III. Evaluate for signs of metastasis before surgery because it affects the prognosis.
IV. Because micrometastasis may be present before surgery, monitor the animal for a relapse of dermatological symptoms and eventual metastasis of the tumor (see Chapter 56).

Hyperestrogenism in the Female Dog

Definition

I. Hyperestrogenism is an uncommon endocrine disease in the female dog and is the result of elevated estrogen levels or abnormal sex hormone ratios.
II. It is also known as *ovarian imbalance type I.*
III. It is usually seen in middle-aged, intact female dogs.
IV. There is a higher incidence in English and French bulldogs.

Causes and Pathophysiology

I. Cystic ovaries or a functional ovarian tumor cause abnormal hormone levels.
II. Hormonal imbalances interfere with normal hair follicle cycling and result in alopecia.

Clinical Signs

I. Bilaterally symmetrical alopecia primarily of the lateral flanks, inguinal, perineal regions
II. Possible alopecia of the neck, chest, caudal and medial hind legs
III. Comedones, especially affecting the vulva
IV. Gynecomastia, enlarged nipples and vulva
V. Hyperpigmentation
VI. Seborrhea
VII. Estrous cycle abnormalities
VIII. ± Endometritis, pyometra

Diagnosis

I. Abdominal ultrasonography or exploratory surgery identifies abnormal ovarian tissue.
II. Ovarian tissue is submitted for histopathologic examination.
III. Estrogen assays may show elevated blood estrogen levels.
IV. Hematological examination and a bone aspirate are indicated to evaluate a hypoplastic bone marrow (nonregenerative anemia, thrombocytopenia, leukopenia) secondary to estrogen toxicity.
V. Histopathological examination of the skin may reveal the following:
   A. Results are similar to other endocrinopathies, especially hypothyroidism and tumor-associated skin disease in male dogs.
   B. Hair follicles are in growth cycle arrest.
   C. Hairless telogen hairs are present in high numbers.
VI. Regrowth of hair occurs in response to ovariohysterectomy.
VII. If an ovarian neoplasm is suspected, then thoracic radiographs are done to evaluate for metastasis.

Differential Diagnosis

I. Hyperadrenocorticism
II. Hypothyroidism
III. Alopecia X
IV. Follicular dysplasia

Treatment and Monitoring

I. Ovariohysterectomy resolves the dermatological signs.
II. Because micrometastasis can be present before surgery, monitor the animal for a relapse of dermatological symptoms and eventual metastasis of any tumor.

MISCELLANEOUS CONDITIONS

See Table 87-1.

TABLE 87-1

Miscellaneous Disorders of Symmetrical Alopecia

CONDITION	CAUSES	SIGNALMENT/CLINICAL SIGNS	DIAGNOSIS	TREATMENT/PROGNOSIS
Color dilute alopecia (color mutant alopecia)	Dilutions of black and brown hair to blue and fawn, respectively, are caused by abnormalities of coat color genes	Common in blue and fawn Doberman pinschers but also reported in other breeds with dilute colored hair coats Affected animals have recurrent bacterial folliculitis and thinning of the hair coat, primarily on the dorsum	Histopathology of skin biopsies reveals abnormal deposition and distribution of melanosomes within the hair shaft and hair follicle	Recurrent bacterial folliculitis is treated with appropriate antibacterials Mild topical antibacterial and antiseborrheic products are recommended Melatonin can be used at 3 mg PO SID-BID for dogs <10 kg and at 6 mg PO SID-BID for dogs >10 kg

Continued

TABLE 87-1

Miscellaneous Disorders of Symmetrical Alopecia—*cont'd*

CONDITION	CAUSES	SIGNALMENT/CLINICAL SIGNS	DIAGNOSIS	TREATMENT/PROGNOSIS
Excessive shedding	Previously reported in the literature; condition is not a primary disease but is secondary to folliculitis, seasonal changes, etc.			
Feline acquired symmetrical alopecia	Previously reported in the literature; many dermatologists thought these cats were suffering from allergic disease or psychogenic alopecia		New cases are required to confirm this condition is a unique entity	
Feline psychogenic alopecia	Alopecia from excessive licking or grooming is associated with a primary anxiety disorder	No age or sex predilection exists Condition is most commonly reported in Siamese and Abyssinian cats Animal has symmetrical or patchy alopecia caused by excessive grooming	Diagnosis is made by ruling out other causes of feline pruritus Skin scrapings, fungal cultures, flea preventatives, elimination food trials, and evaluation for environmental allergies are performed Only 10% of cats referred to a behaviorist for this disease suffered from it, 76% were allergic, and 14% suffered from a combination of allergies and psychogenic alopecia (Waisglass et al., 2006)	If the underlying cause of the anxiety cannot be resolved, antianxiety medications can be attempted with amitriptyline 5 mg PO BID or clomipramine 1.25-2.5 mg PO SID
Short-hair syndrome of silky breeds	Previously reported in the literature; many dermatologists thought these dogs had color mutant alopecia		New cases are required to confirm this condition is a unique entity	
Telogen defluxion	Alopecia is caused by a sudden arrest of hair follicles in the anagen cycle, and synchronization into the telogen phase is caused by a stressful event	Animal has a history of a stressful condition, such as life-threatening illness, surgery, pregnancy, or anesthesia Alopecia usually develops over most of the body but tends to spare the head	Diagnosis is based on the history of a stressful experience and examination of affected hair follicles revealing telogen hair follicles (slightly clubbed and lacking root sheaths)	Condition resolves when the cause of the hair cycle arrest is removed Histopathology of skin lesions reveals that most hair follicles are in the telogen phase

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CHAPTER 88

Papular, Pustular, and Subcutaneous Skin Diseases

Candace A. Sousa

GENERAL CONSIDERATIONS

Papule

Definition

I. A papule (Figure 88-1) is a solid circumscribed elevation of the skin that varies in diameter from 1 to 10 mm.
II. Papules are usually caused by an infiltration of inflammatory cells into the epidermis (intraepidermal) or dermis, subepidermal edema, or epidermal hypertrophy.
  A. They can be pink, red or black in color.
  B. They may or may not be associated with a hair follicle.
III. Papules can be classified by their location.
  A. A follicular papule occurs when the inflammatory infiltrate accumulates within the epidermis of the follicle or in the perifollicular dermis.
  B. A nonfollicular papule is located within the skin, but is not associated with a hair follicle.
  C. An interfollicular papule is a nonfollicular papule found only within the haired skin and in an interfollicular location.

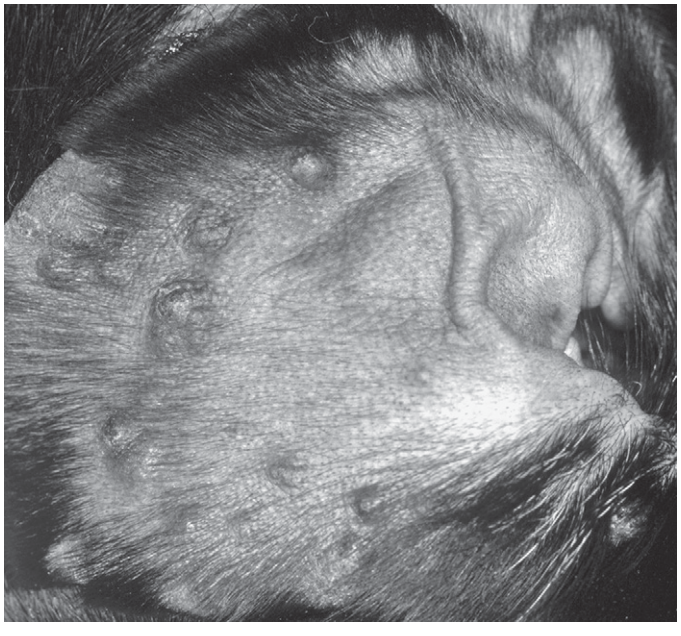

FIGURE 88-1 Papules on the inner aspect of the pinna, secondary to an infestation with *Sarcoptes scabiei.*

Causes

I. Follicular papule
  A. Staphylococcal folliculitis
  B. Demodicosis
  C. Dermatophytosis ("ringworm")
II. Nonfollicular or interfollicular papule
  A. *Sarcoptes scabiei*
  B. Flea bites
  C. Mosquito bites
  D. Contact hypersensitivity
  E. Pemphigus foliaceus
  F. Drug eruptions

Pustule

Definition

I. A pustule (Figure 88-2) is a small (<1 cm) circumscribed collection of purulent material.
II. Pus is a liquid inflammatory product composed of leukocytes.
III. Pustules may be intraepidermal, subepidermal, or follicular in location.
  A. They are usually yellow in color but may be white, green, or red.
  B. Most pustules contain neutrophils, but eosinophils can also be found.
  C. Most pustules are infectious in origin, but some may be sterile.

Causes

I. Infections
  A. Staphylococcal pyoderma and folliculitis
  B. Impetigo
II. Noninfected, sterile conditions
  A. Juvenile cellulitis
  B. Pemphigus foliaceus
  C. Acne
  D. Eosinophilic pustulosis
  E. Subcorneal pustular dermatosis

FIGURE 88-2 Pustule associated with impetigo in a puppy.

Diagnostic Approach to Papules and Pustules

I. Skin scraping
   A. Deep to rule out demodicosis
   B. Superficial to look for scabies
II. Surface cytology
   A. Identification of cocci (most likely *Staphylococcus* spp.) or other bacteria
   B. Identification of the predominant cell type (if any)
III. Wood's lamp examination
IV. Dermatophyte culture
V. Aspirate cytology of a pustule
   A. Identification of cocci (most likely *Staphylococcus* spp.) or other bacteria
   B. Identification of the predominant cell type (if any)
   C. Identification of the presence of acantholytic keratinocytes
VI. Response to therapeutic trial
   A. Minimum 21-day course of an antistaphylococcal antibiotic
   B. Treatment for scabies and fleas
VII. Bacterial culture and susceptibility
   A. If no response to appropriate antibiotic therapy is seen
   B. Before prescribing a drug that may be expensive or potentially dangerous
   C. To identify a sterile pustular disease
VIII. Skin biopsy

INFECTIOUS DISEASES

Superficial Staphylococcal Pyoderma and Folliculitis

Definition and Causes

I. They are infections within, or colonization of, the epidermis and hair follicle.
II. In dogs, *Staphylococcus intermedius* is isolated in >90% of the cases.
III. Other causes in dog include the following:
   A. *Staphylococcus aureus*
   B. *Staphylococcus schleiferi* subsp. *schleiferi*
   C. *Staphylococcus schleiferi* subsp. *coagulans*
IV. Staphylococcal pyoderma or folliculitis is very rare in cats.

Pathophysiology

I. *S. intermedius* is a normal inhabitant of the skin and hair coat, oral cavity, ear canal, and mucous membranes of dogs.
II. Colonization of the skin and hair follicles occurs secondary to changes in the cutaneous microclimate that result in conditions favorable to the growth of staphylococci.
III. The most common underlying causes are ectoparasitic infestations, pruritus from allergic dermatoses, and endocrinopathies.

Clinical Signs

I. Pustules: either interfollicular or follicular
II. Papules, erythema, scaling, epidermal collarettes, and/or hyperpigmentation
III. Short-coated dogs: only patchy alopecia
IV. ± Pruritus

Diagnosis

I. History of previous improvement after an appropriate course of antibiotic therapy
II. Compatible or suspicious clinical signs
III. Cytological identification of cocci (possibly with other bacteria) in a sample taken from a pustule, from the underside of a crust, or from the surface a lesion
IV. Bacterial culture of the contents of a pustule or material collected from a collarette
V. Elimination of the condition and a clinical cure after appropriate antibiotic therapy

Differential Diagnosis

I. Demodicosis with secondary staphylococcal pyoderma
II. Dermatophytosis
III. Pemphigus foliaceus

Treatment

I. Any underlying or predisposing factors are treated to maximize the chance of a clinical cure and minimize recurrences.
II. If only a few lesions are seen, then topical therapy alone can be used.

TABLE 88-1

Antibiotics Useful in Treating Canine Bacterial Pyoderma

DRUG	BRAND NAME	DOSE
Amoxicillin/clavulanate	*Clavamox*	13.75 mg/kg PO BID
Cephalexin	Generic forms	22 mg/kg PO BID
Cefadroxil	*CefaTabs*	22 mg/kg PO BID
Cefpodoxime	*Simplicef*	5-10 mg/kg PO SID
Clindamycin	*Antirobe*	5.5-33 mg/kg PO BID or 11 mg/kg PO SID
Difloxacin	*Dicural*	5-10 mg/kg PO SID
Enrofloxacin	*Baytril*	5-20 mg/kg PO SID
Erythromycin	Generic forms	10 mg/kg PO TID
Lincomycin	*Lincocin*	22 mg/kg PO BID or 15.4 mg/kg PO TID
Marbofloxacin	*Zeniquin*	2.75-5.5 mg/kg PO SID
Orbifloxacin	*Orbax*	2.5-7.5 mg/kg PO SID
Oxacillin	Generic forms	22 mg/kg PO TID
Sulfadimethoxine/ormetoprim	*Primor*	Day 1: 55 mg/kg PO SID, then 22 mg/kg PO SID
Trimethoprim/sulfamethoxazole	Generic forms	15 mg/kg PO BID
Trimethoprim/sulfadiazine	*Tribrissen*	15 mg/kg PO BID

A. Clean with an antiseptic shampoo that contains benzoyl peroxide, ethyl lactate, or chlorhexidine SID to QOD for 7 to 14 days.
B. Apply topical antimicrobial ointments or creams that contain mupirocin, neomycin, benzoyl peroxide, or chlorhexidine, SID to BID for 7 to 14 days.

III. If the lesions are widespread or do not improve with topical treatment, then administer systemic antibiotics for a minimum of 21 days (Table 88-1).

Monitoring of Animal

I. Recheck the animal 7 to 14 days after treatment is initiated, and continue therapy for at least 7 days after resolution of all signs.
II. Prognosis for complete resolution of the condition is good, especially if the underlying cause is controlled or eliminated.

Impetigo

Definition and Causes

I. Impetigo is an uncommon superficial bacterial infection of the sparsely haired regions of the body.
II. The lesions are caused almost exclusively by *Staphylococcus* spp.
III. The condition occurs most commonly in puppies and young dogs.
IV. In most cases no specific underlying cause can be identified, but a dirty environment, poor nutrition, and parasitism have been implicated in a few cases.
V. Pathophysiology is unknown.

Clinical Signs

I. Numerous small, nonfollicular papules, pustules, and yellowish crusts are concentrated in the glabrous areas of the inguinal and axillary regions of the body.
II. Lesions are not usually painful or pruritic.

Diagnosis

I. Tentative diagnosis is based on finding nonfollicular papules and pustules in a typical location in a young dog.
II. Cytologic examination of the contents of a pustule demonstrates neutrophils and coccoid bacteria.
III. Histopathologic examination of the skin demonstrates nonfollicular, subcorneal, or intragranular neutrophilic pustules; bacterial cocci may or may not be identified.
IV. Bacterial culture of a sample taken from an intact pustule most commonly grows *Staphylococcus* spp.

Differential Diagnosis

I. Demodicosis with secondary staphylococcal pyoderma
II. Dermatophytosis
III. Pemphigus foliaceus
IV. Flea bite hypersensitivity
V. Subcorneal pustular dermatosis

Treatment

I. Any underlying or predisposing factors are treated to maximize the chance of a clinical cure and to minimize recurrences.
II. If only a few lesions are seen, then topical therapy alone can be used.
A. Clean with an antiseptic shampoo that contains benzoyl peroxide, ethyl lactate, or chlorhexidine SID to QOD for 7 to 14 days.
B. Apply topical antimicrobial ointments or creams that contain mupirocin, neomycin, benzoyl peroxide, or chlorhexidine, SID to BID for 7 to 14 days.

III. If the lesions are widespread or do not improve with topical treatment, then administer systemic antibiotics for at least 21 days (see Table 88-1).

Monitoring of Animal

I. Recheck the animal 7 to 14 days after treatment is initiated and continue therapy for at least 7 days after resolution of the condition.
II. Prognosis for complete resolution of the condition is good.

Skin Fold Pyoderma (Intertrigo)

Definition and Causes

I. Intertrigo is an overgrowth or colonization of skin folds by normal skin bacteria ± yeast.

II. Skin folds develop as normal conformation (i.e., facial folds in brachycephalic breeds; lip folds, tail folds, vulvar folds in other breeds) or from obesity.
III. Moisture, sebum, secretions (tears, saliva) and exfoliated keratinocytes accumulate in these areas, which also have poor air circulation.
IV. Bacterial and yeast overgrowth occurs and leads to inflammation as well as the typical clinical signs.

Clinical Signs

I. ± Alopecia
II. Erythema, papules, maceration
III. Malodor

Diagnosis

I. Tentative diagnosis is based on the location of the lesion (within an area of skin-to-skin contact), particularly in a facial fold, lip fold, vulvar recess, tail fold, axillae, or on the ventral midline.
II. Cutaneous cytological examination demonstrates the presence of bacteria (predominantly cocci) and possibly yeast.
III. Cotton-tipped swabs can be used to sample material from affected areas to prove they are the source of the odor.

Differential Diagnosis

I. Superficial staphylococcal pyoderma
II. Demodicosis
III. Dermatophytosis
IV. *Malassezia* spp. dermatitis

Treatment and Monitoring

I. The fold is eliminated if possible.
   A. This can be accomplished by surgery, particularly with lip, facial, or vulvar recess folds.
   B. Weight reduction helps minimize folds in the axillae and ventral midline.
II. Institute maintenance cleaning every 1 to 3 days with an antiseptic shampoo that contains chlorhexidine, benzoyl peroxide, or ethyl lactate.
III. Apply topical antibiotic or antiseptic ointment, cream or spray that contains mupirocin, neomycin, benzoyl peroxide, or chlorhexidine SID.
IV. Prognosis for improvement is excellent, but the animal may need lifelong topical maintenance therapy if the folds are not removed surgically.

Deep Bacterial Pyoderma and Furunculosis

Definition and Causes

I. Deep bacterial pyoderma and furunculosis are infectious diseases involving the dermis or subcutaneous tissues.
II. They most commonly begin as a superficial staphylococcal pyoderma or folliculitis.
III. Once the hair follicle ruptures, furunculosis occurs, which results in a pyogranulomatous inflammation in the dermis.
IV. These conditions are usually secondary to another underlying condition (e.g., demodicosis, endocrinopathy, dermatophytosis).

Clinical Signs

I. Condition can be focal, multifocal, or generalized.
II. Papules, pustules, alopecia, hemorrhagic bullae, erosions, ulcers, ± crusts are common.
III. Often serosanguineous to purulent material drains from fistulous tracts.
IV. Lesions may be painful or pruritic.
V. Regional lymph nodes are often enlarged.

Diagnosis

I. History and typical physical examination findings
II. Neutrophils and bacteria on cytological examination
III. Dermatohistopathologic findings
   A. Suppurative folliculitis and furunculosis
   B. Bacteria (often difficult to identify)
IV. Bacterial culture identifies the bacterial pathogen or pathogens and aids in the selection of the proper systemic antibiotic.

Differential Diagnosis

I. Deep staphylococcal pyoderma secondary to demodicosis
II. Deep fungal infection
III. Mycobacteriosis
IV. Neoplasia

Treatment

I. Any underlying cause must be identified and treated.
II. Systemic antibiotics (see Table 88-1) are administered for a minimum of 4 weeks or for >2 weeks after complete resolution of clinical signs (often for a total of 6 to 12 weeks).
III. Antiseptic shampoos (e.g., benzoyl peroxide, chlorhexidine, ethyl lactate) are used once to twice weekly to aid in removal of the crusts and exudate, with a minimum contact time of 10 minutes before rinsing.

Monitoring of Animal

I. If the underlying cause can be corrected, then the prognosis for a complete clinical cure is good.
II. When the underlying cause cannot be identified or treated, then the condition usually recurs.
III. Fibrosis, scarring, and permanent alopecia may result.
IV. Some dogs must be treated continuously to keep the condition under control.

Subcutaneous Abscesses and Cellulitis

Definition and Causes

I. A subcutaneous abscess is a collection of inflammatory cells, usually neutrophils, within the subcutaneous tissue.
II. Cellulitis is a diffuse purulent inflammatory reaction within subcutaneous tissues.
III. The most common cause is a bacterial infection, although fungal infections and even sterile processes can cause a similar signs.

Pathophysiology

I. Bacteria are introduced into the subcutaneous tissues either through a breach in the epidermis, as a result of a

wound or injury, or after the rupture of a hair follicle (furunculosis).
II. In addition to *Staphylococcus* spp., other bacteria such as *Pasteurella multocida*, *Escherichia coli*, *Proteus* spp., or *Pseudomonas* spp. can be involved.
III. In some cases the infecting bacteria spread hematogenously to distant sites and organs (e.g., heart, kidneys).

Clinical Signs

I. Painful swelling of the skin
II. ± Draining tracts
III. Erythema and necrosis of overlying skin
IV. ± Pyrexia, anorexia, lethargy

Diagnosis

I. Tentative diagnosis is based on compatible clinical signs.
II. Aspiration and cytologic examination of material from the site demonstrates neutrophils and occasional bacteria.
III. Bacterial culture of material obtained via aspiration yields a positive culture, with one or more organisms.

Differential Diagnosis

I. Neoplasia
II. Sterile nodular panniculitis
III. Subcutaneous fungal or atypical mycobacterial infections

Treatment

I. If an abscess is identified, the abscess is surgically opened to provide drainage.
II. Necrotic tissue is removed, and the cavity is flushed with an antiseptic solution (e.g., chlorhexidine, betadine).
III. Antibiotics are given for a minimum of 14 days.
   A. A broad-spectrum antibiotic such as amoxicillin/clavulanate 15 to 22 mg/kg PO BID is started empirically.
   B. Choice of drug is then based on the results of a bacterial culture and susceptibility testing.

Monitoring of Animal

I. Complete healing of an abscess usually occurs within 2 weeks.
II. The cause of the deep infection (e.g., bite wounds, superficial pyoderma) must be identified and treated to prevent a recurrence.
III. Some lesions heal with a scar.

Dermatophytosis

See Chapter 86.

INFLAMMATORY AND IDIOPATHIC CONDITIONS

Canine Acne

Definition

I. Acne is an uncommon condition in young dogs (3 to 12 months of age) that may arise from abnormal follicular keratinization.
II. It is also known as *muzzle folliculitis* and *furunculosis*, or *chin pyoderma*.
III. It affects predominantly short-haired dogs.

Causes and Pathophysiology

I. An undetermined genetic predisposition followed by local trauma may be the initial cause.
II. Further trauma causes the short hairs to break below the skin surface, leaving the follicle open to bacterial colonization.
III. In some cases the infected follicle ruptures and introduces pieces of hair and skin into the dermis, which leads to furunculosis.

Clinical Signs

I. Lesions are seen most commonly on the chin and lips.
II. The condition is generally not pruritic or painful.
III. Lesions consist of alopecia and follicular papules that become pustular, then enlarge and ulcerate.
IV. Serosanguineous to seropurulent material drains from fistulas.
V. Suppurative folliculitis and furunculosis then develop.

Diagnosis

I. Presumptive diagnosis is based on clinical lesions in a short-haired breed of dog <1 year of age.
II. Cutaneous cytological examination of the contents of a pustule or the exudate from a draining fistula demonstrates neutrophils and bacterial cocci.
III. Definitive diagnosis is made by skin biopsy.
   A. Early lesions may have comedones.
   B. Late lesions have signs of deep pyoderma.
IV. If a bacterial culture is performed, *Staphylococcus* spp. is generally identified, although mixed bacterial infections are possible.

Differential Diagnosis

I. Superficial or deep bacterial pyoderma secondary to demodicosis
II. Dermatophytosis
III. Juvenile cellulitis

Treatment

I. Minimize trauma to the chin.
II. Early lesions are treated with topical antimicrobial shampoos or gels.
   A. The use of products that contain benzoyl peroxide can enhance the removal of debris from the hair follicle and decrease the number of bacteria on the hair coat and skin surface.
   B. Clean the chin or apply the gel SID until the condition is resolved.
   C. Antibacterial ointments that contain mupirocin can be applied SID until the infection is controlled.
III. In many cases, systemic antibiotic therapy is also needed.
   A. If pustules and evidence of secondary staphylococcal folliculitis are present, then antibiotics are given for a minimum of 21 days or >7 days beyond resolution of signs (see Table 88-1).

B. If hair follicles have ruptured and a resultant furunculosis occurs, then antimicrobial medications may be needed for >8 weeks.

IV. Dogs that are severely affected may benefit from topical or systemic glucocorticoids.
   A. Topical triamcinolone is applied SID for 14 days.
   B. Oral prednisone, prednisolone, or methylprednisolone (0.5 mg/kg PO SID) may be given for 7 days, then decreased to the lowest possible dose.

Monitoring of Animal

I. Instruct owners to keep the chin washed as long as there are visible lesions.
II. Antibiotic therapy is continued until the pustules are gone.
III. Most cases heal with scarring.

Feline Acne

Definition and Causes

I. Feline acne an uncommon disorder in cats arising from follicular hyperplasia and follicular keratinization.
II. Pathogenesis is unknown.

Clinical Signs

I. Early lesions consist of comedones, mildly erythematous crusted papules, and pustules on the chin.
II. Lesions may involve the skin adjacent to the upper and lower lips.
III. Lesions progress to nodules as the follicles rupture and lead to furunculosis.
IV. The chin then becomes swollen, with multiple draining fistulae or abscesses.
V. Lesions heal with alopecia and scarring.

Diagnosis

I. Diagnosis is based on the presence of compatible clinical signs and by ruling out other possible conditions.
II. On histopathologic examination, hair follicles are distended with keratin; some may be inflamed or ruptured.

Differential Diagnosis

I. Demodicosis
II. Dermatophytosis
III. *Malassezia* spp. colonization
IV. Facial excoriation associated with methimazole therapy

Treatment and Monitoring

I. Secondary bacterial folliculitis or furunculosis is treated with systemic antibiotics for 2 to 4 weeks.
II. Hair surrounding the lesions is clipped and the skin gently washed with a shampoo that contains benzoyl peroxide or ethyl lactate SID to QOD until the lesion heals (then as needed).
III. Topical antibacterial products such as 2% mupirocin, 0.75% metronidazole gel, or products that contain clindamycin or tetracycline may also be helpful.
IV. In very severe cases, oral vitamin A (8000 IU PO SID) or isotretinoin (2 mg/kg PO SID) may be tried.
V. Prognosis for improvement is good, but affected cats may require lifelong topical therapy.

Juvenile Cellulitis

Definition and Cause

I. Juvenile cellulitis is an uncommon, idiopathic form of panniculitis of young puppies, usually 3 to 16 weeks old.
II. It is most commonly seen in purebred dogs.
III. It has also been called *puppy strangles,* because the submandibular nodes are enlarged and appear to be strangulating the dog.
IV. Pathophysiology is unknown.

Clinical Signs

I. Sudden onset of pustules and discharge occurs on the lips, eyelids, and in the ear canals, as well as on the muzzle.
II. Lesions then fistulate and drain.
III. Submandibular lymphadenopathy is common.
IV. In rare cases, lesions appear on the trunk.
V. Many puppies are febrile, anorexic, and depressed, and some exhibit joint pain.

Diagnosis

I. Presumptive diagnosis is often made from the typical signalment and clinical signs.
II. Cytological examination of contents of pustules or draining lesions reveals pyogranulomatous inflammation, with no organisms.
III. Bacterial culture of an intact lesion yields no growth.
IV. Definitive diagnosis is made by skin biopsy, which demonstrates pyogranulomatous dermatitis and panniculitis.

Differential Diagnosis

I. Demodicosis with secondary bacterial pyoderma
II. Staphylococcal pyoderma

Treatment

I. Any secondary bacterial pyoderma is treated with appropriate systemic antibiotics (see Staphylococcal Pyoderma).
II. Gently wash affected areas SID with an antibacterial shampoo containing chlorhexidine or benzoyl peroxide to remove the crusts and exudate.
III. Give prednisone 2 mg/kg PO SID for 1 to 4 weeks until the condition is controlled, then taper slowly over several weeks.

Monitoring of Animal

I. Prognosis is good.
II. In severe cases, healing may be associated with permanent scarring.

Sterile Eosinophilic Pustulosis

Definition and Cause

I. It is a rare, sterile, superficial, pustular skin disease of dogs.
II. Cause and pathogenesis are unknown.

Clinical Signs

I. No breed, age, or sex predilection has been noted.
II. The disease manifests as an acute onset of multifocal to generalized papules and pustules that are follicular or interfollicular, and result in scaling and epidermal collarettes.
III. Lesions are generally concentrated on the trunk.
IV. Most dogs are pruritic.
V. Occasionally dogs are febrile, anorexic, or have peripheral lymphadenopathy.

Diagnosis

I. Other differential diagnoses are ruled out using appropriate diagnostic tests and therapies.
II. Cytological examination of a pustule reveals primarily eosinophils and occasional neutrophils.
III. Most dogs have circulating eosinophilia on a complete blood count.
IV. Bacterial culture of an intact pustule yields no growth.
V. Definitive diagnosis is made by skin biopsy, which reveals eosinophilic intraepidermal pustules, folliculitis, and (rarely) eosinophilic furunculosis.

Differential Diagnosis

I. Superficial bacterial pyoderma, impetigo, folliculitis
II. Pustular dermatophytosis
III. Demodicosis with secondary staphylococcal pyoderma
IV. Subcorneal pustular dermatosis
V. Pemphigus foliaceus
VI. Drug eruption

Treatment and Monitoring

I. Any secondary bacterial pyoderma is treated with appropriate systemic antibiotics (see Staphylococcal Pyoderma).
II. Prednisone 2 to 4 mg/kg PO SID to BID is given until lesions resolve, then tapered to the lowest effective dose and frequency.
III. Alternatively, dapsone 1 mg/kg PO TID can be used until the lesions resolve, then tapered.
IV. Prognosis is poor, but many dogs can be kept in remission with low doses of these medications.

Subcorneal Pustular Dermatosis

Definition and Cause

I. It is a rare, idiopathic, sterile, pustular dermatosis of dogs.
II. The cause is unknown.
III. The condition has been reported most commonly in the miniature schnauzer.
IV. In some cases the condition is associated with a reaction to shampoos.

Clinical Signs

I. It is a multifocal to generalized pustular disease primarily involving the head and trunk.
II. Secondary erythema, crusting, scaling, alopecia, and epidermal collarettes can be seen.
III. Systemic signs are rare.

Diagnosis

I. Tentative diagnosis is based on compatible clinical signs.
II. Carefully performed bacterial cultures of the contents of an intact pustule are usually negative, although a few colonies of nonpathogenic bacteria can occasionally be isolated.
III. Definitive diagnosis is made by skin biopsy, which reveals subcorneal pustular dermatitis without acantholysis.

Differential Diagnosis

I. Staphylococcal pyoderma, impetigo, folliculitis
II. Pemphigus foliaceus
III. Sterile eosinophilic pustulosis
IV. Autoimmune dermatoses: particularly pemphigus foliaceus, systemic lupus erythematosus

Treatment and Monitoring

I. The condition is poorly responsive to antibiotics or glucocorticoid therapy, which helps support a tentative diagnosis.
II. Dapsone is the therapy of choice.
   A. Dogs are given 1 mg/kg PO TID for 2 to 4 weeks.
   B. Once lesions resolve, the dose is tapered to the lowest effective dose and frequency.
   C. In some cases, therapy can be discontinued.
III. If no response occurs with dapsone, then treatment with high doses of oral corticosteroids may be effective (see Chapter 91).
IV. Prognosis is good if the animal responds to treatment with dapsone.

Contact Dermatitis

See Chapter 85.

PARASITIC DISORDERS

Demodicosis

See Chapter 86.

Sarcoptic Mange

See Chapter 85.

Flea Bite Hypersensitivity

See Chapter 85.

Mosquito Bite Hypersensitivity

Definition and Causes

I. It is a rare, seasonal condition of cats that have been sensitized to the bite of a mosquito.
II. Cats with dark hair on the pinnae or face may be at increased risk, because the pigment may act as an attractant for mosquitoes.
III. Thinly haired regions of the pinnae, face, and footpads may be more easily accessible to mosquitoes.
IV. Reaction may be both an immediate and a delayed hypersensitivity.

Clinical Signs

I. Papules, pustules, crusts, and erosions are concentrated on the haired portion of the dorsal muzzle and occasionally on the outer pinnae.
II. Occasionally the margins of the footpads are involved and can be swollen, crusted, fissured, or ulcerated.
III. Cats exhibit mild to severe pruritus.
IV. In advanced cases the muzzle can be swollen and alopecia develops, with or without nodules and pigmentary changes to the skin (hyperpigmentation and hypopigmentation).
V. Peripheral lymphadenopathy is variable.

Diagnosis

I. Tentative diagnosis is based on the history of dermatitis in a compatible location that coincides with the mosquito season.
II. Lesions should resolve when the cat is confined to a mosquito-free environment for 1 week.
III. Peripheral eosinophilia is common.
IV. Dermatohistopathologic examination helps rule out other differential diagnoses, but the findings are often nondiagnostic.
   A. Hyperplastic, superficial to diffuse perivascular dermatitis with eosinophils is seen.
   B. In some cases, eosinophils are found in the wall of the hair follicle and can even lead to eosinophilic furunculosis.

Differential Diagnosis

I. Adverse reaction to food
II. Dermatophytosis
III. Cutaneous herpesvirus dermatitis
IV. Autoimmune dermatoses: particularly pemphigus foliaceus
V. Flea bite hypersensitivity

Treatment

I. Cats are confined to a mosquito-free environment, particularly at dawn and dusk when mosquitoes are most active.
II. Water-based pyrethrin sprays are applied topically SID to the affected areas in an effort to repel mosquitoes.
III. If the cat is very pruritic or the lesions are very extensive, then prednisone 3 to 5 mg/kg PO SID for 1 to 3 weeks may be used, then tapered.
IV. Methylprednisolone acetate can be administered at 20 mg IM every 2 to 4 weeks, as needed during the mosquito season (for cats that cannot be medicated orally).

Monitoring of Animal

I. Prognosis for healing is good, but permanent scarring is possible.
II. The condition is likely to return in subsequent years unless the cat is confined to a mosquito-free environment or a mosquito repellent is applied daily.

IMMUNE-MEDIATED DERMATOSES

Pemphigus Foliaceus

See Chapter 91.

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CHAPTER 89

Nodular Dermatoses

Stephen L. Lemarie

GENERAL APPROACH TO NODULAR DERMATOSES

Definition and Causes

I. A nodule is a circumscribed, solid, cystic or edematous elevation >1 cm in diameter that usually extends into the deeper layers of the skin (subcutis, panniculus, muscle).
II. Causes are numerous.
  A. Bacterial infections
  B. Fungal infections
  C. Parasitic infections
  D. Noninfectious inflammation
  E. Neoplasia

Pathophysiology

I. Cellular infiltrates may be inflammatory, reactive, and/or neoplastic.
II. Disruption of the overlying epidermis frequently occurs as a result of inflammation or ischemia.

Clinical Signs

I. Nodule consistency: firm, cystic, edematous
II. Nodule integrity: ulcerated, eroded, fistula
III. Depth of disease: dermal, subcutis, panniculus, muscle
IV. Distribution: solitary, multiple, generalized, mucous membrane involvement

Diagnosis

I. Cytology: draining tract exudates, fine-needle aspirate
II. Biopsy: multiple lesions, complete intact nodules
III. Culture and sensitivity: entire nodule or full-thickness section of lesion

Differential Diagnosis

See Box 89-1.

Treatment and Monitoring

I. Treatment is based on a complete diagnostic evaluation that establishes a definitive diagnosis.
II. Prognosis and monitoring is dependent on the diagnosis.
III. Monitoring considerations include whether the lesion is localized or systemic, the presence of any concurrent immunosuppressive disease, and potential for side effects from medical therapy.

Box 89-1

Differential Diagnosis for Nodular Dermatoses

Bacterial Infections

Staphylococcal furunculosis: see Chapter 86
Mycobacterial infections
Botryomycosis
Actinomyces spp. and *Nocardia* spp. infections

Fungal Infections

Dermatophytic granuloma: see Chapters 86 and 88
Blastomycosis
Histoplasmosis
Cryptococcosis
Coccidioidomycosis
Sporotrichosis

Miscellaneous Infections

Pythiosis
Protothecosis

Parasites

Demodicosis-related furunculosis: see Chapter 86
Leishmaniasis

Noninfectious Inflammation

Sterile eosinophilic pustolosis: see Chapter 88
Sterile nodular panniculitis
Xanthoma
Calcinosis cutis
Calcinosis circumscripta
Sterile nodular granuloma and pyogranuloma
Juvenile cellulitis: see Chapter 88
Nodular dermatofibrosis
Vasculitis: see Chapter 91

Neoplasia

Mast cell tumor
Others: see Tables 89-3, 89-4, 89-5

INFECTIOUS DISORDERS

Botryomycosis

Definition and Causes

I. Botryomycosis is an uncommon skin infection of dogs and cats in which bacterial organisms form macroscopic or microscopic tissue grains.
II. The causative organism is usually *Staphylococcus* spp., but occasionally other bacteria (*Streptococcus* spp., *Pseudomonas* spp., or *Proteus* spp.) are isolated.
III. Infections are associated with a presumed immunologic reaction to nonbranching bacteria and may be sequela to a penetrating injury or bite wound.

Clinical Signs

I. Single to multiple, firm, nonpainful, and typically nonpruritic nodules are seen.
II. Nodules may be fistulated.
III. Purulent discharge may contain white granules or grains.

Diagnosis

I. Cytological examination of exudates reveals suppurative inflammation (with or without granules) containing dense bacterial colonies.
II. Dermatohistopathologic examination reveals pyogranulomatous inflammation of the dermis that may extend into the superficial and deeper subcuticular areas.
III. Within pyogranulomas are discrete accumulations of bacteria that are imbedded in brightly eosinophilic material compatible with a Splendore-Hoeppli reaction (presumed to consist of antigen-antibody complexes).
IV. Bacterial culture of tissue and/or exudates with tissue grains yields the causative agent.

Differential Diagnosis

I. Actinomycosis, nocardiosis
II. Foreign-body reaction
III. Systemic mycoses
IV. Neoplasia
V. Atypical mycobacteriosis

Treatment

I. Surgical excision of nodules is performed.
II. Long-term antibiotic therapy (4 to 8 weeks) is based on culture and sensitivity results.
III. In most cases, antibiotic therapy alone is not effective.
IV. Prognosis is good with combined medical and surgical therapy.

Actinomycosis and Nocardiosis

Definition and Causes

I. Actinomycosis and nocardiosis are uncommon cutaneous and subcutaneous (and sometimes systemic) diseases of the dog and cat.
II. *Actinomyces* spp. are gram-positive, non–acid-fast, filamentous, anaerobic, and microaerophilic rods.
III. *Actinomyces* spp. are commensal inhabitants of the oral cavity and gastrointestinal tract of many mammals and may exist as saprophytes.
IV. *Nocardia* spp. are gram-positive, partially acid-fast, filamentous, aerobic, rods that are common saprophytes.

Pathophysiology

I. Infections are typically a result of wound contamination or inoculation of the agents into tissue.
II. Highest incidence is in outdoor dogs and cats, especially hunting dogs.
III. Disease is more common in immunosuppressed animals.

Clinical Signs

I. History of previous bite wounds or penetrating injury is common.
II. Clinical signs include solitary to multiple, intact or ulcerated dermal and subcutaneous nodules, cellulitis, fistulous tracts, and abscess formation.
III. Drainage can be serosanguineous to purulent.
  A. Tissue grains are most common with actinomycosis.
  B. *Nocardia asteroides,* the most common agent of nocardiosis, typically does not produce tissue grains.
IV. Lesions of actinomycosis are commonly present in the cervical, mandibular, and submandibular areas.
V. Lesions of nocardiosis typically occur on the feet, limbs, and trunk.

Diagnosis

I. Cytological examination of actinomyces exudate or aspirate
  A. Neutrophilic to pyogranulomatous inflammation
  B. Individual or aggregates of gram-positive, non–acid-fast, beaded, filamentous organisms with occasional branching
II. Cytological examination of nocardiosis exudate or aspirate
  A. Neutrophilic to pyogranulomatous inflammation
  B. Individual or aggregates of gram-positive, partially acid-fast, beaded, branching filamentous organisms
III. Histopathologic examination
  A. Deep punch or wedge biopsy of nodules or fistulous tracts is recommended.
  B. Pyogranulomatous inflammation with aggregates of bacterial organisms is usually detected.
  C. Special stains can be requested to help identify organisms.
IV. Bacterial culture and sensitivity
  A. Aerobic and anaerobic cultures are submitted.
  B. Organisms are often difficult to grow.

Differential Diagnosis

I. Atypical mycobacterial infection
II. Systemic mycoses
III. Opportunistic fungal infection
IV. Neoplasia

Treatment

I. Surgical excision and debulking of diseased tissue
II. Long-term antibiotics based on culture and sensitivity, if possible
  A. Actinomycosis
    1. Penicillin G (PO, SC, IM, IV) or penicillin V (PO) at ≥60,000 U/kg TID
    2. Minocycline 5 to 25 mg/kg IV, PO BID
    3. Clindamycin 5 mg/kg SC BID
    4. Amoxicillin 20 to 40 mg/kg IM, SC, PO QID
    5. Erythromycin 10 mg/kg PO TID
  B. Nocardiosis
    1. Sulfadiazine 80 mg/kg PO TID or 110 mg/kg PO BID
    2. Sulfamethazine 50 mg/kg PO TID
    3. Sulfisoxazole 50 mg/kg PO TID
    4. Trimethoprim-sulfadiazine 15 to 30 mg/kg PO, SC BID
    5. Ampicillin 20 to 40 mg/kg IV, IM, SC, PO QID
    6. Erythromycin 10 mg/kg PO TID
    7. Minocycline 5 to 25 mg/kg PO, IV BID

Monitoring of Animal

I. Prognosis for cure with both diseases is guarded.
II. Animals that are systemically ill are also evaluated for systemic disease.

Atypical Mycobacteriosis

Definition and Causes

I. Atypical mycobacteriosis is an uncommon nodular disease of dogs and cats caused by fast-growing, saprophytic mycobacteria present in the environment that are inoculated in the dermis and panniculus by trauma or contamination of a wound.
II. It is most often associated with infections of Runyon group IV mycobacteria.
  A. *Mycobacterium fortuitum*, *M. phlei*, *M. smegmatis*, *M. chelonei*
  B. Nonchromogenic, rapidly growing, gram-positive, acid-fast, aerobic, non–spore-forming bacilli
III. Group IV mycobacteria are ubiquitous in nature.

Pathophysiology

I. Cats appear to be more susceptible to the development of mycobacterial skin infections than other animals.
II. History of trauma is usually reported before the onset of clinical disease.
III. Rapidly growing atypical mycobacteria are rare causes of skin disease in dogs.

Clinical Signs

I. In the cat, skin lesions are most commonly found over the ventral abdomen and inguinal fat pads.
  A. Lesions are characterized by chronic or recurrent fistulous tracts and ulcers, as well as purpuric macules and nodules that ulcerate.
  B. Underlying adipose tissue is thickened, firm, and nodular on palpation.
  C. In some cases large cutaneous lesions are present that migrate along fascial planes.
  D. Most cats are unaffected systemically, and disseminated disease is rare.
II. Lesions in dogs are usually associated with trauma or fight wounds.
  A. Lesions are characterized by recurrent abscesses, draining tracts, and nonpainful subcutaneous nodules that ulcerate and drain.
  B. Prognosis for remission with medical and surgical intervention is better for dogs than cats.
  C. Pulmonary and disseminated disease associated with atypical mycobacteria (without cutaneous involvement) can occur in the dog.

Diagnosis

I. Submission of deep wedge biopsies for culture is necessary for diagnosis.
  A. Because of the low number of organisms usually present in the lesions, the need to repeat biopsies several times is not uncommon.
  B. When possible, intact nodules are selected for biopsy.
  C. Special culture media are requested.
  D. Dehiscence of the biopsy area is not uncommon.
II. *Mycobacterium fortuitum* is most commonly isolated, followed by *M. smegmatis*, *M. phlei*, and *M. chelonei*.
III. Cultures of exudate from draining lesions are typically negative.
IV. Cytological examination of exudate from lesions reveals pyogranulomatous inflammation, and organisms are rarely seen.
V. Tissue samples that include adipose tissue are submitted for culture and sensitivity testing and histopathology.
VI. Histopathologic findings consist of varying degrees of granuloma formation, pyogranulomatous dermatitis, cellulitis, and panniculitis.
VII. Acid-fast bacteria are observed in approximately 50% of cases and are usually present extracellularly in clear vacuoles surrounded by a rim of neutrophils (Greene, 1998).

Differential Diagnosis

I. Nocardiosis, actinomycosis
II. Systemic mycoses
III. Neoplasia

Treatment

I. Treatment is based on culture and sensitivity results.
II. Antibiotic treatment is typically prolonged; some animals are never cured and relapse once antibiotics are discontinued.
III. Fluoroquinolones and clarithromycin are the best choices for empiric treatment while culture and sensitivity results are pending.
  A. Higher than normal doses have been recommended for fluoroquinolones (10 to 20 mg/kg PO/day), although

caution must be exercised when administering enrofloxacin to cats (doses >5 mg/kg/day have been associated with blindness).
   B. Clarithromycin can be administered at 5 to 15 mg/kg PO BID.
IV. Wide surgical excision of lesions is helpful, although wound dehiscence is common if all affected tissue is not removed.

Canine Leproid Granuloma Syndrome

Definition and Causes

I. It is a poorly characterized mycobacterial disease of dogs in which nodular mycobacterial granulomas are present in the skin and subcutis.
II. The cause is an unidentified mycobacterial organism.

Pathophysiology

I. Pathogenesis is unknown; however, it has been speculated that biting flies may be responsible for inoculating mycobacteria into the skin of susceptible dogs.
II. The syndrome occurs most commonly in New South Wales, Australia, although worldwide distribution is likely.
III. The disease is most common in short-haired breeds, boxers, or boxer-cross dogs.

Clinical Signs

I. Single or multiple firm nodules are present that may ulcerate.
II. Nodules are not painful and are found most often on the head and dorsal surface of the pinnae.
III. Nodules may also occur on the distal limbs and trunk.
IV. Affected dogs are not systemically ill, and internal organ or lymph node involvement is not a feature of the syndrome.

Diagnosis

I. Diagnosis is made by submitting nodules for histopathology.
II. Organisms are infrequently identified on cytological examination of material collected by fine-needle aspiration of the nodules.
III. Lesions contain variable numbers of acid-fast bacilli surrounded by granulomatous inflammation.
IV. Culture and sensitivity of affected tissue should be attempted, but no mycobacterial organisms have been isolated to date.

Differential Diagnosis

I. Bacterial granulomas
II. Systemic mycoses
III. Neoplasia

Treatment and Monitoring

I. Favorable response to treatment with doxycycline or amoxicillin-clavulanate has been reported.
II. Some dogs have demonstrated spontaneous resolution of the nodules.
III. A small number of dogs develop chronic lesions despite treatment.
IV. Prognosis is usually good, with lesions typically regressing within 3 to 4 weeks.

Systemic Mycoses

Definition

I. Systemic mycoses with cutaneous manifestations include blastomycosis, histoplasmosis, coccidioidomycosis, and cryptococcosis.
II. Nodular lesions are a common cutaneous manifestation of systemic mycoses.

Causes

I. Blastomycosis is a systemic mycotic infection affecting numerous organ systems caused by *Blastomyces dermatitidis* (see Chapter 111).
II. Histoplasmosis is caused by the soilborne, dimorphic fungus *Histoplasma capsulatum*.
III. Coccidioidomycosis is caused by the soilborne fungus *Coccidioides immitis*.
IV. Cryptococcosis in dogs and cats is caused by *Cryptococcus neoformans*.

Pathophysiology

I. Blastomycosis
   A. Primary mode of infection is inhalation of spores from mycelial growth.
   B. Large-breed male dogs are most commonly infected; cats are rarely infected.
II. Histoplasmosis
   A. Free-living mycelial stage produces microconidia that are infective.
   B. Inhalation of the microconidia is the likely route of infection.
III. Coccidioidomycosis: inhalation of arthroconidia
IV. Cryptococcosis: inhalation of airborne organisms most likely route

Clinical Signs

I. Blastomycosis
   A. Cutaneous disease occurs in up to 40% of dogs (Greene, 1998).
   B. Lesions include intact or ulcerated nodules and plaques, subcutaneous abscesses, draining tracts, and large firm papules.
   C. Multiple lesions are usually present and can occur anywhere, although the face, nasal planum, and digits are commonly affected.
   D. Cats have similar lesions, with the digits and footpads most often affected.
II. Histoplasmosis
   A. Cats are a susceptible host, and most cases occur in cats <4 years of age.
      1. Skin disease is uncommon, but lesions are usually multiple and occur anywhere on the body.
      2. Lesions consist of draining tracts, papules, ulcers, and nodules.

3. The face, nose, and pinnae may be more commonly affected.

B. Most affected dogs are <4 years of age, and skin lesions are similar to those in cats.

III. Coccidioidomycosis
A. Skin lesions in dogs are usually multiple and almost always occur over bony prominences.
B. Lesions typically consist of nodules, papules, ulcers, draining tracts, and abscesses.
C. Lesions in cats consist of nodules, subcutaneous granulomas, draining tracts, and abscesses.
D. Skin lesions are the most frequent type of infection in cats and occur with or without underlying bony involvement.

IV. Cryptococcosis
A. Skin or subcutaneous lesions are present in up to 50% of feline cases (Greene, 1998).
1. Cutaneous lesions commonly consist of multiple papules to nodules of varying sizes, as well as abscesses, ulcers, and draining tracts.
2. Skin lesions are most common on the face, pinnae, and paws.
3. Nasal lesions are common and classically are firm to boggy swellings over the bridge of the nose or fleshly polypoid masses in the nostril.

B. In general, cryptococcosis is an uncommon disease in the dog; only 20% of cases have skin lesions (Greene, 1998).
1. Skin lesions may consist of abscesses, nodules, papules, ulcers, and draining tracts.
2. Lesions of the tongue, gums, and hard palate may also occur.

Diagnosis

I. Cytological and histopathologic examination of nodules show pyogranulomatous inflammation.
II. Blastomycosis organisms are round to oval yeast structures measuring 5 to 20 µm in diameter that demonstrate broad-based budding and have a thick refractile, double-contoured cell wall.
III. Histoplasmosis organisms are round yeast 2 to 4 µm in diameter that are often contained within macrophages.
IV. Coccidioidomycosis organisms can have two forms.
A. The spherule form is 20 to 200 µm in diameter, and the endospore form is 2 to 5 µm in diameter.
B. Spherules are often found in exudate from draining skin lesions.
V. Cryptococcosis organisms are round to elliptical organisms 2 to 20 µm in diameter that display narrow-based budding and have a thick, clear or refractile halo.
VI. For a discussion of serological testing for the systemic mycoses, see Chapters 2 and 111.

Differential Diagnosis

I. Neoplasia
II. Mycobacterial infection
III. Actinomycosis, nocardiosis

Treatment and Monitoring

I. See Table 89-1.
II. Treatment duration may be >6 months, and prognosis for some systemic mycoses is guarded.

Sporotrichosis

Definition and Causes

I. Sporotrichosis is a subcutaneous nodular dermatosis caused by a dimorphic fungus.
II. The causative agent, *Sporothrix schenckii*, exists as a saprophyte in soil and organic matter.

Pathophysiology

I. The organism has a worldwide distribution.
II. In most cases, sporotrichosis is acquired via inoculation of the organism into tissues.
III. Sporotrichosis can occur in three forms: cutaneous, cutaneolymphatic, and disseminated.
IV. More than one form may be present in an individual.

Clinical Signs

I. Skin lesions in dogs with the cutaneous form consist of multiple firm nodules and plaques.
A. Lesions favor the head, pinnae, and trunk but can occur anywhere.
B. Nodules may ulcerate and form draining tracts.
C. The cutaneolymphatic form arises as a nodule on a distal limb, with subsequent ascending infection via lymphatics.
D. Secondary nodules associated with regional lymph nodes may develop.

II. In cats, skin lesions consist of draining puncture wounds, abscesses, and cellulitis.
A. Lesions are often found on the head, distal limbs, and base of tail, and they are sometimes associated with fight wounds.
B. Lesions may become very exudative, with crusting, progressive ulceration, and necrosis that affect the underlying soft tissues.
C. Autoinoculation associated with grooming behavior can result in the development of additional lesions.

Diagnosis

I. Diagnosis can be made by cytological or histological identification of the organism.
II. Large numbers of organisms are usually present in the exudate of lesions from cats, but very low numbers of organisms are retrieved from canine lesions.
III. Organisms are cigar shaped, round or oval, measure 2 to 10 µm, and are found extracellularly or within phagocytic cells.
IV. Tissue may be submitted for culture.
V. In dogs, fluorescent antibody tests are helpful in establishing a diagnosis when the organism is not detected and fungal cultures are negative.

TABLE 89-1

Antifungal Therapies for Selected Deep Fungal Diseases in the Dog and Cat

	DRUG	SPECIES	DOSE (mg/kg)	ROUTE	INTERVAL	DURATION
Blastomycosis						
	Itraconazole	Dog	5	PO	SID	60 days
		Cat	5	PO	BID	60 days
	Fluconazole	Dog	5	PO	BID	60 days
	Amphotericin lipid complex	Dog	1	IV	3 times/week	Stopped when cumulative dose reaches 12 mg/kg
	Amphotericin	Cat	0.25	IV	3 times/week	Stopped if azotemia occurs or cumulative dose reaches 4 mg/ kg
		Dog	0.5	IV	3 times/week	Stopped if azotemia occurs or cumulative dose reaches 4-6 mg/ kg, then imidazole started Stopped when cumulative dose is 8-10 mg/kg if given alone
Coccidioidomycosis						
	Ketoconazole	Dog	5-10	PO	BID	8-12 months
		Cat	50 mg/dose	PO	SID-BID	12 months
	Itraconazole	Dog	5	PO	BID	12 months
		Cat	25-50 mg/dose	PO	SID-BID	12 months
	Fluconazole	Dog	5	PO	BID	12 months
		Cat	25-50 mg/dose	PO	SID-BID	12 months
	Amphotericin	Dog	0.4-0.5	IV	every 48-72 hrs	Until cumulative dose of 8-11 mg/kg reached
	Lufenuron	Dog	5	PO	SID	4 months
Cryptococcosis						
	Flucytosine	Cat	30	PO	QID	1-9 months *or*
			50	PO	TID	1-9 months *or*
			75	PO	BID	1-9 months
		Dog	50-75	PO	TID	1-12 months
	Amphotericin (deoxycholate)	Cat	0.1-0.5	IV	3 times/week	Until cumulative dose of 4-10 mg/kg reached
		Dog	0.25-0.5	IV	3 times/week	Until cumulative dose of 4-10 mg/kg reached
	Amphotericin (lipid complex)	Cat	0.5-0.8	SC	3 times/week	Each dose added to 400 mL of 0.45% saline, 2.5% dextrose to total cumulative dose of 8-26 mg/kg
		Dog	1	IV	3 times/week	With lipid complex drug, individual dose and cumulative dose may be increased until cumulative dose of 8-12 mg reached
	Ketoconazole	Cat	5-10	PO	BID	6-10 months *or*
			10-20	PO	SID	6-10 months
		Dog	5-15	PO	BID	6-10 months *or*
			30	PO	SID	6-10 months
	Itraconazole	Cat	5-10	PO	BID	6-10 months *or*
			10-20	PO	SID	6-10 months
	Fluconazole	Dog, cat	5-15	PO	SID-BID	6-10 months

TABLE 89-1

Antifungal Therapies for Selected Deep Fungal Diseases in the Dog and Cat—*cont'd*

DRUG	SPECIES	DOSE (mg/kg)	ROUTE	INTERVAL	DURATION
Histoplasmosis					
Itraconazole	Dog, cat	10	PO	SID-BID	4-6 months
Fluconazole	Dog, cat	2.5-5	PO	SID-BID	4-6 months
Amphotericin	Dog, cat	0.25-0.5	IV	QOD	Continued until cumulative dose of 5-10 mg/kg reached in dogs and 4-8 mg/kg in cats
Sporotrichosis					
SSKI (potassium iodide)	Dog	40	PO	TID	>2 mo
	Cat	20	PO	BID	>2 mo
Ketoconazole	Dog	5-15	PO	BID	>2 mo
	Cat	5-10	PO	BID	>2 mo
Itraconazole	Dog	5-10	PO	SID-BID	>2 mo
	Cat	5-10	PO	SID-BID	>2 mo

Differential Diagnosis

I. Systemic mycoses
II. Neoplasia
III. Mycobacterial disease
IV. Actinomycosis, nocardiosis

Treatment and Monitoring

I. See Box 89-1.
II. Treatment duration may be >6 months, and prognosis is guarded.
III. Because of the zoonotic potential of this organism, all individuals handling possible cases should wear gloves and properly dispose of contaminated material.

MISCELLANEOUS NODULAR DISEASES

See Table 89-2.

NEOPLASIA

Mast Cell Tumor

Definition and Causes

I. Mast cell tumors (MCTs) are malignant tumors that are the most common skin tumor of dogs and the second most common tumor of cats.
II. The etiology is unknown.
III. Researchers have proposed a viral etiology because many dogs with MCT have genetic mutations in c-kit, which may be responsible for the genesis and/or progression of MCT.

Clinical Signs

I. Most often reported in middle-aged to older animals
   A. It is occasionally found in dogs as young as 4 months.
   B. Breeds with a predilection include the boxer, Boston terrier, bull terrier, bull mastiff, Staffordshire bull terrier, fox terrier, English bulldog, dachshund, Labrador retriever, golden retriever, beagle, pug, Chinese shar-pei, Rhodesian ridge back, and Weimaraner.
   C. Siamese cats are predisposed.
II. All canine cutaneous MCTs are considered potentially malignant.
   A. Tumors are generally alopecic, erythematous, edematous nodules that vary in size from several millimeters to several centimeters.
   B. Lesions are common on the trunk, head, and extremities.
   C. Lesions on distal extremities and lips may occur as poorly defined areas of swelling.
   D. Massive degranulation of neoplastic mast cells may occasionally occur, resulting in generalized edema, altered coagulation, severe hypotension, and/or terminal hemorrhagic gastroenteritis.
III. MCTs in cats are usually discrete, firm, tan, alopecic papules and nodules, ranging in size from a few millimeters to 2 cm.
   A. Head, legs, upper thighs, and the dorsal tail are the most common areas affected.
   B. Most MCTs in cats are benign neoplasms, with low local recurrence rates.
   C. Atypical, poorly granulated MCTs sometimes recur as multiple miliary nodules that eventually regress spontaneously.
   D. Rarely, numerous and widespread papular to small nodular cutaneous MCTs arise from cutaneous spread of primary visceral mast cell neoplasia.

Diagnosis

I. Cytological examination
   A. Neoplastic round cells with eccentrically placed nuclei and abundant metachromatic cytoplasmic granules

TABLE 89-2

Miscellaneous Nodular Diseases

DISEASE/DEFINITION	SIGNALMENT/PATHOGENESIS	CLINICAL PRESENTATION	DIAGNOSIS	TREATMENT/PROGNOSIS
Leishmaniasis is a protozoal infection caused by numerous *Leishmania* spp.	Occurs in dogs and cats Rodents, other domestic and wild mammals can serve as reservoirs for disease Transmitted by sandflies *Phlebotomus* (Old World) and *Lutzomyia* (New World)	Clinical presentation includes the following: exfoliative dermatitis and silvery scale, nodular and pustular dermatitis, nasal and digital hyperkeratosis Numerous organ systems can be affected	Definitive diagnosis is by cytologic or histologic identification of amastigotes from lymph nodes or bone marrow ELISA, complement fixation, and indirect fluorescent antibody tests are available but do not confirm active disease PCR assays are also available	Meglumine antimonate 20-50 mg/kg SC BID or 200-300 mg/kg IV QOD Allopurinol 11-15 mg/kg PO SID Combination therapy may improve clinical response rates Prognosis is poor for cure Public health hazard often results in euthanasia of animal
Pythiosis is caused by an aquatic pathogen, *Pythium insidiosum*, a member of the class of Oomycetes	Disease occurs in dogs and rarely in cats Infection occurs after exposure and/or consumption of water contaminated with motile flagellate zoospores Most common in wet tropical and subtropical climates	Three forms of disease have been described: subcutaneous, nasopharyngeal, gastrointestinal Cutaneous lesions occur on the limbs of dogs and the trunk or back of cats Lesions consist of soft, boggy proliferative nodules that ulcerate and form draining tracts	Cytology: macerated tissue in 10% KOH sometimes reveals poorly septate, wide and branching hyphae Histopathology: pyogranulomatous dermatitis with eosinophils and hyphae Other tests: culture of affected tissues and ELISA serology	Early and complete surgical removal of affected tissue can be curative Therapy with antifungal agents is usually unsuccessful Prognosis is poor
Protothecosis is a saprophytic, achlorophyllous algae	Rare in dogs and cats Highest incidence reported in immunosuppressed animals Infection occurs via the gastrointestinal tract or through contact with injured skin	*Cats:* large, firm cutaneous nodules common over the distal extremities, head, and base of the tail *Dogs:* disseminated disease with multiorgan involvement, skin lesions consisting of nodules and draining tracts over the extremities, and mucocutaneous junctions	Cytology: pyogranulomatous inflammation with spherules that often contain endospores Histopathology: nodular to diffuse pyogranulomatous inflammation with large numbers of organisms	Wide surgical excision is done for localized lesions Systemic antifungal treatments are usually ineffective Prognosis is poor if the disease is disseminated or lesions are not resectable

ELISA, Enzyme-linked immunosorbent assay; *PCR,* polymerase chain reaction; *KOH,* potassium hydroxide.

TABLE 89-2

Miscellaneous Nodular Diseases—*cont'd*

DISEASE/DEFINITION	SIGNALMENT/PATHOGENESIS	CLINICAL PRESENTATION	DIAGNOSIS	TREATMENT/PROGNOSIS
Sterile nodular panniculitis is an idiopathic inflammatory disease of subcutaneous fat	Rare in dogs and cats Dachshunds and poodles may be predisposed	The trunk is most commonly affected, with deep cutaneous nodules Lesions may become cystic, ulcerate, and develop draining tracts Animals with multiple lesions may exhibit anorexia, lethargy, and pyrexia	Excisional biopsy: suppurative, pyogranulomatous, granulomatous, eosinophilic, necrotizing or fibrosing, septal or diffuse panniculitis Negative cultures for bacteria, mycobacteria, and fungi are supportive	Excision of a solitary lesion is performed Multiple lesions: tetracycline and niacinamide at 500 mg PO TID of each drug for dogs >10 kg or 250 mg PO TID of each drug for dogs <10 kg; cyclosporine 5 mg/kg PO SID until resolution, then tapered Severe or refractory cases: prednisone 2 mg/kg PO SID (dogs) or 4 mg/kg PO SID (cats) until resolution, then tapered Prognosis is good
Xanthoma is a benign granulomatous lesion associated with an abnormality in lipid metabolism	Causes in cats include hereditary hyperlipoproteinemia, idiopathic forms, feeding high-fat foods and/or treats, and diabetes mellitus	Condition consists of multiple whitish or yellow papules, and nodules or plaques that may be ulcerated Head, distal extremities, feet, and bony prominences are typically affected	Histopathology: nodular to diffuse infiltration of foamy macrophages and variable numbers of multinucleate histiocytic giant cells	Lesions resolve with resolution of underlying disease Low-fat diets are fed to cats with hypertriglyceridemia
Calcinosis circumscripta is a focal area of dystrophic calcification that occurs at sites of repetitive or previous trauma	Uncommon in dogs Highest incidence in young, large-breed dogs Described in association with hypertrophic osteodystrophy and polyarthritis Very rare in cats	Single, firm, haired or alopecic dome-shaped subcutaneous or deep dermal masses are seen that may ulcerate and discharge a white, gritty substance Elbows, metatarsal, and phalangeal areas are commonly affected	Cytology: amorphous, gritty white material Histopathology: multifocal accumulations of finely or coarsely granular, amorphous, basophilic debris in the deep dermal or subcutaneous tissue that is surrounded by granulomatous inflammation	Complete surgical excision is curative Resolution of associated disease may cause lesions to diminish Prognosis is good

Continued

TABLE 89-2

Miscellaneous Nodular Diseases—*cont'd*

DISEASE/DEFINITION	SIGNALMENT/PATHOGENESIS	CLINICAL PRESENTATION	DIAGNOSIS	TREATMENT/PROGNOSIS
Sterile granuloma and pyogranuloma are probably immune-mediated, but the exact pathogenesis is unknown	Uncommon in dogs Highest incidence in the collie, golden retriever, boxer, and other large, short-haired breeds	Nonpainful, nonpruritic firm dermal papules and nodules are seen that may become alopecic or ulcerated Most common location is over the muzzle, periocular areas, ear, pinnae, and feet	Cytology: pyogranulomatous inflammation with no microorganisms Histopathology: nodular to diffuse pyogranulomatous dermatitis Negative fungal, bacterial and mycobacterial cultures are supportive	Excision of solitary lesions Prednisone 1-2 mg/kg PO BID, then tapered Tetracycline and niacinamide 500 mg PO TID of each drug for dogs >10 kg or 250 mg TID for dogs <10 kg Azathioprine 2 mg/kg PO SID, then 2 mg/kg PO QOD for maintenance Prognosis is good, although continuous therapy is needed for some dogs
Nodular dermatofibrosis is associated with renal cystic disease and uterine leiomyomas	Rare in dogs Highest incidence in middle-aged to older German shepherd dogs It may have an autosomal dominant mode of inheritance	Sudden appearance of multiple firm, well-circumscribed nodules up to 4 cm Most common location is the limbs, head, and ears Skin disease can precede clinical signs of underlying cause by months to years	Histopathology: circumscribed dermal or subcutaneous mass composed of structurally normal collagenous bundles Radiography, ultrasonography or exploratory laparotomy may be needed to diagnose underlying renal or uterine disease	Removal of skin lesions may be done for cosmetic reasons Nephrectomy is indicated for unilateral kidney disease Ovariohysterectomy is done for uterine leiomyomas Long-term prognosis is poor

B. Possible agranular mast cells
C. Eosinophils common

II. Histopathologic examination
A. Dermal and/or subcutaneous masses composed of round cells arranged in sheets and cords
B. Round to oval cells with central round nuclei, abundant cytoplasm, and metachromatic granules
C. Variable numbers of eosinophils

III. Systemic evaluation
A. Prognostic factors
1. A worse prognosis has been associated with rapid growth, a deep and fixed position, ulceration, systemic signs, and location on a mucocutaneous junction, the muzzle, or ear.
2. Masses in the inguinal, preputial, or perianal regions may exhibit less aggressive behavior.

B. Staging
1. Staging tests for asymptomatic dogs with cutaneous MCTs are often normal.
2. The test that is positive most often is regional lymph node aspiration.
3. Buffy coat preparation and bone marrow aspiration are usually negative.
4. Ultrasonography is indicated to evaluate the liver, spleen, and sublumbar lymph nodes.
5. Thoracic radiography is done to evaluate the sternal lymph nodes.

Treatment

I. All MCTs are widely excised as early as possible, taking 2- to 3-cm lateral margins and one tissue plane deep to the tumor.

II. MCTs are very radiosensitive, and radiation therapy is a common adjunctive therapy when incomplete margins are detected after surgery.

III. Chemotherapy may be used for large tumors, residual microscopic disease after excision of grade II tumors, or for grade III tumors.
A. This treatment has limited value for disseminated disease.
B. Lomustine 60 to 90 mg/m^2 PO every 3 weeks for five doses is often given.
C. Vinblastine, vincristine, and chlorambucil can be considered.
D. Prednisone is given as a palliative measure.

IV. Ancillary therapy includes famotidine 0.5 mg/kg PO SID and diphenhydramine 2 mg/kg PO TID.

Monitoring of Animal

I. Reevaluate the animal every 3 to 4 months for presence of new cutaneous lesions and for metastasis to regional lymph nodes and/or internal organs.

II. For animals on lomustine, monitor for neutropenia, thrombocytopenia, and hepatotoxicity.

III. The Patnaik grading scheme has shown that 83%, 44%, and 6% of dogs with grade I, II and III tumors, respectively, were alive approximately 4 years after surgery (Bergman, 2005).

IV. Grading scheme is not useful for cats.

V. Prognosis for cats with primary cutaneous MCTs is good.

Epithelial and Hair Follicle Tumors

See Table 89-3.

Mesenchymal Tumors

See Table 89-4.

Histiocytic and Lymphocytic Tumors

See Table 89-5.

TABLE 89-3

Epithelial and Hair Follicle Tumors

TUMOR/DEFINITION	SIGNALMENT	CLINICAL SIGNS	DIAGNOSIS	TREATMENT/PROGNOSIS
Squamous cell carcinoma: malignant neoplasm of keratinocytes	Common in dogs and cats Affects older animals Scottish terrier, Pekingese, boxer, poodles, and Norwegian elkhound predisposed	Solitary, proliferative, cauliflower-like lesions Often ulcerated Most common on unpigmented pinnae, nose, and eyelids of cats	Cytology: epithelial cells arranged individually or in clusters with retained nuclei and nuclear atypia Histopathology: poorly defined masses of neoplastic keratinocytes, common mitotic figures, ± keratin pearls	Wide surgical excision Laser ablation or cryotherapy for small, superficial lesions Radiation therapy for nonresectable lesions Prognosis variable Better prognosis for small, well-differentiated tumors Most tumors locally invasive and slow to metastasize Nail bed tumors more aggressive and metastasize more readily
Basal cell tumor: neoplasm of basal cells of the epidermis, hair follicles, sebaceous glands, or sweat glands	Common in older cats Siamese, Himalayan, and Persian cats predisposed Uncommon in older dogs Cocker spaniel, poodles, Shetland sheepdog, Kerry blue terrier, and Siberian husky predisposed	Common locations: head, neck, thorax, dorsum Lesions solitary, discrete, firm to fluctuant nodules Lesions may be pigmented or cystic	Cytology: cuboidal epithelial cells with scant blue cytoplasm, rare atypia Histopathology: lobulated intradermal to subcutaneous masses, cords, or nests of cells	Surgical excision usually curative Prognosis good as tumors exhibit benign behavior Basal cell carcinomas are low-grade malignancies; rarely metastasize
Trichoblastoma: benign hair follicle tumor arising from primitive hair germ epithelium	Common in older dogs and cats Poodles and cocker spaniels predisposed	Up to 2 cm in size Firm alopecic masses on the head and neck of dogs and cranial trunk of cats	Cytology: keratinized epithelial cells, free keratin Histopathology: ribbons to nodules of small, basophilic, undifferentiated basal cells	Surgical excision Prognosis good
Trichoepithelioma: benign hair follicle tumor from cells that differentiate into hair follicle or shaft structures	Older dogs and cats Uncommon Bassett hound, golden retriever, miniature schnauzer, standard poodle, spaniels, and Persian cats predisposed	Up to 2 cm in size Alopecic, firm, gray to white lobulated masses Most common on the trunk and legs of dogs and the tail and legs of cats	Cytology: see Trichoblastoma Histopathology: multiple well-circumscribed nodules of basal cells that resemble primitive follicular bulbs and contain central cystic areas of keratinization	See Trichoblastoma
Tricholemmoma: benign hair follicle tumor arising from follicular outer root sheath cells	Rare Occurs in middle-aged to older dogs and cats Afghan hound predisposed	Up to 7 cm in size Firm, discrete nodules Most common on the head and neck	Cytology: see Trichoblastoma Histopathology: well-circumscribed nodules of small polyhedral cells with clear cytoplasm, surrounded by a thick basement membrane	See Trichoblastoma

TABLE 89-3

Epithelial and Hair Follicle Tumors—*cont'd*

TUMOR/DEFINITION	SIGNALMENT	CLINICAL SIGNS	DIAGNOSIS	TREATMENT/PROGNOSIS
Trichofolliculoma: likely a hamartoma because it resembles the entire follicular or folliculosebaceous unit	Uncommon in dogs Rare in cats	Solitary dome-shaped nodule <2 cm Possible central pore or depression	Cytology: see Trichoblastoma Histopathology: well-circumscribed dermal nodule composed of one or several primary follicles that are large, dilated, and keratinized through to the granular cell layer	See Trichoblastoma
Pilomatricoma: benign hair follicle tumor arising from germinative cells of the follicular matrix	Uncommon in dogs Occurs in middle-aged to older dogs Poodles, Kerry blue terrier, Old English sheepdog, Airedale terrier predisposed	Solitary, firm-to-hard, well-circumscribed masses up to 10 cm Most common over rump and shoulders	Cytology: see Trichoblastoma Histopathology: discrete nodule formed by multiple cystic structures lined by basilar epithelial cells, cysts containing keratinized ghost cells	See Trichoblastoma
Infundibular keratinizing acanthoma: benign hair follicle tumor of unknown cause	Uncommon in dogs Norwegian elkhound, Lhasa apso, Pekingese, Yorkshire terrier, and German shepherd dog predisposed	Up to 4 cm in size Solitary or multiple, partially alopecic nodules, usually with a central pore	Cytology: cornified squamous epithelial cells, and amorphous cellular debris Histopathology: well-circumscribed dermal nodule oriented around central cyst filled with laminated keratin	Surgical excision Prognosis good
Sebaceous adenoma: benign cutaneous neoplasm of glandular or combined ductal and glandular origin	Occurs in older dogs Cocker spaniel, Siberian husky, miniature poodle, coonhound, beagle, dachshund, and Persian cats predisposed	Lesions solitary or multiple, dome-shaped or papillated tumors that usually measure <1 cm	Cytology: normal-appearing sebaceous cells with foamy, pale-blue cytoplasm and small, dark nuclei Histopathology: multiple, large lobules of sebaceous cells that show normal maturation from the basal reserve cell layer to large, pale, lipid-laden central cells	Observation only or surgical excision Prognosis good
Sebaceous epithelioma: neoplasm that differentiates primarily into basal reserve cells of sebaceous glands	Common in dogs Rare in cats Predisposed breeds same as for sebaceous adenomas	Firm, nodular fungiform or plaquelike masses Range from several millimeters to several centimeters in size	Cytology: small, uniform, sometimes pigmented epithelial cells, with low numbers of sebaceous cells Histopathology: multiple, large, irregular islands of epithelial reserve cells, well-circumscribed smaller lesions, irregular and infiltrative larger masses	Observation or surgical excision Prognosis good

Continued

TABLE 89-3

Epithelial and Hair Follicle Tumors—*cont'd*

TUMOR/DEFINITION	SIGNALMENT	CLINICAL SIGNS	DIAGNOSIS	TREATMENT/PROGNOSIS
Sebaceous carcinoma: rare, malignant neoplasm of sebocytes	Older dogs and cats Cocker spaniel, Cavalier King Charles spaniel, Scottish terrier, and Siberian husky predisposed	Solitary, firm nodules up to 7.5 cm in size Occur commonly on head of dogs and cats	Cytology: basophilic basal-type cells, with nuclear and cellular atypia Histopathology: irregular but circumscribed, multilobular dermal lesions with variable sebaceous differentiation, cytoplasmic vacuolation, and eosinophilic cytoplasm	Complete surgical excision Tumors locally invasive and lymph node involvement possible Prognosis guarded
Apocrine secretory adenoma: benign neoplasm arising from apocrine gland or ductal cells	Uncommon in dogs and cats Great Pyrenees, chow chow, malamute, and Old English sheepdog predisposed	Well-circumscribed, firm or fluctuant dermal nodules that are usually solitary Lesions in dogs typically 0.5-4 cm in size Usually <2 cm size in cats	Cytology: medium to round or oval epithelial cells that contain eccentric nuclei and large intracytoplasmic droplets of secretory product Histopathology: discrete dermal nodules comprised of multiple ducts, tubules, or cysts lined by cuboidal to columnar epithelium with clear or eosinophilic fluid, inflammation common	Complete surgical excision Prognosis good
Apocrine secretory adenocarcinoma: malignant neoplasm of apocrine gland or ductal cells	Uncommon in dogs and cats Usually in older dogs and cats Coonhound, Norwegian elkhound, and Siamese cat predisposed	Solitary, usually circumscribed masses Size ranges from 0.5-10 cm in dogs and 0.2-3 cm in cats Common on legs and head of dogs and on legs and abdomen of cats	Cytology: variably sized epithelial cells with scant basophilic cytoplasm Histopathology: similar to apocrine secretory adenoma, well-differentiated, composed of neoplastic glandular structures	Complete surgical excision Radiation therapy for incompletely excised lesions Prognosis guarded Tumors possibly locally invasive; can recur and/or metastasize after surgery

TABLE 89-4

Mesenchymal Tumors

TUMOR/DEFINITION	SIGNALMENT	CLINICAL SIGNS	DIAGNOSIS	TREATMENT/PROGNOSIS
Melanocytoma: benign neoplasm arising from melanocytes	Common in dogs Uncommon in cats Highest incidence in canine breeds with dark pigmentation of the skin and in cats with black or gray coat color	Solitary, circumscribed, alopecic, fleshy, dome-shaped masses that are 0.5-4.0 cm in size Occur on head and pinnae of cats and trunk and head of dogs	Cytology: variably shaped cells, with brown to green-black pigment in the cytoplasm Histopathology: variably pigmented melanocytes arranged in clusters, cords or whorls, low mitotic index	Surgical excision Prognosis good
Melanoma: malignant dermal or junctional melanocytic tumor	Older dogs and cats Dogs with heavily pigmented skin and cats with black or gray hair coats predisposed	Sessile, polypoid, or plaquelike Up to 10 cm in size Gray, brown, or black in color Common on head and legs of dogs and head, thorax, and tail of cats	Cytology: see Melanocytoma Histopathology: invasive tumors with cellular atypia and frequent mitotic figures, common ulceration, and necrosis; spindle, round to polygonal, dendritic, epithelioid, and balloon cell types	Radical surgical excision Radiation therapy Palliative chemotherapy Prognosis poor Recurrence and metastasis common
Fibrosarcoma: malignant neoplasm arising from fibroblasts	Most common malignant mesenchymal neoplasm in cats Uncommon in dogs Gordon setter, Irish wolfhound, Brittany spaniel, golden retriever, and Doberman pinscher at higher risk	Firm, poorly circumscribed, often multilobular masses Size is 1-15 cm Alopecia and ulceration common Vaccine-induced fibrosarcoma in cats primarily a complication of rabies and feline leukemia virus vaccines	Cytology: variably shaped and sized mesenchymal cells, possible multiple nuclei Histopathology: ill-defined (infiltrative) margins, composed of large spindle cells arranged in interlacing bundles of varying Vaccine-induced tumors demonstrate peripheral inflammation, epithelioid macrophages, multinucleated giant cells (also contain bluish, amorphous material presumed to be adjuvant)	Treatment of choice is wide surgical excision or amputation Radiation therapy Chemotherapy for palliation Prognosis for small tumors good if completely removed Large, deep truncal vaccine-induced tumors have poor to guarded prognosis
Fibroma: benign fibrocytic neoplasm of dermis or subcutis	Uncommon in dogs and cats Doberman pinscher, boxer, and golden retriever predisposed	Solitary, firm or rubbery, circumscribed masses with an ovoid, dome-shaped or polypoid conformation Most common on head and legs of dogs and cats	Cytology: uniform spindle cells, round to oval nuclei, indistinct nucleoli Histopathology: bundles of collagen that are thick and have repetitive patterns, possible broad swirls of collagen, rare mitotic figures	Observation only or surgical excision Prognosis good

Continued

TABLE 89-4

Mesenchymal Tumors—*cont'd*

TUMOR/DEFINITION	SIGNALMENT	CLINICAL SIGNS	DIAGNOSIS	TREATMENT/PROGNOSIS
Lipoma: benign tumor of lipocytes	Common in dogs Middle-aged to older dogs and cats Labrador retriever, Doberman pinscher, miniature schnauzer, cocker spaniel, dachshund, weimaraner, and Siamese cat predisposed	Well-circumscribed, ovoid or discoid masses with soft or rubbery consistency Most occur on trunk and legs	Cytology: oily aspirate, variable numbers of lipocytes with ballooning cytoplasm and a small, flat nucleus near the cell membrane Histopathology: well-circumscribed dermal or subcutaneous nodules composed of mature lipocytes, with a delicate capsule	Observation for small lesions Surgical excision for larger or rapidly growing tumors Prognosis generally good Infiltrative lipomas often recur and cause destruction of underlying tissues
Liposarcoma: malignant tumor of subcutaneous lipoblasts	Uncommon in dogs Very rare in cats Middle-aged to older animals Shetland sheepdog and beagle predisposed	Variably circumscribed, soft or fleshy masses that measure ≥2 cm Arise in the subcutis but frequently involve the dermis Most tumors involve axial region and proximal legs	Cytology: bizarre cellular morphology, indistinct cell margins, numerous lipid droplets Histopathology: well-circumscribed but unencapsulated; large round to polygonal cells arranged in solid sheets; low mitotic activity; hemorrhage, necrosis, fibrosis, and ulceration possible	Radical surgical excision Systemic chemotherapy Prognosis guarded to poor Tumors locally invasive Metastasis possible but rare
Hemangioma: benign neoplasm of blood vessel endothelial cells, possibly induced by chronic solar damage in dogs with light skin, thin hair coats	Uncommon in dogs Rare in cats Middle-aged to older animals Airedale terrier, Gordon setter, boxer, soft-coated wheaten, and wirehaired fox terriers predisposed to spontaneous lesions Whippet, beagle, Dalmatian, American bull terrier, and basset hound predisposed to solar-induced lesions	Well-circumscribed, dome-shaped or polypoid masses with red or red black coloration Solar-induced lesions alopecic with ulceration and hemorrhage; occur over ventral abdomen, inguinal region, medial thighs, and axilla	Cytology: blood with few (normal) endothelial cells Histopathology: well-circumscribed, nonencapsulated tumor composed of vascular spaces filled with erythrocytes	Surgical excision Avoidance of ultraviolet exposure Solar-induced lesions may undergo malignant transformation Prognosis generally good

TABLE 89-4

Mesenchymal Tumors—*cont'd*

TUMOR/DEFINITION	SIGNALMENT	CLINICAL SIGNS	DIAGNOSIS	TREATMENT/PROGNOSIS
Hemangiosarcoma: malignant neoplasm of vascular endothelial cells; primary or metastatic sites; solar-induced lesions possible	Uncommon in older dogs and cats Italian greyhound, whippet, Irish wolfhound, vizsla, American bull terrier, and basset hound predisposed	Dermal or subcutaneous lesions Dermal lesions ill-defined, red to dark-blue plaques or nodules and ≤2 cm in size Subcutaneous lesions poorly circumscribed, dark-red or blue-black, spongy masses up to 10 cm in size	Cytology: neoplastic endothelial cells varying from normal in appearance to large pleomorphic cells with basophilic cytoplasm and prominent nucleoli Histopathology: plump endothelial cells aligned on delicate collagen trabeculae or dermal collagen bundles, vascular spaces not uniformly enclosed by endothelial cells, low to moderate mitotic activity Check for metastasis with radiography and ultrasonography	Radical surgical excision for dermal tumors Surgical excision and adjunctive chemotherapy (vincristine, doxorubicin, cyclophosphamide) for tumors that involve deeper structures Prognosis good for completely excised dermal lesions Prognosis guarded to poor for locally invasive tumors and metastases
Hemangiopericytoma: neoplasm of pericytes	Occurs in the dog Not reported in cats Exact incidence unknown Cannot be diagnosed without immunohistochemistry to rule out other cell types The term *canine spindle cell tumor with whorling pattern* is considered more accurate for tumors not evaluated by immunohistochemistry Large-breed dogs at greater risk Siberian husky, Irish setter, German shepherd dog, and mixed breeds predisposed	Solitary, deep dermal and subcutaneous, multinodular, fairly well-circumscribed masses with firm or slightly soft consistency Lesions favor trunk or legs	Cytology: small, spindle-shaped to stellate tumor cells with round to oval nuclei and wispy, light blue cytoplasm Histopathology: unencapsulated subcutaneous and/or dermal masses comprised of small spindle and polygonal cells arranged in interlacing bundles, sheets or concentric whorls	Radical surgical excision or amputation Radiation therapy Prognosis variable Tumors may recur locally; metastasis rare
Reactive fibrohistiocytic nodule: benign tumor of histocytes that may be macrophages or dendritic cells, suggestive of a reactive process	Uncommon in dogs Most affected dogs <3 years of age No breed or sex predilections	Solitary or occasionally multiple, firm cutaneous nodules measuring <1 cm Most often occur on face, scrotum, and legs See Chapter 77	Histopathology: circumscribed, unencapsulated dermal nodules composed predominantly of histiocytic cells arranged in solid sheets	Surgical excision Sublesional injection of methylprednisolone 10-40 mg for single lesions Prednisone 2-4 mg/kg PO SID until regression for multiple lesions Azathioprine 2 mg/kg PO QOD for refractory lesions Prognosis good

Continued

TABLE 89-4

Mesenchymal Tumors—*cont'd*

TUMOR/DEFINITION	SIGNALMENT	CLINICAL SIGNS	DIAGNOSIS	TREATMENT/PROGNOSIS
Anaplastic sarcoma with giant cells: poorly differentiated mesenchymal neoplasm of various origins	Uncommon Older dogs and cats No known breed predilections	Solitary, large, firm, poorly circumscribed, subcutaneous and dermal masses Legs and shoulders most common sites	Cytology: pleomorphic, round to fusiform mesenchymal cells, giant multinucleate cells with dyskaryosis Histopathology: unencapsulated mass, variable amounts of collagen, spindle cells, large round cells and multinucleated giant cells forming dense bundles or sheets	Radical surgical excision or amputation Prognosis guarded Tumors locally invasive to underlying bone/muscle Metastasis possible
Transmissible venereal tumor: exact origin unknown; cells express vimentin, are mesenchymal in origin, and contain 58 or 59 chromosomes	Recognized only in dogs Transmission from infected dogs or bitches during coitus or by licking and rubbing Exact incidence unknown	Tumors vary in size from small nodules to large masses Nodular, pedunculated, papillary, or multilobular Mainly observed on genital skin or mucosa	Cytology: large pleomorphic round cells with vacuolated cytoplasm, nuclei with coarse chromatin, variable mitotic figures Histopathology: sheets and rows of round or polyhedral cells with indistinct cell boarders, large round granular to vesicular nuclei, large single nucleolus, numerous mitotic figures	Surgery for small localized lesions but recurrence possible Vincristine 0.025 mg/kg IV once weekly until remission Radiation therapy effective Prognosis good Metastasis rare Spontaneous regression possible

TABLE 89-5

Histiocytic and Lymphocytic Tumors

TUMOR/DEFINITION	SIGNALMENT	CLINICAL SIGNS	DIAGNOSIS	TREATMENT/PROGNOSIS
Canine cutaneous histiocytoma: neoplasm of Langerhans' cells	Most common in dogs <3 years of age Head, neck, ears, and extremities most often affected Persistent or recurrent histiocytomas most common in the shar-pei and shar-pei–cross dog Rare in cats	Rapidly growing, erythematous, round nodules up to 2.5 cm in size Alopecia and ulceration common Persistent and recurrent lesions localized to one region or widespread	Cytology: large, round cells with moderate amounts of cytoplasm, round or kidney bean–shaped nuclei Histopathology: round to polygonal cells arranged in cords and dense sheets, obliteration of adnexal structures, moderate mitotic activity, lymphocytic inflammation in older lesions Persistent and recurrent histiocytomas: aggregates of plasma cells, neoplastic cells extending deeper into subcutaneous tissues, moderate to high mitotic activity	Observation only because most lesions regress spontaneously Surgical excision for lesions that do not regress Cryotherapy for lesions in locations where excision is difficult Prognosis good See Chapter 77
Cutaneous plasmacytoma: neoplasm of plasma cell origin	Uncommon in dogs; average age in dogs 10 years Rare in cats Cocker spaniel, Airedale terrier, Kerry blue terrier, Scottish terrier, and standard poodle predisposed	Sessile, firm, raised masses <2 cm Lesions numerous in some cases Pinnae, lips, digits, chin, and oral cavity common locations Occasionally exhibit malignant behavior and may metastasize	Cytology: round cell with perinuclear halo, moderate amounts of darkly basophilic cytoplasm, round eccentric nuclei, frequent mitoses and binucleate to multinucleate cells Histopathology: circumscribed but unencapsulated masses mostly confined to dermis, tumor cells occasionally extending to the epidermis, round cells with discrete borders and central to paracentral nuclei, common mitotic figures	Surgical excision Cryotherapy for lesions in locations where excision is difficult Prognosis good in dogs Prognosis guarded in cats because systemic disease and metastasis common See Chapter 77
Epitheliotropic lymphoma: malignant neoplasm arising from memory T cells	See Chapter 91	See Chapter 91	See Chapter 91	See Chapter 91
Nonepitheliotropic lymphoma: malignant neoplasm arising from T or rarely B lymphocytes	Uncommon in dogs and cats Weimaraner, boxer, St. Bernard, basset hound, Irish setter, cocker spaniel, German shepherd dog, golden retriever, and Scottish terrier predisposed	Solitary or multiple, discrete dermal and subcutaneous nodules or infiltrative plaques Rapid progression and metastasis to regional lymph nodes in most cases Subsequent systemic involvement common	Cytology: many large, round discrete cells, large and round nuclei, variable amounts of light-blue cytoplasm, variable size, shape, and number of nucleoli Histopathology: deep dermal and subcutaneous unencapsulated mass composed of sheets or nodular perivascular aggregates of relatively monomorphic cells Search for internal involvement	Surgical excision for solitary nodules Combination chemotherapy (may induce temporary remissions) Prognosis poor

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CHAPTER 90

Regional Dermatoses

Emily Rothstein

CLAW DISEASE

Asymmetrical Claw Disease

Definition and Causes

I. Asymmetrical claw disease is an abnormality in one claw or multiple claws on one paw.
II. Secondary bacterial infections are the most common cause.
  A. Trauma to the claw may occur in the dog or cat and often leads to infection.
  B. Examples include bite wounds, crush injuries, torn claws, exposure to chemicals, and thermal burns.
  C. Arteriovenous fistulae may develop from penetrating wounds or after onychectomy.
III. Fungal infections are less common.
  A. *Trichophyton mentagrophytes:* dog
  B. *Microsporum canis:* cat
  C. *Candida* spp.: dog and cat
  D. *Blastomyces dermatitidis:* dog
  E. *Cryptococcus neoformans:* cat
  F. *Sporothrix schenckii:* cat
  G. *Geotrichum candidum:* dog
  H. *Malassezia pachydermatis:* more common in dogs
IV. Neoplasia may also affect the claws.
  A. Dog
    1. Squamous cell carcinoma: more likely in older dogs, black dogs (Labrador retriever, standard poodle, giant schnauzer, Bouvier de Flandres)
    2. Melanoma
    3. Mast cell tumor
    4. Keratoacanthoma
    5. Inverted papilloma
    6. Miscellaneous: atrichial sweat gland adenosarcoma, fibrosarcoma, leiomyosarcoma, lymphoma, myxosarcoma, nerve sheath tumor, osteosarcoma
  B. Cat
    1. Squamous cell carcinoma
    2. Metastasis of primary lung tumor (Scott et al., 2000)

Pathophysiology

I. Trauma or damage to the claw often creates abnormal growth and allows embedding of debris, leading to secondary infection.
II. Neoplasia damages the claw and/or third phalanx.

Clinical Signs

I. Lameness, pain, pruritus: varying degrees, dependent on cause
II. Paronychial changes
  A. Swelling and edema
  B. Hair loss
  C. Oozing and/or crusting
  D. Erosion, ulceration, and/or necrosis
  E. Hyperpigmentation, lichenification
  F. Brown discoloration of claws and surrounding hairs
III. Claw abnormalities
  A. Onychoclasis: breakage of claw
  B. Onychocryptosis: ingrown claw
  C. Onychodystrophy: abnormal claw formation
  D. Onychogryphosis: hypertrophy and abnormal claw curvature
  E. Onychomadesis: sloughing of claw
  F. Onychomalacia: softening of claw
  G. Onychorrhexis: longitudinal striations associated with brittleness and breakage of claw
  H. Onychoschizia: splitting and/or lamination of claw, usually beginning distally
IV. Regional lymphadenopathy possible
V. Occasionally only systemic signs: fever, depression, anorexia

Diagnosis

I. Possible trauma and/or previous surgical procedure
II. Cytological examination of claw fold debris
  A. Bacterial or fungal infections often induce pyogranulomatous to granulomatous inflammation, composed of degenerative neutrophils and macrophages.
  B. Look for organisms, such as cocci, rods, and/or yeast.
  C. Examine for neoplastic cells.
III. Culture and sensitivity
  A. Bacterial cultures are especially helpful if rods are seen on cytological examination.
  B. Fungal cultures can be submitted from proximal claw shavings or avulsed claw material.
IV. Radiography
  A. Radiographs of the foot are evaluated for bony changes of the corresponding digit if neoplasia or osteomyelitis is suspected.
  B. Thoracic radiographs may show evidence of a primary lung tumor, metastatic disease, or systemic fungal disease.

V. Laboratory tests
   A. They are usually normal and not very helpful.
   B. Complete blood cell count (CBC) may show evidence of inflammation.
VI. Histopathology of claw, including the third phalanx and claw fold
   A. It is the most helpful way to diagnose neoplasia.
   B. Two techniques are available and both require general anesthesia.
      1. Removal of the third phalanx and claw using the standard declaw procedure allows procurement of claw, claw fold, ungual crest, and the entire third phalanx.
      2. Onychobiopsy involves using an 8 mm biopsy punch to biopsy horizontally along the claw (Mueller and Olivry, 1999).
         a. Medially, the claw and bone are sampled.
         b. Laterally, the skin of the claw fold is sampled.

Treatment

I. Remove any broken, loose, and/or painful claws.
II. Start appropriate antimicrobial therapy.
   A. Antibiotics are administered for at least 4 to 8 weeks and 2 weeks beyond clinical cure.
   B. Empiric drugs for cocci include one of the following:
      1. Cephalexin 22 to 30 mg/kg PO BID
      2. Amoxicillin/clavulanate 13.75 mg/kg PO BID
      3. Potentiated sulfonamides (trimethoprim-sulfamethoxazole, trimethoprim-sulfadiazine) 15 to 30 mg/kg PO BID
   C. Fluoroquinolones are usually reserved for severe disease and/or presence of rods.
   D. If possible, the choice of antibiotic drugs is based on culture and sensitivity results for infections with rods.
III. Antifungal medications are typically administered once daily for at least 3 to 6 months.
   A. Ketoconazole 5 to 20 mg/kg PO SID with food
   B. Itraconazole 5 to 10 mg/kg PO SID with food
IV. Fungal infections are difficult to resolve and may require amputation of the third phalanx.
V. Foot soaks may make the pet more comfortable.
   A. Antimicrobial medications: diluted chlorhexidine diacetate or gluconate (0.5% to 4%), iodophor (povidone-iodine)
   B. Epsom salts: 2 tablespoons mixed in 1 qt of warm water
VI. Radical surgical excision of the third phalanx is indicated for melanoma and squamous cell carcinoma.

Monitoring of Animal

I. Antimicrobial drugs are continued for at least 2 weeks for bacterial infections and for at least 3 months beyond clinical resolution for fungal infections.
II. Dogs with squamous cell carcinoma have a longer survival time because these tumors metastasize rarely; however, monitoring of regional lymph nodes is indicated.

Symmetrical Claw Disease

Definition and Causes

I. It includes abnormalities of multiple claws on multiple paws.
II. Widespread claw disease is often associated with other underlying diseases.
   A. Congenital, developmental disorders
      1. Dermatomyositis of the Shetland sheepdog and collie
      2. Acrodermatitis of the bull terrier
   B. Systemic disorders
      1. Hypothyroidism: dog
      2. Hyperthyroidism: cat
      3. Hyperadrenocorticism
      4. Diabetes mellitus
      5. Atopic dermatitis
      6. Disseminated intravascular coagulation
      7. Metabolic epidermal necrolysis
      8. Acromegaly: dog
      9. Lymphoma: dog
      10. Zinc deficiency: dog
   C. Infections
      1. Demodicosis
      2. Feline immunodeficiency virus (FIV), feline leukemia virus (FeLV)
      3. Leishmaniasis
   D. Immune-mediated disorders
      1. Pemphigus foliaceus
      2. Pemphigus vulgaris
      3. Bullous pemphigoid: dog
      4. Systemic lupus erythematosus (SLE)
      5. Vasculitis
      6. Cold-agglutinin disease
      7. Symmetrical lupoid onychodystrophy: dog
   E. Miscellaneous conditions
      1. Idiopathic onychodystrophy of the dachshund, Siberian husky, and very old dogs (Scott et al., 2000)
      2. Idiopathic onychomadesis of the German shepherd dog, whippet, English springer spaniel (Scott et al., 2000)
      3. Keratinization defects, such as primary seborrhea of the American cocker spaniel (Scott et al., 2000, Angus, 2004)

Pathophysiology

I. Any disorder that affects the ungula crest also affects the production of the claw.
II. Neoplasia disrupts the crest and claw.
III. Immune-mediated diseases and lupoid onychodystrophy affect claw growth.
IV. Systemic diseases can affect the paronychial skin (leading to secondary infection) and the ungual crest, both of which affect claw formation.

Clinical Signs

I. Local signs are similar to asymmetrical claw disease, except that numerous claws on multiple paws are involved.

II. Systemic signs relating to the underlying disease process are also evident.

Diagnosis

I. Obtain a complete history, including exposure to drugs and recent vaccinations.
II. Perform a thorough physical examination, including the claws and claw folds.
III. Cytologically examine claw fold debris.
  A. With pemphigus foliaceus, numerous acanthocytes and/or neutrophils (with or without bacteria) and eosinophils may be present.
  B. Neutrophils (inflammation), microorganisms (infection), and neoplastic cells are sometimes found.
IV. Skin scrapings and plucked hairs are helpful to diagnose demodicosis.
V. Perform appropriate laboratory tests for possible underlying diseases.
VI. Antinuclear antibody (ANA) test may support the diagnosis of SLE but is not specific for this disease.
VII. Histopathology of the claw, including the third phalanx and claw fold is helpful for diagnosis.
  A. Third phalanx and claw may be removed using a standard declaw procedure.
  B. Onychobiopsy may be performed.

Differential Diagnosis

I. Loss of claws
  A. SLE
  B. Bullous pemphigoid
  C. Pemphigus vulgaris
  D. Vasculitis
  E. Idiopathic onychomadesis
II. Breakage, onychodystrophy
  A. Endocrine disorders: hypothyroidism, hyperadrenocorticism
  B. Infections: leishmaniasis, FeLV, FIV, infections secondary to diabetes mellitus or hyperadrenocorticism
  C. Idiopathic: dachshund, Siberian husky
  D. Lupoid onychodystrophy
  E. Nutritional: zinc deficiency

Treatment

I. Secondary infections are treated (see Asymmetrical Claw Disease).
II. Immune-mediated diseases, such as pemphigus complex, pemphigoid, SLE, and vasculitis require aggressive therapy.
  A. Corticosteroids
    1. Cats often respond better to prednisolone and triamcinolone than the other corticosteroids.
    2. Prednisone and prednisolone induction dose is 2.2 to 6.6 mg/kg PO SID, then tapered over weeks to months.
    3. Triamcinolone induction dose is 0.2 to 0.6 mg/kg PO SID.
    4. Dexamethasone induction dose is 0.2 to 0.6 mg/kg PO SID.
  B. Azathioprine dose (dogs only) is 1.5 to 2.5 mg/kg PO SID.
  C. Chlorambucil is especially helpful in feline diseases.
    1. Examples: SLE, pemphigus vulgaris, pemphigus foliaceus
    2. Dose: 0.1 to 0.2 mg/kg PO SID to QOD
  D. Tetracycline or doxycycline with niacinamide can take 6 to 12 weeks to take effect and can be used in conjunction with other drugs initially.
    1. Dose in dogs <10 kg: tetracycline 250 mg PO TID or doxycycline 100 mg PO SID and niacinamide 250 mg PO TID
    2. Dose in dogs >10 kg: tetracycline 500 mg PO TID or doxycycline 100 mg PO BID and niacinamide 500 mg PO TID
  E. Omega-6 and omega-3 fatty acid supplements are given at twice the manufacturers' dosing instructions.
  F. Pentoxifylline *(Trental)* may be used in dogs at 10 to 20 mg/kg PO BID to TID for vascultitis.
III. Treatment of symmetrical lupoid onychodystrophy involves several options.
  A. Food elimination trial for at least 8 weeks
  B. Omega-6 and omega-3 fatty acid supplements for at least 3 to 4 months
  C. Vitamin E 400 IU PO BID
  D. Tetracycline or doxycycline and niacinamide (described previously)
  E. Corticosteroids as described previously for immune-mediated diseases
  F. Removal of third phalanx and claw on all affected digits (Boord et al., 1997)
IV. Idiopathic disorders can be treated with the following:
  A. Gelatin (Knox) for strengthening claws
    1. Dachshund: 10 g PO BID
    2. Other dogs: 1 g/kg SID
  B. Biotin 5 µg/kg/day PO indefinitely
  C. Pentoxifylline 10 to 20 mg /kg PO BID in dogs to treat altered vasculature
  D. Removal of third phalanx and claw on all affected digits (Boord et al., 1997)
V. Neoplasia is treated with amputation of the affected toe or toes.

Monitoring of Animal

I. Claws grow very slowly (1 to 1.5 mm/wk); therefore they should be monitored for several months.
II. Immune-mediated diseases require specific monitoring measures.
  A. CBC: for blood dyscrasias from azathioprine and chlorambucil
  B. Biochemistry profile: for elevated liver enzymes with corticosteroids and azathioprine
III. With certain underlying causes or conditions, therapy is lifelong.

FOOTPAD DISEASE

Feline Plasma Cell Pododermatitis

Definition and Causes

I. It is a rare disease of the footpads of the cat that is characterized by the accumulation of plasma cells.
II. The cause is unknown, but thought to be immune-mediated.

Clinical Signs

I. No breed, age, or sex predilection exists.
II. Initially soft, nonpainful swelling of footpads occurs.
  A. More than one pad on more than one foot is typically involved.
  B. Digital pads are most commonly affected, followed by the metatarsal or metacarpal pads.
  C. Lightly pigmented pads may look violaceous (purple).
  D. Pads appear striated with white scale.
III. Later, the pads can become ulcerated and painful.
IV. Rarely, immune-mediated glomerulonephritis or plasma cell stomatitis also occurs.

Diagnosis

I. Clinical signs are suggestive.
II. Cytological examination of fine-needle aspirates of the pad often reveals numerous plasma cells.
III. Laboratory test results are variable.
  A. CBC can reveal neutrophilia and increased lymphocytes.
  B. Biochemistry profile often reveals elevated globulins.
  C. Serum protein electrophoresis may show a polyclonal gammopathy.
  D. Tests for FeLV and FIV are usually negative; however, one study showed 50% of cats tested were positive for FIV (Guaguere et al., 1992).
IV. Bacterial culture is negative, unless the ulcerated pad is secondarily infected.
V. Histopathologic examination of the footpad is usually diagnostic.
  A. Initial lesions show either a superficial or deep perivascular plasmacytic dermatitis.
  B. Later lesions are characterized by a diffuse accumulation of plasma cells.
  C. Presence of neutrophils is variable; they increase in the presence of ulceration.

Differential Diagnosis

I. Granuloma, pyogranuloma
  A. Infection with bacteria and fungal organisms
  B. Immune-mediated diseases
    1. Eosinophilic granuloma complex can exhibit similar pad swelling.
    2. Pemphigus foliaceus can begin as scaling or crusting of pads.
    3. Animals with mosquito bite hypersensitivity can have erythematous plaques that ulcerate or are crusty.
    4. Animals with vasculitis can experience ulceration of footpads.
II. Neoplasia
  A. Fibrosarcoma or malignant fibrous histiocytoma can appear as a nodular disease.
  B. Nodules are usually firm on palpation and affect only one footpad.

Treatment and Monitoring

I. No treatment needed: asymptomatic problem, with possible spontaneous regression in some cats
II. Corticosteroids
  A. Prednisolone 4.4 mg/kg PO SID until lesions resolve, then tapered
  B. Triamcinolone 0.4 to 0.6 mg/kg PO SID until lesions resolve, then tapered
  C. Dexamethasone 0.5 mg/kg PO SID until lesions resolve, then tapered
III. Chrysotherapy (gold salts)
  A. Aurothioglucose 1 mg/kg IM every 7 days until lesions resolve (2 to 3 months), then every 14 days for 2 to 3 treatments, then every 30 days for maintenance
  B. Monthly monitoring for anemia, thrombocytopenia, and glomerulonephritis
IV. Doxycycline 25 mg/day PO (Bettenay et al., 2003)
  A. Animal is encouraged to drink water; if this medication becomes lodged in the esophagus, it can cause erosive esophagitis.
  B. Improvement may take 6 to 8 weeks.
V. Surgery to remove single lesions

Canine Footpad Hyperkeratosis

See Nasal Planum Disorders.

NASAL PLANUM DISORDERS

Canine Nasal and Footpad Hyperkeratosis

Definition

I. Increased keratinization (an increase in the horny layer of the skin) of nasal planum
II. May occur on the footpads, especially in the Dogue de Bordeaux, Kerry blue terrier, and Irish terrier

Pathophysiology

I. Infectious agents typically affect the keratinocytes.
II. Metabolic and nutritional changes affect the production of the stratum corneum.
III. Anything that changes the maturation and/or cornification of the stratum corneum leads to hyperkeratosis.

Causes

I. Congenital, developmental disorders
  A. Nasal hyperkeratosis in the Labrador retriever (Page et al., 2003; Peters et al., 2003)
  B. Primary seborrhea of the American cocker spaniel (see Chapter 93)

C. Congenital hyperkeratosis of the Dogue de Bordeaux, Kerry blue terrier, and Irish terrier

II. Infections
A. Canine distemper virus
B. *Leishmania infantum*

III. Idiopathic disorders: usually geriatric or brachycephalic dogs

IV. Secondary to other systemic diseases: metabolic epidermal necrosis, hepatocutaneous syndrome, superficial necrolytic dermatitis (Scott et al., 2000)

V. Immune-mediated disorders
A. Pemphigus foliaceus: nasal changes accompanied by pad hyperkeratosis and diffuse crusting
B. Pemphigus erythematosus: nasal changes accompanied by depigmentation and crusting along bridge of nose
C. Discoid lupus erythematosus: nasal changes accompanied by depigmentation, loss of cobblestones, or bumpy texture to nasal planum
D. SLE: accompanied by numerous systemic clinical signs (see Chapter 76)

VI. Zinc-responsive dermatosis

VII. Trauma to paranasal gland

VIII. Neoplasia: cutaneous lymphoma

Clinical Signs

I. Nasal hyperkeratosis
A. Thickening and dryness of the nasal planum occurs.
B. Depending on the underlying cause, depigmentation, crusting, and erosions or ulcerations can be observed.

II. Pad hyperkeratosis
A. Hyperkeratosis usually involves the entire surface of all footpads.
B. In congenital disorders, it may be noted by 6 months of age.
C. Fissures may develop and lead to secondary bacterial infections and pain.

III. Possible systemic signs: SLE, occasionally pemphigus foliaceus, hepatocutaneous syndrome, infectious diseases

Diagnosis

I. Classical clinical signs: hyperkeratosis, ± depigmentation, crusting

II. Signalment suggestive
A. Congenital and nutritional disorders occur in younger animals.
B. Immune-mediated and metabolic disorders usually occur in mature animals.

III. Biopsy of lesions
A. Samples are obtained from affected tissues (haired skin, nasal planum, foot pads) without any surgical preparation.
B. Two to three samples are submitted.
C. Because the nasal planum and footpads are vascular and well innervated, biopsies from this area are done under general anesthesia.

IV. Histopathology
A. Epidermal hyperplasia (hyperkeratosis) is the classic lesion.
B. Epidermal pallor and necrosis are seen below the parakeratotic and hyperkeratotic areas in metabolic epidermal necrosis.
C. Follicular and epidermal parakeratosis and hyperkeratosis are seen with zinc-responsive dermatosis.
D. Acantholysis is seen with pemphigus foliaceus.
E. Lichenoid and/or hydropic interface dermatitis are found in SLE.
F. Pigmentary incontinence and apoptosis are also characteristic of immune-mediated disorders.

Differential Diagnosis

I. Young age of onset
A. Labrador nasal hyperkeratosis: typically 6 to 12 months
B. Canine distemper virus
C. Primary seborrhea of the American cocker spaniel
D. Footpad hyperkeratosis

II. Older, adult age of onset
A. Canine distemper virus
B. Idiopathic nasal hyperkeratosis

III. Depigmentation present
A. Immune-mediated disease
B. Lymphoma

Treatment

I. For primary seborrhea or idiopathic nasal hyperkeratosis, no treatment is needed.

II. Symptomatic therapy with keratolytic medications may help in congenital hyperkeratosis and idiopathic hyperkeratosis.
A. Urea and propylene glycol 5% gel *(KeraSolv)*
B. Petroleum jelly to soften the tissue
C. Salicylic acid gel
D. Trimming nonviable tissue away from the footpads

III. Oral immunosuppressive drugs are indicated for pemphigus foliaceus, SLE, and possibly pemphigus erythematosus (described previously).

IV. Topical immunosuppressive drugs may be tried for discoid lupus and pemphigus erythematosus.
A. Fluocinolone 0.01% and dimethyl sulfoxide 60% *(Synotic)* BID, then tapered
B. Betamethasone valerate 0.1% cream BID, then tapered
C. Tacrolimus 0.1% *(Protopic)* SID to BID

V. Supportive care may be needed for dogs with systemic signs.
A. Canine distemper virus
B. SLE

VI. Leishmaniasis is treated with meglumine antimonate 20 to 50 mg/kg SC BID or 200 to 300 mg/kg IV QOD or allopurinol 11 to 15 mg/kg PO SID (Lemarie, 2003)

VII. Zinc supplementation is usually administered lifelong for zinc-responsive dermatosis (see Chapter 93).

Monitoring of Animal

I. Prognosis is variable.

II. For idiopathic hyperkeratosis, prognosis is excellent because the disorder is purely cosmetic.

III. For the following conditions, prognosis is fair for control of the disease or the underlying cause:
   A. Primary seborrhea of the American cocker spaniel
   B. Pemphigus erythematosus, pemphigus foliaceus
   C. Discoid lupus erythematosus
IV. For many diseases, the prognosis is guarded.
   A. Metabolic epidermal necrosis, hepatocutaneous syndrome
   B. Leishmaniasis
   C. Canine distemper virus

Nasal Depigmentation

See Chapter 92.

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CHAPTER 91

Erosive and Ulcerative Diseases of the Skin

Russell Muse | Nicola Williamson

INFECTIOUS DISORDERS

Mucocutaneous Pyoderma

Definition

I. Mucocutaneous pyoderma is a syndrome characterized by erythema, swelling, and adherent crusts around mucocutaneous junctions (Gross et al., 2005).
II. German shepherd dogs and their crosses may be at an increased risk, but dogs of any age, breed, or sex may be affected.

Causes and Pathophysiology

I. Bacterial overgrowth and infection develop and cause inflammation.
II. Additional immunologic factors increase the severity of the inflammation.
III. Underlying pathophysiology is not currently understood.

Clinical Signs

I. Initially swelling and erythema of the lips occur, especially at the commissures and lower lip folds.
II. Crust develops that entrap hairs, which allows erosions and fissures to form.
III. Purulent exudates may be seen, as well as variable pain, pruritus, and odor.
IV. Extension to the periocular areas, the nasal planum, nares, vulva, and philtrum may be noted.

Diagnosis

I. Cytological impression smear reveals intracellular and extracellular bacteria organisms (cocci, rod-shaped organisms, or mixed infection).
II. Ideally biopsy of erythematous noncrusted, nonulcerated tissue reveals several typical histopathologic changes.
   A. Perivascular to lichenoid infiltrate that is composed of plasma cells, neutrophils, and mixed mononuclear cells
   B. Lymphocytic exocytosis extending into the hair follicle
   C. Crusting, neutrophilic, and serocellular debris in older lesions

Differential Diagnosis

I. Lupus erythematosus
II. Pemphigus complex: pemphigus foliaceus, pemphigus erythematosus, or mucous membrane pemphigus
III. Lip fold pyoderma
IV. Zinc-responsive dermatitis
V. Drug eruption

Treatment

I. Clip the hair and clean the affected tissue with antimicrobial shampoos.
II. Apply topical antibiotics, such as mupirocin or polymyxin/neomycin combinations, BID for 2 to 4 weeks.
III. Oral antibiotics are often needed for 3 to 6 weeks.
   A. Antibiotic therapy may be chosen empirically when treating the cocci seen on cytologic impression smears.
      1. Clindamycin 5 mg/kg PO BID
      2. Cephalexin 22 mg/kg PO BID to TID
      3. Amoxicillin and clavulanate 13.75 mg/kg PO BID
   B. Antibiotic therapy is best when based on culture and sensitivity testing for treating rod-shaped bacteria or mixed infections.
IV. Corticosteroids may be needed to decrease the inflammatory response if antibiotic therapy does not completely resolve the condition.

Monitoring of Animal

I. Relapses are common.
II. Daily maintenance and routine cleaning with topical and oral antimicrobial agents may be needed for life.

IMMUNE-MEDIATED DISORDERS

Bullous Pemphigoid

Definition and Cause

I. It is a rare vesicobullous subepithelial disorder that involves the skin and mucous membranes of the dog and cat.
II. Genetic-related factors are probably involved.

Pathophysiology

I. Autoantibodies form principally against the basement membrane type XVII collagen molecule (also known as *bullous pemphigoid antigen 2* [BPAG2 or BP180]).
II. No gender, age, or breed predilections have been noted in dogs or cats.

Clinical Signs

I. Dogs
   A. Firm vesicles with irregular borders rupture and lead to erosions, ulcers, and crusting.
   B. Lesions may be located on the concave aspect of the pinnae, abdomen, axilla, and/or mucocutaneous junctions.
   C. Oral lesions are noted in <50% of the cases (Gross et al., 2005).
   D. Systemic signs are generally absent.
II. Cats: generally few lesions, erosions on the face

Differential Diagnosis

I. Pemphigus vulgaris
II. Epidermolysis bullosa (EB)
III. Erythema multiforme and toxic epidermal necrolysis
IV. Lupus complex disorders (vesicular and systemic)
V. Mycosis fungoides (cutaneous lymphoma)
VI. Drug eruption

Diagnosis

I. Routine laboratory tests (biochemistry profile, complete blood count [CBC]) are usually normal.
II. Histopathologic examination of biopsied skin reveals multiple changes.
   A. Subepidermal accumulation of neutrophils and eosinophils develops early, with subsequent vesicle formation.
   B. Intact and degenerating eosinophils are seen at the dermal-epidermal junction of preblistered and blistered areas, especially with Luna stains.
   C. Cutaneous cleavage occurs in the lamina lucida because type IV collagen is at the base of the dermal-epidermal cleft.
III. Direct immunofluorescence of tissue shows a linear and continuous deposition of immunoglobulin (Ig) G at the dermal-epidermal junction in 90% of dogs and cats; IgM and complement component 3 (C3) are also occasionally noted (Gross et al., 2005).
IV. Indirect immunofluorescence assays show variable titers of circulating IgG antibodies directed at the epidermal side of the split through the lamina lucida of the basement membrane (Gross et al., 2005).

Treatment

I. Immunosuppressive dose of prednisone and azathioprine are used in most cases (Table 91-1).
II. Tetracycline and niacinamide combination may be helpful in mild cases (see Table 91-1).

Monitoring of Animal

I. Some cases can be managed medically and maintained in remission.
II. Because many cases may require lifelong therapy, routine monitoring of immunosuppressive drug therapy is required.

Mucous Membrane Pemphigoid

Definition and Causes

I. It is a rare, chronic, autoimmune vesicobullous subepithelial autoimmune disease affecting the mucous membranes, mucocutaneous junctions, and haired skin of dogs and cats.
II. Autoantibodies are directed against various basement membrane proteins.
III. German shepherd dogs may be predisposed.

Pathophysiology

I. IgG Type 1 and 4 autoantibodies are directed against the epidermal side of the epithelium and target various segments of Type XVII collagen (Gross et al., 2005).

TABLE 91-1

TABLE 91-1

Rights were not granted to include this table in electronic media.
Please refer to the printed publication.

II. This attack leads to separation of the epidermis and the dermis and to vesicle formation.

Clinical Signs

I. Erosions with ulcers are the predominant clinical findings; however, vesicles may be found in nontraumatized skin.
II. Lesions are predominately located at the mucocutaneous junction of the lips, nasal planum, paranasal skin, periorbital skin, pinnae, genitalia, or anus.
III. Bulbar conjunctiva may also be affected.

Diagnosis

I. Diagnosis is based on histopathologic examination of affected skin.
   A. Subepidermal vesicles are seen, with variable inflammation consisting of predominantly red blood cells, neutrophils, and eosinophils.
   B. Superficial dermis may contain neutrophils, eosinophils, and lymphocytes in a lichenoid pattern in dogs.
II. Direct immunofluorescence of affected skin may reveal IgG at the basement membrane in dogs.
III. Indirect immunofluorescence assays may reveal circulating IgG antibodies in both dogs and cats (Gross et al., 2005).

Differential Diagnosis

I. Bullous pemphigoid
II. EB
III. Lupus complex: vesicular cutaneous lupus erythematosus, systemic lupus erythematosus (SLE)
IV. Pemphigus vulgaris
V. Mucocutaneous pyoderma
VI. Drug eruption

Treatment and Monitoring

I. Immunosuppression is the primary therapy (see Table 91-1).
II. Therapy is often lifelong.
III. Prognosis is good with appropriate therapy.
IV. Animal is monitored as for cutaneous, discoid lupus erythematosus (see following section).

Cold Agglutinin Disease

Definition and Causes

I. It is a cutaneous disease and type II hypersensitivity associated with the precipitation of proteins by cooling, with subsequent vascular insult.
II. It is associated with a cold-reaction (IgM) erythrocyte antigen.
III. Underlying causes that may precipitate this disorder include lead poisoning in dogs, and upper respiratory infections and lead poisoning in cats (Scott et al., 2001).
IV. Idiopathic forms also occur in both dogs and cats.

Pathophysiology

I. Cryoglobulins and cryofibrinogens precipitate from serum and plasma, respectively, on cooling and then dissolve on warming.
II. Cutaneous lesions result from vascular insufficiency and secondary circulatory stasis, thromboembolism, and vasculitis.

Clinical Signs

I. Skin lesions include erythema, purpura, necrosis, and ulceration.
II. Pain is usually noted.
III. Lesions usually involve the extremities, paws, pinnae, and tip of the tail.
IV. Lesions worsen with exposure to cold.

Diagnosis

I. History
II. Physical examination
III. Demonstration of titers of cold agglutinin
IV. In vitro autohemagglutination at room temperature
   A. Blood collected in tubes with heparin or ethylenediaminetetraacetic acid (EDTA) agglutinates when applied to a slide.
   B. Cooling exacerbates the agglutination.
V. Positive Coomb's test at 4° C

Differential Diagnosis

I. Vasculitis
II. SLE
III. Dermatomyositis
IV. Disseminated intravascular coagulopathy
V. Frostbite

Treatment and Monitoring

I. Identification and correction of any underlying precipitating factors
II. Avoidance of cold weather
III. Immunosuppressive therapy

Cutaneous Drug Eruptions

Definition

I. It is a reaction to a drug or its metabolite that occurs in a sensitized animal and causes cutaneous lesions.
II. Signs vary greatly between animals and usually do not resemble known pharmacological reactions.
III. Signs typically decrease within days to weeks of discontinuing the offending drug.

Causes and Pathophysiology

I. Two categories of reactions occur.
   A. Predictable reactions are dose dependent.
   B. Unpredictable reactions are related to the following:
      1. Immunologic responses
      2. Nonimmunologic responses
         a. Metabolic disorders or enzyme deficiencies
         b. Direct effect of mast cells, basophils, arachidonic acid, activation, or complement activation
         c. Drug interactions
         d. Exacerbation of preexisting skin disease

II. Inciting drugs may be administered via inhalation, orally, topically, or by injection.
III. Any medication can potentially cause a cutaneous drug reaction.
IV. Drugs reported to cause reactions include ampicillin, asparaginase, aurothioglucose, carprofen, cephalosporin, cyclosporine, diethylcarbamazine, doxorubicin, 5-fluorocytosine, griseofulvin, itraconazole, ketoconazole, levamisole, methimazole, penicillin, phenothiazines, prednisone, primidone, streptomycin, sulfonamides, tetracycline, trimethoprim-sulfa, and vaccines.

Clinical Signs

I. Reactions can mimic any dermatosis.
II. No age or sex predilection exists.
III. Some breeds of dogs are predisposed.
   A. Bichon frisé, Maltese terrier, Pekingese, poodle, and silky terrier are predisposed to local injection reactions.
   B. Doberman pinschers are predisposed to reactions from oral sulfonamides.
   C. Miniature schnauzers are predisposed to reactions from gold therapy, oral sulfonamides, and certain shampoos.
IV. Lesions include alopecia, altered pigmentation, urticaria, purpura, angioedema, erythroderma, maculopapular rash, self-induced trauma secondary to pruritus, erythema multiforme, and toxic epidermal necrolysis.
   A. Erythema multiforme is thought to be a host-specific T-cell hypersensitivity directed against keratinocyte-associated antigens that results in lymphocyte-induced cell death.
      1. Minor lesion: target lesions seen, only one mucosal surface affected, <10 % of body surface area affected
      2. Major lesion: >1 mucosal surface affected, 10% to 50% of body surface affected, <10% epidermal detachment
   B. Toxic epidermal necrolysis is a very rare disease in dogs and cats that is often rapidly progressive and life threatening.
      1. Cytotoxic T cells and mononuclear cells may cause apoptosis of keratinocytes.
      2. Cutaneous lesions are thought to be caused by toxic cytokines, especially tumor necrosis factor (TNF)-α.
   C. Stevens-Johnson syndrome is a severe form of erythema multiforme in which >50% of the body surface is affected and 10% to 30% epithelial detachment occurs.

Diagnosis

I. All other causes of similar skin lesions must be eliminated.
II. Most drug reactions occur within 1 to 3 weeks after initiation of therapy, while the drug is still being administered or remains in the body.
III. If the animal has had prior exposure to the drug, then reactions may occur within hours to days of readministration.
IV. Removal of the offending drug results in improvement within 5 to 14 days.
V. Rechallenge with the suspected drug is not recommended.
VI. Histologically, multiple changes are possible, including perivascular dermatitis, interstitial dermatitis, intraepidermal vesiculopustular dermatitis, interface dermatitis, subepidermal vesicular dermatitis, vasculitis and vasculopathy, and panniculitis.
VII. Laboratory abnormalities are usually nonspecific.

Treatment and Monitoring

I. The offending drug is discontinued, and all chemically related drugs are avoided.
II. Supportive care and symptomatic therapy are administered as needed.
III. Use of corticosteroids is controversial.
IV. Affected animals usually improve within 5 to 14 days of discontinuing the offending agent.
V. Some reactions may be life threatening.

Cutaneous or Discoid Lupus Erythematosus

Definition and Cause

I. Cutaneous lupus erythematosus is an ulcerative dermatosis involving the nasal planum of the dog and cat; the condition is part of the lupus complex of diseases.
II. Probably caused by a combination of genetic factors and photoactivation of the skin, which may induce an autoimmune response.
III. Collie, Shetland sheepdog, German shepherd dog, and Siberian husky may be predisposed.
IV. No sex or age predilections are noted.

Pathophysiology

I. Stimulation of B lymphocytes by autoreactive T cells causes antibody production against various nuclear and cytoplasmic proteins.
II. Basal layers of the epidermis are often targeted, ultimately causing cell death (apoptosis) and weakening of the dermal-epidermal junction.
III. This damage allows separation of the dermis and the epidermis, with secondary erosion and ulceration.

Clinical Signs

I. Early lesions include a progression of changes from erythema and depigmentation to loss of the cobblestone architecture of the planum nasale and variable scaling.
II. Further progression leads to erosion, ulceration, and crusting, with possible hemorrhage.
III. Residual scarring and leukoderma are common.
IV. Areas affected may include the following:
   A. Junction of the haired skin and the nasal planum
   B. Ventral and medial aspects of the alar folds
   C. Occasionally the lips, oral cavity (tongue, palate), pinnae, and genitalia

Diagnosis

I. Compatible history and signalment are suggestive.
II. Routine diagnostic tests are as follows:
   A. Skin scraping: negative

B. Dermatophyte culture: negative
C. Cytological impression smears: lack of acantholytic cells to distinguish from pemphigus complex diseases

III. Histopathologic examination of the affected skin reveals multiple changes.
A. Ideally, obtain biopsies from sites of recent depigmentation.
1. Basal cell apoptosis is typical.
2. Interface to lichenoid pattern may be seen, with lymphocytes and plasma cells predominating.
3. Pigmentary incontinence occurs from damage to melanocytes.
4. Focal thickening of the basement membrane zone may be seen.
B. Avoid obtaining biopsies from heavily crusted, ulcerated, or scarred areas.

IV. Direct immunofluorescence may reveal deposition of granular deposits of IgG, IgM, or C3 at the dermal-epidermal junction.
V. Indirect immunofluorescence assays of serum are generally negative.

Differential Diagnosis

I. Other lupus complex diseases: SLE, vesicular variant of cutaneous lupus erythematosus
II. Mucocutaneous pyoderma
III. Pemphigus foliaceus, pemphigus erythematosus
IV. Contact dermatitis
V. Mycosis fungoides
VI. Vogt-Koyanagi-Harada (VKH)-like syndrome
VII. Actinic dermatitis
VIII. Vitiligo
IX. Demodicosis or dermatophytosis: if the lesions are in haired areas

Treatment

I. Avoid exposure to the sun or use sunscreens to protect against aggravation of the lesion by ultraviolet light.
II. Topical therapy is indicated and may be successful in mild cases.
A. Topical corticosteroids
1. Begin with potent forms (e.g., betamethasone, fluocinolone) initially BID for 5 to 7 days.
2. Dose is then tapered to a lower frequency, and lower-potency products are used (e.g., triamcinolone, hydrocortisone).
B. Tacrolimus 0.1% *(Protopic)*
1. Can be applied BID for 14 days, then tapered to two to three times weekly
2. Can be used when corticosteroids are contraindicated or ineffective
C. Topical cyclosporine: some anecdotal success

III. Systemic therapy is indicated when topical therapy is ineffective or the case is severe (see Table 91-1).

Monitoring of Animal

I. After treatment has been initiated, animal is reexamined at 1 to 2 weeks to evaluate response to therapy.
II. Once clinical remission has been achieved, animal is reexamined at 1-month intervals as the drug doses are being tapered and then every 6 months while on maintenance therapy.
III. Baseline laboratory tests (biochemistry profile, CBC, urinalysis) are evaluated before starting corticosteroids, after 1 month, and then every 6 months.
IV. Urine cultures are performed yearly in animals on corticosteroids.
V. Animals on azathioprine or chlorambucil therapy require the following:
A. CBC and platelet counts are performed before therapy, then every 2 weeks for 12 weeks, and then every 6 months for life.
B. Biochemistry profile is submitted every 6 months to monitor for hepatotoxicity.
C. Urine cultures are performed yearly.

Exfoliative Cutaneous Lupus Erythematosus

Definition and Cause

I. It is an acquired, generalized exfoliative dermatopathy.
II. Previously reported as hereditary lupoid dermatosis of the German shorthaired pointer (Bryden et al., 2005).
III. The cause is poorly understood but is probably hereditary.

Pathophysiology

I. Findings are suggestive of a cytotoxic T-cell reaction and a major histocompatibility complex, cell-mediated immunologic reaction.
II. To date, the German shorthaired pointer is the only breed affected.
III. No specific age or sex predilections are known, although young (median age, 10 months) and female (ratio, 2:1) dogs were affected in one study (Bryden et al., 2005).

Clinical Signs

I. Scale, alopecia, follicular casting, crusting, and ulcerations occur in variable degrees on the muzzle, pinnae, and dorsal trunk; they may become generalized.
II. Lymphadenopathy, pain, pruritus, and pyrexia are variable.

Diagnosis

I. Compatible history and signalment are suggestive.
II. Typical physical examination findings are seen.
III. CBC reveals possible thrombocytopenia, lymphopenia, and anemia.
IV. Routine diagnostics (skin scraping and dermatophyte culture) are negative.
V. Histopathologic examination of affected skin reveals the following:
A. Generally a moderate to diffuse hyperkeratosis is present.
B. Moderate to marked multifocal lymphocytic interface dermatitis occurs, with focal apoptosis throughout the stratum spinosum.

C. Lymphocytic exocytosis of the epidermal and follicular epithelium may also be seen.

VI. Direct immunofluorescence of affected skin has revealed a deposition of IgG in the epidermal basement membrane.
A. Occasional presence of IgM, IgA, C3
B. IgG and IgM on basement membrane of the hair follicle (Bryden et al., 2005)

VII. Serum indirect immunofluorescence assays may reveal circulating antihair follicle IgG antibodies (Bryden et al., 2005).

VIII. Immunohistochemistry shows CD3- and CD8-positive T lymphocytes in the epidermis, superficial dermis, infundibulum of the hair follicle, and sweat glands.

Differential Diagnosis

I. Primary keratinization defects
II. Other lupus complex diseases: cutaneous lupus, SLE
III. Pemphigus foliaceus, pemphigus erythematosus
IV. Sebaceous adenitis
V. VKH-like syndrome
VI. Contact dermatitis
VII. Demodicosis, dermatophytosis
VIII. Drug eruption

Treatment

I. The disease is poorly responsive to therapy.
II. Topical therapy with antiseborrheic (sulfur, salicylic acid) shampoos is most helpful to remove excess scale.
III. Systemic therapy may be tried.
A. Fatty acid supplements and combination therapy with tetracycline and niacinamide have been used in many dogs without much success.
B. Prednisone 2.2 mg/kg PO SID in conjunction with topical therapy has resulted in some temporary remissions.
C. Azathioprine at varying doses has also been used with limited success (see Table 91-1).
D. Anecdotally, cyclosporine 5 mg/kg PO SID has resulted in improvement in some animals.

Monitoring of Animal

I. Therapy is usually only palliative, and a waxing and waning course is typical.
II. Euthanasia is a common outcome.

Vesicular Cutaneous Lupus Erythematosus

Definition

I. It is an ulcerative dermatitis described in the Shetland sheepdog and the collie.
II. The condition was formerly referred to as *idiopathic ulcerative dermatosis* (Jackson, 2006).
III. It is possibly a photosensitive vesicular variant of cutaneous, discoid lupus erythematosus, although the lesions are typically not in sun-exposed areas.

Causes

I. It is poorly understood but may involve genetic factors and photosensitivity.
II. To date, the Shetland sheepdog, collie, and their crosses have only been affected.
III. No age or sex predilections have been documented, although middle-aged to older dogs are usually affected.

Pathophysiology

I. Pathophysiology is not completely understood, but findings are suggestive of a lymphocyte-mediated attack on basal epidermal keratinocytes.
II. Autoantibodies targeting nuclear antigens have also been found.

Clinical Signs

I. Transient vesicobullous eruptions develop in areas of erythema and progress into ulcers with defined borders.
II. Groin and axillae are most commonly involved.
III. Other areas occasionally affected include the mucocutaneous junctions of the eyes, mouth, anus, as well as footpads and genitals.
IV. Pain, secondary pyoderma, and a concurrent myositis may be noted.

Diagnosis

I. History and signalment are helpful.
II. Complete physical examination is performed to look for typical clinical findings.
III. Routine diagnostic tests (skin scrapings, biochemistry profile, CBC) are normal.
IV. Antinuclear antibody (ANA) test is negative.
V. Impression cytology may show neutrophils in ulcerated areas, with intracellular bacteria indicative of a secondary pyoderma.
VI. Histopathologic examination reveals multiple changes.
A. Interface to lichenoid inflammation of predominantly lymphocytes
B. Vacuolization of the basal epidermis and apoptosis of the basal cell layer
C. Apoptosis in the suprabasilar layer, with satellitosis in the epithelium of the hair follicle
D. Subepidermal vesicles leading to dermal-epidermal separation

VII. Direct immunofluorescence of affected tissue has revealed IgG at the basal cell region and the basement membrane zone.

Differential Diagnosis

I. Bullous pemphigoid
II. Erythema multiforme and toxic epidermal necrolysis
III. Other lupus complex diseases: SLE, cutaneous lupus erythematosus
IV. Pemphigus vulgaris
V. Dermatomyositis

Treatment

I. Treatment is similar to cutaneous lupus erythematosus (see Table 91-1).
II. In addition, pentoxifylline 10 to 20 mg/kg PO TID has had some positive effects.

Systemic Lupus Erythematosus

Definition

I. SLE is a rare, multisystemic, autoimmune disease that involves the skin, urinary tract, joints, or hematologic system of the dog and cat (see also Chapter 76).
II. The skin is involved in 20% to 54% of cases (Gross et al., 2005; Helton-Rhodes, 2006).

Causes

I. Organ specific and nonspecific circulating autoantibodies are directed against a variety of tissue antigens (Gross et al., 2005).
II. Photoaggravation may also play a role.
III. Dogs that are predisposed include the Finnish spitz, collie, Shetland sheepdog, German shepherd dog, and poodle.
IV. Himalayan, Siamese, and Persian cats may be predisposed (Scott et al., 2001).

Pathophysiology

I. Tissue damage arises from immune complex deposition, direct cytotoxicity, or cell-mediated autoimmunity.
II. Pathogenesis of the skin lesions in SLE is unclear; however, multiple factors may be involved.
  A. Ultraviolet light may serve as a trigger for autoantigen expression once it penetrates to the level of the epidermal basal cells.
  B. Specific autoantibodies found in plasma attach to keratinocytes and induce cytotoxicity of keratinocytes.
  C. Injured keratinocytes release lymphocyte attractant and other cytokines, including interleukin (IL)-1, IL-2, and TNF-α.
  D. Apoptosis is inappropriately activated, and subsequent changes cause weakening and separation of the dermal-epidermal junction.

Clinical Signs

I. Clinical signs in dogs
  A. Ulcerative stomatitis is commonly seen.
  B. Mucocutaneous ulcerations develop from bullae in the mucocutaneous junction.
  C. Ulcers may also develop on the footpads.
  D. Panniculitis, urticaria, purpura, erythema, scale, crusting, and depigmentation may be noted.
  E. Face, ears, or distal extremities are commonly affected.
  F. See Chapter 76 for noncutaneous signs of SLE.
II. Clinical signs in cats
  A. Generalized seborrhea, exfoliative erythroderma, alopecia, scaling, and crusting are commonly seen.
  B. Footpads, face, neck, and limbs are commonly affected.
  C. Noncutaneous findings include fever, glomerulonephritis, hemolytic anemia, and weight loss (Gross et al., 2005).

Diagnosis

I. Biochemistry profile and CBC may reveal systemic or hematologic abnormalities.
II. Direct-impression smears of skin lesions are nondiagnostic.
III. ANA tests are positive in 85% to 90% of cases (Helton-Rhodes, 2006).
IV. Histopathologic examination may show multiple changes.
  A. The histopathologic pattern is similar to cutaneous lupus erythematosus.
  B. Evidence of vasculitis and panniculitis may also be present.
V. Direct immunofluorescence of affected tissue may show granular deposition of IgG or C3 at the basement membrane zone.

Differential Diagnosis

I. Other lupus complex diseases: discoid lupus, exfoliative cutaneous lupus
II. Bullous pemphigoid
III. Pemphigus vulgaris
IV. Panniculitis: infectious or sterile causes
V. Drug eruption
VI. Vasculitis
VII. Erythema multiforme and toxic epidermal necrolysis

Treatment

I. See Table 91-1.
II. Gold salts are avoided because of possible problems with concurrent glomerulonephritis.

Monitoring of Animal

I. Prognosis is guarded to poor.
II. Monitoring is similar to that for cutaneous, discoid lupus (see previous discussion).

Epidermolysis Bullosa

Definition and Causes

I. EB represents a group of mechanobullous diseases of various causes in dogs and cats.
II. A defect in the structural integrity of the epidermis or basement membrane zone results in loss of epithelial integrity and blister formation.
III. Various breeds are predisposed (Table 91-2).

Pathophysiology

I. Autoantibody formation develops against different structures, depending on the specific disease.
II. This results in loss of the skin integrity and subsequent blister formation.

Clinical Signs

I. Most subtypes of this disorder cause erosions and ulcerations of the pinnae, footpads, oral cavity, claws, and over the bony prominences of the face (see Table 91-2).
II. Lesions associated with dystrophic EB may be more severe and widespread than other forms.

TABLE 91-2

Clinical Features of the Various Forms of Epidermolysis Bullosa

DISEASE TYPE	EPIDERMAL STRUCTURE TARGETED	BLISTER LAYER	CLINICAL SIGNS	SPECIES/BREED	HISTOPATHOLOGIC FINDINGS	DIRECT IMMUNOFLUORESCENCE	INDIRECT IMMUNOFLUORESCENCE
Epidermolysis bullosa simplex	Intermediate filaments	Basal layer	Superficial erosions of the skin in axillae and groin	Collie, Shetland sheepdog	Although not definitively demonstrated in dogs and cats, histopathological pattern is similar to junctional epidermolysis bullosa	Unknown	None
Junctional epidermolysis bullosa (lethal and nonlethal forms)	Anchoring filaments	Lamina lucida of basement membrane zone	*Dogs:* erosions, ulcers on face, pinnae, footpads, and oral cavity *Cats:* shedding of claws with paronychia	Dogs: toy poodle, Beauceron, German shorthaired pointer Cats: Siamese	Vesicle (dermal-epidermal separation, sparse dermal inflammation) Basement membrane zone on floor of blister	Negative	Negative
Dystrophic epidermolysis bullosa	Anchoring fibrils of Type VII collagen	Beneath lamina densa	*Dogs:* footpad and oral ulcers, scarring of pinnae, tail *Cats:* loss of claw, ulcers of tongue, gums, footpads	Dogs: Akita, Beauceron, golden retriever Cats: domestic shorthair, Persian	Severe neutrophilic inflammation Fibrinous suppurative exudates Basement membrane on floor of blister	Negative	Unknown
Epidermolysis bullosa acquisita	Anchoring fibrils of Type VII collagen	Beneath lamina densa	Erythema occurs and develops into vesicles and ulcers in axillae, groin, oral cavity, mucocutaneous junction, and footpads	Great Dane possibly predisposed	Neutrophils increase in subepidermal skin before blister formation, then separation and necrosis occur Basement membrane zone on roof of blister	Positive IgG in a thick and continuous band at basement membrane	Positive IgG-1, IgG-4

Diagnosis

I. Diagnosis of EB can only reliably be made via biopsy.
II. Wedge section biopsies are recommended (as opposed to punch biopsies) to allow for complete removal of the intact blister for sectioning and histopathologic examination.
III. Histopathologic changes are noted in Table 9-2.
IV. Periodic acid–Schiff (PAS) stains can be used to highlight the lamina densa.
    A. Lamina densa is on the floor of the blister in junctional EB.
    B. Lamina densa is on the roof of the blister in dystrophic EB.

Differential Diagnosis

I. Bullous pemphigoid
II. Mucous membrane pemphigus
III. SLE
IV. Pemphigus vulgaris
V. Drug eruption
VI. Erythema multiforme

Treatment and Monitoring

I. Immunosuppressive therapy is warranted (see Table 91-2).
II. Levamisole 2.5 mg/kg PO QOD alone or in combination with corticosteroids may be helpful.
III. Therapy is variably successful.
IV. Prognosis is dependent on severity.

Feline Eosinophilic Granuloma Complex

Definition and Causes

I. Eosinophilic granuloma complex is a reaction pattern usually caused by a hypersensitivity response to an antigen.
II. Hypersensitivity reactions may arise from the following:
    A. Environmental allergens
    B. Foods
    C. Ectoparasites
        1. Fleas
        2. *Otodectes* spp.
        3. *Cheyletiella* spp.
        4. *Notoedres* spp.
        5. Lice
        6. Arthropod insects
    D. Drugs
    E. Bacterial infections
    F. Fungal infections
        1. Dermatophytosis
        2. *Malassezia* spp.
    G. Viral infections
        1. Feline leukemia virus
        2. Feline immunodeficiency virus
III. Eosinophilic granulomas, eosinophilic plaques, and indolent or rodent ulcers are included in the complex.

Clinical Signs

I. Eosinophilic granuloma
    A. Lesions may be linear and ulcerative.
    B. Typically nodules and/or plaques are alopecic, erythematous, eroded, or ulcerated.
    C. Pruritus is uncommon.
    D. The most common form is a nodular lesion of the mouth or chin (chin edema, "pouty" chin).
    E. Linear plaques may be found on the caudal thighs.
    F. Footpads and conjunctiva may also be affected.
II. Eosinophilic plaque
    A. It typically occurs as areas of alopecia, erosion, and/or ulceration.
    B. Lesions are commonly located on the ventral abdomen, medial thigh, axillary region, flexor surface of the elbows, neck, and dorsal aspect of the trunk.
    C. Pruritus is a common feature.
III. Indolent ulcer
    A. It is also known as a *rodent ulcer*.
    B. An erosive or ulcerated lesion is typically found in the middle of the upper lip or on the upper lip near the canine teeth.
    C. The hard palate may be involved.
    D. Lesions are not usually pruritic or painful.
    E. Regional lymphadenopathy can occur.

Diagnosis

I. Compatible history
II. ± Eosinophils on cytology
III. ± Peripheral eosinophilia
IV. ± Lymphadenopathy
V. Skin biopsy: diagnostic

Differential Diagnosis

I. Infections: bacterial, fungal, viral
II. Neoplasia

Treatment

I. Control any underlying allergies.
II. Consider administering systemic antibiotics for 2 to 4 weeks.
III. Use corticosteroids to induce remission.
    A. Prednisolone 2 to 4 mg/kg PO BID until lesions resolve (2 to 8 weeks), then gradually tapered to the lowest possible dose
    B. Methylprednisolone acetate 4 mg/kg or 20 mg IM, SC every 2 to 3 weeks until lesions resolve
        1. Dose is then decreased to every 2 to 3 months, only as needed.
        2. Improvement is usually seen within 2 to 4 weeks.
    C. Triamcinolone 0.8 mg/kg PO SID until resolution, then tapered
    D. Dexamethasone 0.4 mg/kg PO SID until resolution, then tapered
IV. Cases refractive to corticosteroids may respond to the following:
    A. Trimethoprim-sulfadiazine 125 mg PO BID
    B. Doxycycline 25 mg PO BID
    C. Cyclosporine 25 mg PO SID
V. Surgical excision may be considered for small, unresponsive lesions.
VI. Laser, cryotherapy, or radiation therapy are useful for unresponsive lesions.

Monitoring of Animal

I. Monitor body weight and appetite.
II. Monitor blood glucose and urinalysis for evidence of diabetes mellitus.
III. Monitor urine cultures for urinary tract infections.

Pemphigus Complex

Definition and Causes

I. The term *pemphigus complex* is used to describe an uncommon group of autoimmune diseases in the dog and cat.
II. Lesions are vesiculobullous to pustular in nature and arise from autoantibody-mediated disruption of desmosomes and intercellular adhesions between keratinocytes resulting in acantholysis.
III. Five forms have been identified in dogs and cats.
IV. The disorders are differentiated by clinical lesions, intraepithelial acantholysis, and the location of the desmosomes that are attacked.
   A. Pemphigus foliaceus: most common form in dogs and cats
   B. Pemphigus erythematosus
      1. Represents a mild form of pemphigus foliaceus
      2. May be a crossover between pemphigus foliaceus and SLE
   C. Pemphigus vulgaris: second rarest and most severe variant
   D. Pemphigus vegetans: rarest form, considered to be a benign variant of pemphigus vulgaris
   E. Paraneoplastic pemphigus: recently described in dogs with neoplasia

Pathophysiology

I. Type II (cytotoxic) hypersensitivity causes pemphigus lesions.
II. Pemphigus antibodies bind to desmosomal antigens, leading to the breakdown of cell-to-cell adhesion molecules, with acantholysis and blister formation.

Clinical Signs

I. Signalment: no sex or age predisposition
II. Pemphigus foliaceus
   A. Predisposed breeds include the dachshund, Schipperke, Finnish spitz, bearded collie, chow chow, Akita, and Newfoundland.
   B. Doberman pinschers and Labrador retrievers are overrepresented with drug-induced pemphigus foliaceus.
III. Pemphigus erythematosus
   A. Age: usually middle-aged animals
   B. Predisposed breeds: Shetland sheepdog, collie, German shepherd dog
IV. Specific clinical features
   A. Pemphigus foliaceus
      1. Typically includes scales, crusts, or pustular dermatitis.
         a. Crusts are often honey-colored to brown in appearance.
         b. It often begins on the face and ears.
         c. It is not a vesicular condition.
      2. Depigmentation of the nose is common, but oral cavity involvement is rare.
      3. Feet, footpads, nail beds, and the inguinal area may become affected.
      4. The disease generally progresses over 6 months.
      5. Cats tend to have paronychia and involvement of the nipples.
      6. The disease may wax and wane and be accompanied by secondary bacterial pyoderma, peripheral lymphadenopathy, lethargy, anorexia, and fever.
      7. Severe pain and pruritus are variable.
      8. Three clinical forms have been recognized.
         a. Spontaneous: Akita, chow chow
         b. Drug-induced (often after exposure to trimethoprim-sulfa drugs): Doberman pinscher, Labrador retriever
         c. Dogs with a history of chronic skin disease
   B. Pemphigus erythematosus
      1. Erythema and a pustular dermatitis are usually confined to the face and ears.
         a. Depigmentation of the nose may be the initial lesion.
         b. Depigmented noses are predisposed to photodermatitis, which may exacerbate the condition.
      2. Occasionally footpads or genitalia may be involved.
      3. Pain and pruritus are variable.
   C. Pemphigus vulgaris
      1. This form of pemphigus is a vesiculobullous disease and can progress to erosions and ulcers.
      2. Most cases have lesions in the oral cavity.
         a. Mucocutaneous junctions (eyelids, nostrils, lips, anus, prepuce, vulva) may be affected.
         b. Cutaneous lesions may also be evident, especially in the axillae and groin.
      3. Onychomadesis (sloughing of claws) or ulcerative paronychia (infection or inflammation of the claw folds) may be the only presenting sign.
      4. Positive Nikolsky's sign (the outer layer of the skin is easily removed when positive pressure is applied to the edge of a lesion) indicates poor cellular cohesion.
      5. Secondary bacterial pyodermas and lymphadenopathy may be present.
      6. Pain and pruritus are variable.
      7. Fever, anorexia, and depression may be noted in severely affected animals.
   D. Pemphigus vegetans
      1. Vesiculopustular disease that develops into papillomatous and verrucous lesions that may exude serum and be covered in pustules.
      2. Animals are generally healthy.
      3. Pain and pruritus are variable.
      4. Nikolsky's sign may be present.
      5. It may be a benign form of pemphigus vulgaris.
   E. Paraneoplastic pemphigus: possibly associated with lymphoma, splenic sarcoma, Sertoli cell tumor in the dog (Elmore et al., 2005)

Diagnosis

I. Hematological changes are nonspecific.
   A. Leukocytosis with a left shift may be evident if a secondary bacterial infection is present.
   B. Moderate normochromic, normocytic anemia, hyperglobulinemia, and hypoalbuminemia may also be detected.
II. In a low number of cases, ANA titers may be positive with pemphigus erythematosus.
III. Cytological examination of pustules may reveal numerous acanthocytes, neutrophils (nondegenerate unless secondary infection exists), and eosinophils.
   A. Acantholytic cells may form sheets or rafts.
   B. Secondary bacterial pyoderma can cause small numbers of acantholytic cells.
IV. Primary lesions (pustules, bullae and vesicles) are biopsied whenever possible.
   A. Acantholytic cells and intraepidermal clefting are present in all forms of pemphigus.
   B. Pemphigus foliaceus and pemphigus erythematosus have subcorneal or intraspinous clefts.
   C. Pemphigus vulgaris has suprabasilar clefting or vesicle formation secondary to acantholysis.
   D. Pemphigus vegetans may show epidermal hyperplasia and intraepidermal microabscesses that contain acantholytic cells and eosinophils, but controversy exists as to the typical lesion.
   E. Crusts may contain large numbers of acanthocytes that are secondary to pustule or vesicle rupture.
V. Immunofluorescence and immunoperoxidase testing are used to detect antibody deposition in tissues.
   A. Sensitivity of direct immunofluorescence testing in dogs is variable.
      1. Biopsies must be shipped in Michel's medium and maintained at a pH of 7.0 to 7.2.
      2. Lip samples are a possible tissue source.
      3. False-positive results are possible.
         a. Footpad and nose samples
         b. Samples from animals previously treated with corticosteroids
         c. Samples from secondary lesions
         d. Improper sample transportation
   B. Indirect immunofluorescence is not specific or sensitive.
   C. Immunoperoxidase tests may also be performed.
      1. Formalin-fixed samples can be used.
      2. False-positive results may be obtained from animals treated with corticosteroids.

Differential Diagnosis

See Box 91-1.

Box 91-1

Differential Diagnoses for the Pemphigus Complex Diseases

Disease	Differential Diagnoses
Pemphigus foliaceus	Bacterial folliculitis, dermatophytosis, demodicosis, primary or secondary seborrhea, pemphigus erythematosus, systemic lupus erythematosus, discoid lupus erythematosus, cutaneous drug reaction, dermatophilosis, zinc-responsive dermatitis, cutaneous T-cell lymphoma, necrolytic migratory erythema, subcorneal pustular dermatosis, eosinophilic pustulosis, leishmaniasis
Pemphigus erythematosus	Bacterial folliculitis, demodicosis, primary or secondary seborrhea, pemphigus erythematosus, systemic lupus erythematosus, discoid lupus erythematosus, benign familial pemphigus, cutaneous drug reaction, dermatomyositis, zinc-responsive dermatitis, epidermolysis bullosa simplex, uveodermatologic syndrome, leishmaniasis
Pemphigus vulgaris	Bullous pemphigoid, epidermolysis bullosa acquisita, systemic lupus erythematosus, drug reaction, toxic epidermal necrolysis, cutaneous T-cell lymphoma, erythema multiforme, candidiasis infection, ulcerative stomatitis (multiple causes)
Pemphigus vegetans	Pemphigus vulgaris, pemphigus erythematosus, bacterial folliculitis, fungal granulomas, cutaneous neoplasia, benign familial pemphigus
Paraneoplastic pemphigus	Systemic lupus erythematosus, pemphigus vulgaris, mucous membrane pemphigoid, bullous pemphigoid, epidermolysis bullosa acquisita, erythema multiforme, toxic epidermal necrolysis, bullous drug eruptions, vesicular cutaneous lupus erythematosus

Treatment

I. Pemphigus foliaceus and pemphigus vulgaris
   A. In dogs and cats the initial therapy of choice is immunosuppressive doses of oral prednisone (see Table 91-1).
   B. Cats that fail to respond to prednisone may respond to dexamethasone or triamcinolone.
   C. In the dog the addition of azathioprine may help achieve remission, but azathioprine is contraindicated in cats.
   D. Chlorambucil can be used in both cats and dogs as an alternative to azathioprine.
   E. Cyclophosphamide can be used in the dog in combination with prednisone.
   F. Gold therapy (aurothioglucose), although not always available, can be tried in conjunction with prednisone in dogs and cats that are refractory to the previously discussed therapies (see Table 91-1).
      1. All other therapies are discontinued for 4 weeks before initiating gold therapy.

2. Test dose is administered first.
   a. Animals <10 kg: 1 mg IM
   b. Animals >10 kg: 5 mg IM
3. If adverse effects are not detected, then a dose of 1 mg/kg IM is given 1 week later and repeated on a weekly basis.
4. If after 12 weeks no response is seen, then the dose may be increased to 1.5 to 2.0 mg/kg IM weekly.
5. Once remission is achieved, the dosing interval is increased to every 2 weeks, then to every 4 weeks for several months.
6. The oral form of gold *(Auranofin)* has not been efficacious in the dog and is expensive.
7. Gold therapy may take 6 to 12 weeks to be effective.
8. Prednisone may need to be continued at full strength during the initial 6 to 12 weeks of gold therapy.

G. Human immunoglobulin therapy (1 g/kg IV over 6 to 12 hours and given for 1 to 2 days) may also be tried.

II. Pemphigus erythematosus and pemphigus vegetans
   A. Treatment with topical corticosteroids and sun avoidance (especially between the hours of 10 AM and 4 PM) may achieve remission.
   B. Sunscreens with a sun protection factor (SPF) of ≥15 and containing titanium dioxide may be beneficial when applied BID to TID.
   C. Combination of tetracycline and niacinamide may achieve remission in 25% of dogs, but animals must be monitored for gastrointestinal side effects and seizures.
   D. Vitamin E (topically or systemically) may be of benefit.
   E. If the previous measures do not achieve a satisfactory result, or the animal comes out of remission, then the addition of corticosteroids may be beneficial.

III. Paraneoplastic pemphigus: treatment of the underlying neoplasia

Monitoring of Animal

I. All of the medications used to treat pemphigus have potential side effects that necessitate monitoring.

II. When administering prednisone, check a CBC and biochemistry panel every 2 weeks until remission is obtained or tapering begins.
   A. Side effects include a stress leukogram, elevated liver enzymes, and decreased globulins.
   B. Urine cultures are periodically performed to monitor for urinary tract infections secondary to immunosuppression.

III. With azathioprine, chlorambucil, or cyclophosphamide therapy, a CBC and chemistry panel are performed every 2 weeks initially.
   A. Side effects include bone marrow suppression (thrombocytopenia, anemia, leukopenia) and elevated liver enzymes (mild increases are expected).
   B. If side effects occur, then the dose of the medications is decreased.
   C. Urine cultures are periodically conducted to monitor for urinary tract infections secondary to immunosuppression.
   D. Urinalyses are also performed to monitor for drug-induced sterile hemorrhagic cystitis that develops in some dogs on cyclophosphamide for >2 months.

IV. While the animal is receiving chrysotherapy, a CBC and urinalysis are performed before each treatment to monitor for anemia, eosinophilia, and proteinuria; chemistry panels are done monthly to monitor for elevations in liver enzymes.

V. Animals on potent topical steroids are monitored similarly to those on systemic corticosteroids.

VASCULAR DISORDERS

Ischemic Dermatopathy

Definition and Causes

I. *Ischemic dermatopathy* is the term given to multiple cutaneous vasculopathies of dogs that are similar in clinical and histological appearance.

II. This group of diseases includes five separate disorders, with variable causes and clinical signs (Gross et al., 2005).
   A. Group 1 includes dermatomyositis, an inheritable, inflammatory disorder with a juvenile onset affecting skin and muscle; certain breeds are at increased risk.
   B. Group 2 includes a juvenile-onset, ischemic dermatopathy of dogs that is identical to dermatomyositis but has no proven breed or familial predisposition.
   C. Group 3 includes dogs that exhibit postrabies vaccination panniculitis.
   D. Group 4 includes dogs with more severe generalized cutaneous reactions after rabies vaccination.
   E. Group 5 includes dogs with adult-onset, generalized ischemic dermatopathy that have no correlative history of a vaccine reaction.

Pathophysiology

I. Cutaneous hypoxia leads to atrophy of the hair follicles and alopecia.

II. Vascular impairment may occur to the skin over bony prominences, with ulceration, erosions, and crusting.

III. Subsequent scarring may or may not be present.

IV. Breed predispositions are noted in some disorders (Table 91-3).

Clinical Signs

I. Groups I and II
   A. Transient papules with erythema and vesicles leading to ulcers, crusts, and alopecia
   B. Scarring with pigmentary abnormalities (hypopigmentation or hyperpigmentation)
   C. Aggravated by ultraviolet light
   D. No pain or pruritus, subtle involvement of muscles

II. Group III: focal scarring and alopecia at site of injection

III. Groups IV and V: similar lesions to Groups I and II but may be more severe

TABLE 91-3

Ischemic Dermatopathy Disorders of the Dog

DISORDER	BREEDS AFFECTED	AGE OF ONSET	DISTRIBUTION OF LESIONS	CAUSES
Dermatomyositis	Collie, Shetland sheepdog, and their crosses	Juvenile: <6 mo	Face, pressure points on extremities Can be generalized	Genetic predisposition Possible unknown environmental factors
Juvenile-onset ischemic dermatopathy	Chow chow, Welsh corgi, German shepherd dog, miniature schnauzer, dachshund, fox terrier, Maltese	Juvenile: <6 mo	Face, pressure points on extremities Occasionally generalized	Unknown
Postrabies vaccine panniculitis	Toy or miniature breeds	Any age	Site of injection or local extension	Rabies vaccine
Severe generalized vaccine-induced ischemic dermatopathy	Unknown	Adult onset	Generalized	Rabies vaccine
Generalized idiopathic ischemic dermatopathy	Unknown	Adult onset	Generalized	Unknown

From Gross TL, Ihrke PJ, Walder EJ et al: Erosive and ulcerative diseases of the epidermis. p. 116. In Gross TL, Ihrke PJ, Walder EJ et al (eds): Skin Diseases of the Dog and Cat Clinical and Histopathologic Diagnosis. 2nd Ed. Blackwell, Oxford, England, 2005.

Diagnosis

I. Routine diagnostic tests (skin scraping, dermatophyte culture) are negative.
II. Diagnosis is based on histopathology of affected skin.
  A. Scattered degeneration of basal cells (apoptosis) occurs in the epidermis and epithelium of the hair follicles.
  B. Epidermal and dermal pallor occur, as well as hypoxia of the follicles and adnexa.
  C. Lymphocytes and histiocytes predominate.
  D. Once ulceration develops, intense neutrophilia may be noted.
  E. Dermal scarring and atrophic hair follicles may be seen.
  F. Blood vessels may show a vasculitis of low cellularity.
  G. Skeletal muscle inflammation may be found with deep biopsies.
III. Differentiation of the various groups relies on history and signalment.

Differential Diagnoses

I. Demodicosis
II. Dermatophytosis
III. Bacterial pyoderma
IV. Discoid lupus
V. Drug eruption

Treatment and Monitoring

I. Treatment of most of the disorders generally requires immunosuppressive therapy (see Table 91-1).
II. Pentoxifylline 10 to 20 mg/kg PO TID may be helpful in some cases.

Vasculitis

Definition and Causes

I. Vasculitis is an inflammation of the walls of blood vessels and often results from deposition of immune complexes within the walls of the vessels (Type III hypersensitivity).
II. Vasculitis can occur as a primary disorder or arise secondary to exposure to drugs, neoplasia, infections, inflammation, or vaccines.
III. Cutaneous vasculopathies usually result from damage to the postcapillary venules.
IV. Multiple breeds may be predisposed and are represented in various syndromes.
  A. Proliferative thrombovascular necrosis of the pinnae: toy and small breeds
  B. Familial cutaneous vasculopathy: German shepherd dog
  C. Cutaneous and renal glomerular vasculopathy: greyhound
  D. Neutrophilic leukocytoclastic vasculitis: Jack Russell terrier
  E. Focal cutaneous vasculitis and alopecia at the site of rabies vaccines: miniature poodle, Yorkshire terrier, silky terriers

Pathophysiology

I. Activation of complement and other chemoattractants leads to the recruitment of neutrophils, which enzymatically degrade blood vessel walls.
II. Vessel occlusion and thrombosis may develop, causing hypoxic changes to the tissues.
III. Tissue hypoxia results in erosions, ulcers, and necrosis.

Clinical Signs

I. Clinical signs are numerous and variable, depending on the organs involved.
II. Initially macular erythema and edema progresses to papules, plaques, petechiae, and hemorrhagic bullae.
III. Ultimately, erosions, ulcers, and necrosis result.
IV. Affected areas tend to be associated with extremities (legs, footpads, claws), the pinnae, nasal planum, face, scrotum, and tail.
V. Additional systemic signs may include myopathy, polyarthropathy, hepatopathy, anorexia, pain, pruritus, anemia, and thrombocytopenia.

Diagnosis

I. Direct cytological impression smears are nondiagnostic.
II. Digital pressure on erythematous or purpuric lesions does not result in blanching.
III. Laboratory tests (biochemistry profile, CBC, urinalysis) results vary depending on the organ involved.
IV. ANA assay is usually negative.
V. Diagnosis relies on histopathology of affected skin.
   A. Neutrophilic leukocytoclastic vasculitis and inflammation involving the vessel walls
   B. Fibrinoid degeneration of blood vessel walls, with thrombosis
VI. Direct immunofluorescence may exhibit immunoglobulin or complement deposition in the vessel walls (and occasionally in the epidermal basement membrane).

Differential Diagnosis

I. SLE
II. Disseminated intravascular coagulopathy
III. Cold agglutinin disease
IV. Hypersensitivity reactions

Treatment

I. Identify and correct the underlying cause, if possible.
II. Immunosuppressive therapy is usually indicated (see Table 91-1).
III. Pentoxifylline 20 mg/kg PO TID may help combat inflammation and restore perfusion.
IV. Dapsone 1 mg/kg PO TID has been shown to be effective in some cases.
V. Sulfasalazine 20 to 40 mg/kg PO TID has also been effective in some cases.
VI. Cyclosporine 5 mg/kg PO SID has had anecdotal success in some cases.
VII. Prognosis depends on the specific disorder and the severity of the condition.

NEOPLASTIC DISORDERS

Cutaneous (Epitheliotropic) T-Cell Lymphoma

Definition and Causes

I. An uncommon cutaneous lymphoma affecting dogs and cats
II. Malignancy of T lymphocytes of the skin
III. Also known as *mycosis fungoides*

Pathophysiology

I. Pathophysiology is unknown.
II. The disorder is thought to arise from chronic antigenic stimulation of T cells in the skin.

Clinical Signs

I. Four clinical presentations in dogs
   A. Exfoliative erythroderma: pruritic erythema, scaling
   B. Mucocutaneous erythema, depigmentation, ulceration
   C. Solitary or multiple cutaneous plaques or nodules
   D. Infiltrative, ulcerative lesions of the oral mucosa (similar to chronic stomatitis) and hyperkeratotic, depigmented and/or ulcerated footpads
II. Possible peripheral lymphadenopathy, signs of systemic illness
III. Rarely in dogs: lesions only on the nasal planum, nasal philtrum, lips, anus
IV. Cats: well-circumscribed annular areas of alopecia, erythema, and scaling on the head and neck

Diagnosis

I. Suggestive history and signalment
II. Definitive findings on skin biopsy
   A. Epidermis and epithelium of hair follicles are infiltrated with neoplastic lymphocytes.
   B. Pautrier's microabscesses (focal aggregates of atypical, polymorphic lymphocytes within the epithelium) may occur.
   C. In dogs, a tropism for hair follicles and epitrichial sweat glands exists.

Differential Diagnosis

I. Atopic dermatitis
II. Food allergy
III. Vasculitis
IV. Sarcoptic mange
V. Other neoplasms
VI. Chronic stomatitis
VII. Autoimmune diseases: SLE or discoid lupus, pemphigus complex

Treatment and Monitoring

I. Prognosis is variable.
   A. Animals diagnosed late in the course may survive only 5 to 10 months.
   B. Mildly affected dogs may survive for longer periods.
II. Therapy of choice for some is lomustine (CCNU) 10 mg/kg PO every 3 weeks.
   A. Monitor CBC for thrombocytopenia, leukopenia, and anemia before each treatment.
   B. Monitor a biochemistry profile for elevations in liver enzymes before each treatment.
III. Topical nitrogen mustard has limited efficacy.
IV. Limited success has also occurred with combination chemotherapy of prednisone, cyclophosphamide, vincristine, chlorambucil, doxorubicin, and methotrexate.

Feline Thymoma–Associated Exfoliative Dermatitis

Definition and Causes

I. A rare exfoliative disease seen in cats with thymomas (see Chapter 73)
II. Thought to be associated with induction of autoreactive T cells

Clinical Signs

I. Exfoliative dermatitis occurs in middle-aged to older cats and has no sex predilection.
II. Erythema and exfoliation often start on the head, neck, and pinnae; the dermatitis then becomes generalized over weeks to months.
III. Alopecia and hyperpigmentation of the skin can occur.
IV. Accumulations of seborrheic debris may occur interdigitally and around claw beds.
V. Some cats become white from to loss of hair pigment (leukotrichia).
VI. Pruritus may be absent, minimal, or severe (rare).

Diagnosis

I. Biopsy of the skin reveals the following:
   A. The most consistent histological changes are hyperkeratosis and mild transepidermal and follicular apoptosis.
   B. Interface dermatitis may be present and involve follicles to the level of the isthmus.
   C. Basal cell apoptosis may be prominent.
   D. Sebaceous glands can be absent.
   E. Vacuolation of the dermal-epidermal junction may be seen.
   F. Pigmentary incontinence (macrophages filled with pigment) is a classic feature.
II. See Chapter 20 for diagnostic tests for thymomas.

Differential Diagnosis

I. SLE
II. Erythema multiforme
III. Epitheliotropic T-cell lymphoma
IV. Dermatophytosis
V. Demodicosis
VI. Pemphigus foliaceus
VII. Hyperadrenocorticism or diabetes mellitus, with associated bacterial, *Malassezia* spp., or dermatophyte infection

Treatment and Monitoring

I. Removal of the thymic mass is the treatment of choice.
   A. Noninvasive tumors have a good prognosis (median survival, 2 years).
   B. Invasive tumors (15%) have a poor prognosis, with survival rarely occurring beyond the immediate postoperative period.
II. Overall prognosis is poor when the tumor is not excised.
III. Most cats are euthanized within 4 to 5 months of initial onset of cutaneous lesions from worsening of the skin condition.

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CHAPTER 92

Pigmentary Disorders of the Skin

Manon Paradis

DISORDERS OF HYPERPIGMENTATION

Lentigo

Definition and Cause

I. In Latin, *lentigo* (plural, *lentigines*) is the word meaning lentil-shaped spot.
II. *Lentigo* describes the well-circumscribed black macules observed in mature dogs.
III. The cause of these lesions is usually unknown.
IV. Hyperpigmented (Box 92-1) macules or patches result from increased numbers of melanocytes in the epidermis, without evidence of focal proliferation.

Clinical Signs

I. Several well-circumscribed black macules develop over several months.
II. Subsequently they become static and remain unchanged for the life of the dog.
III. The most common location is on the ventrum.
IV. The condition affects mature dogs.
V. It is asymptomatic.

Diagnosis

I. Diagnosis is usually based on history and clinical findings.

Box 92-1

Terminology Pertaining to Pigmentary Changes of Hair and Skin

Term	Definition
Hyperpigmentation or hypermelanosis	Increased pigmentation of the skin or hair coat in areas that should be less pigmented
Melanoderma	Skin hyperpigmentation
Melanotrichia	Hair hyperpigmentation
Hypopigmentation or hypomelanosis	Lack of (or decrease in) pigmentation of the skin or hair coat in areas that should be pigmented
Leukoderma	Depigmented skin or mucosa
Leukotrichia	Depigmented hair shaft

II. Dermatohistopathologic examination reveals an increased number of melanocytes in the epidermis and the presence of melanin pigment in most keratinocytes.

Differential Diagnosis

I. Pigmented neoplasms of the skin, especially melanocytomas and melanomas
II. Papillomavirus-induced lesions: characterized by slightly rough black-pigmented macules to plaques that may transform into squamous cell carcinoma
III. Pigmented epidermal nevi
IV. Lentigo profusa
   A. Hereditary form of lentigo previously reported in pugs
   B. May be papillomavirus-induced lesions or pigmented epidermal nevi
V. Aforementioned conditions: hyperkeratotic surface or thickening

Treatment and Monitoring

I. None indicated: cosmetic condition only
II. Benign skin change

Lentigo Simplex in Orange Cats

Definition and Causes

I. Multiple lentigines affecting mucocutaneous junctions, especially in orange cats
II. Cause unknown
III. Most likely genetically determined

Pathophysiology

I. Hyperpigmented macules or patches result from an increased number of skin melanocytes and a hypermelanosis of the keratinocytes of the basal cell layer of the epidermis.
II. Focal proliferation of epidermis is not evident.

Clinical Signs

I. Lesions start as tiny black spots on the lips and often spread to the nose, gingiva, and eyelids (Figure 92-1).
II. Lentigines progressively increase in size (range from 1 to 9 mm in diameter) and number with age and may eventually coalesce.
III. Lesions may start in orange cats <1 year of age.
IV. Lentigines are not symptomatic.

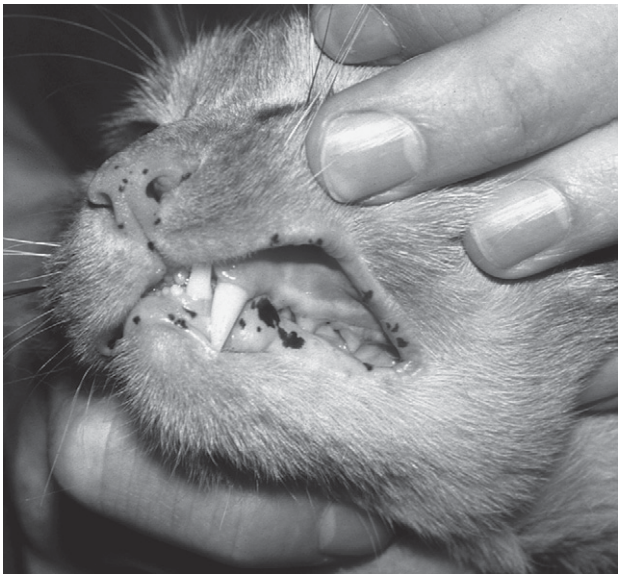

FIGURE 92-1 Lentigo simplex represented by multiple pigmented macules on the lips and nasal planum of an adult orange cat.

Diagnosis

I. Diagnosis is usually based on history and clinical findings.
II. Dermatohistopathologic examination reveals marked hypermelanosis, predominantly of the basal cell layer of the epithelium, and increased numbers of melanocytes.

Differential Diagnosis

I. Melanocytoma (benign melanoma)
II. Malignant melanoma

Treatment and Monitoring

I. None indicated
II. Cosmetic condition only

Postinflammatory Hyperpigmentation

Definition and Causes

I. Skin hyperpigmentation after inflammation is very common (especially in dogs), regardless of the inciting cause of the inflammation.
II. Hyperpigmentation is a common sequela to pyoderma, demodicosis, *Malassezia* spp. dermatitis, and dermatophytosis in dogs.
III. Dermatophytosis is one of the few skin diseases of cats in which hyperpigmentation may be seen.

Pathophysiology

I. Exact mechanism of hyperpigmentation after inflammation is unknown.
II. Hyperpigmentation associated with many pruritic diseases results from chronic irritation because of cutaneous friction in addition to inflammatory processes.

Clinical Signs

I. Postinflammatory skin hyperpigmentation can be focal and well circumscribed, patchy, or diffuse.
II. Focal postinflammatory melanotrichia is seen occasionally in adult dogs with silver or gray hair coats.
III. Cutaneous hyperpigmentation is uncommon in cats.

Diagnosis

I. Diagnosis is usually based on history and clinical findings.
II. Identification of an underlying cause is supportive.

Treatment and Monitoring

I. Identify and treat the underlying cause.
II. Melanoderma usually resolves slowly (over weeks to months), after the underlying cause has been corrected.
III. In most cases melanotrichia resolves at the next shedding cycle.

Hormonal-Associated Hyperpigmentation

Definition and Causes

I. Diffuse skin hyperpigmentation may result from endocrinopathies, such as hyperadrenocorticism, hypothyroidism, hyperestrogenism, and alopecia X.
II. The mechanism of hyperpigmentation is unknown.
III. Hyperpigmentation may result from direct and/or indirect effects of hormones on melanocytes.
IV. Tanning of alopecic skin exposed to ultraviolet light—the most potent stimulus for melanogenesis—may also be a contributing factor.

Clinical Signs

I. Diffuse melanoderma is seen, particularly of hypotrichotic or alopecic skin.
II. Melanotrichia is observed occasionally after treatment of canine hyperadrenocorticism.

Diagnosis

I. Diagnosis is usually based on history and clinical findings.
II. Identification of the underlying endocrinopathy is supportive.

Treatment and Monitoring

I. Identify and treat the underlying endocrinopathy.
II. Hyperpigmentation usually resolves slowly (over weeks to months), after the underlying endocrinopathy has resolved.

DISORDERS OF HYPOPIGMENTATION

Nasal Depigmentation

Definition and Causes

I. Acquired hypopigmentation of the nasal planum
II. Also known as *Dudley nose* or *snow nose*

III. Idiopathic disorder with genetic predisposition in golden retrievers, yellow Labrador retrievers, Siberian huskies and Alaskan malamutes
IV. Loss of pigment production by melanocytes of the nasal planum

Clinical Signs

I. Affected dogs are born with pigmented noses, but the black color of the nasal planum gradually lightens to a light brown (hypopigmentation) or pinkish color (depigmentation) (Figures 92-2 and 92-3).
II. Changes may be permanent or may wax and wane in some dogs.
III. Typically worse during the winter months (hence the colloquial name *snow nose*), with some increase in pigmentation in spring and summer.
IV. Other dermatologic lesions such as ulceration and crusts or pruritus are absent.
V. Normal cobble texture of the nasal planum is preserved, as opposed to autoimmune diseases in which the normal surface architecture is destroyed.

Diagnosis

I. Diagnosis is based on history and clinical findings.
II. Dermatohistopathologic examination reveals a marked reduction of epidermal melanin granules.

Differential Diagnosis

I. Vitiligo (see following section)
II. Cutaneous (discoid) lupus erythematosus
III. Pemphigus erythematosus
IV. Epitheliotropic lymphoma (mycosis fungoides)
V. Uveodermatologic syndrome (Vogt-Koyanagi-Harada–like syndrome; Table 92-1)

Treatment and Monitoring

I. No known treatment is available.
II. It is a cosmetic problem only.
III. The condition is considered a defect in show dogs.

Vitiligo

Definition and Causes

I. Vitiligo is an acquired disorder characterized by selective destruction of melanocytes in skin and hair matrix cells, which results in leukoderma and leukotrichia (see Box 92-1).
II. Vitiligo is presumed to be hereditary in some breeds, such as the Belgian shepherd, rottweiler, Doberman pinscher, and Siamese cat.

Pathophysiology

I. Various theories have been proposed to explain vitiligo, including the production of antimelanocyte antibodies.
II. In general, vitiligo is a spontaneous disorder and is not accompanied by inflammation.

Clinical Signs

I. One or several asymptomatic, possibly symmetrical, macular areas of leukoderma and/or leukotrichia develop, especially of the lips, buccal mucosa, muzzle, nasal planum, and footpads.
II. Depigmentation is usually permanent, but spontaneous repigmentation may occur.
III. It is usually first noted in young adulthood.
IV. The disorder is uncommon in dogs and rare in cats.

FIGURE 92-2 Depigmentation of the nasal planum in an adult Alaskan malamute (also called *Dudley nose* or *snow nose*).

FIGURE 92-3 Depigmentation of the nasal planum in an adult yellow Labrador retriever.

TABLE 92-1

Miscellaneous Acquired Pigmentary Disorders

DISORDER	DEFINITION AND CAUSE	DIAGNOSIS	CLINICAL SIGNS	TREATMENT AND MONITORING
Melanotrichia of feline acromelanism	Cats demonstrating acromelanism (dark extremities or points), such as the Siamese and Himalayan breeds, develop temporary coat color changes consisting of melanotrichia after inflammation or hair clipping	Diagnosis is based on compatible history and clinical findings Changes are confined to cats with acromelanism	Melanotrichia develops at the site of skin inflammation or after clipping of the truncal area	No treatment is required Melanotrichia usually resolves at the next shedding cycle
Acquired aurotrichia ("gilding syndrome")	Acquired pigment changes are seen in the hair coat of miniature schnauzers, presumably caused by a shift in eumelanins and pheomelanins	Diagnosis is based on compatible history and physical examination findings	Miniature schnauzers develop patches of golden hair in a previously normal, gray or black coat	No known treatment exists Spontaneous resolution occurs in 6-24 months
Malnutrition	Malnutrition is the cause—specifically trace element deficiencies such as copper and zinc, as well as low dietary tyrosine or phenylalanine	Diagnosis is based on suggestive history and physical examination findings	Black hair changes to reddish or brown hair	Feed a balanced diet Condition normally resolves when the underlying cause is removed
Endocrinopathies	Lightening of the hair coat occurs in dogs with Sertoli cell tumors, alopecia X, hypothyroidism, or hyperadrenocorticism	Diagnosis is based on suggestive history, physical examination findings, and appropriate diagnostic tests	Old retained hair shafts become dry, frizzy, and lighter in color	Treat the underlying cause Condition normally resolves when the underlying cause is removed
Environmental factors	Color changes occur after exposure to chronic ultraviolet light or other environmental elements (e.g., chlorine, detergents)	Diagnosis is based on suggestive history and physical examination findings	Old retained hair shafts become dry, frizzy, and lighter in color	Avoid excessive exposure to causative environmental factors Condition resolves when the underlying cause is removed
Uveodermatologic syndrome	It is considered an immune-mediated disease, with melanocytes as the target Hair, skin, and the uveal tract of the eyes are affected Alaskan sled dogs and oriental breeds are predisposed; also documented in the Australian shepherd, Irish setter, golden retriever, St. Bernard, and other breeds It may affect dogs of all ages	Diagnosis is based on compatible history and physical examination findings Histopathology of skin biopsies is diagnostic: lichenoid dermatitis with many macrophages, uncommon apoptotic cells in the basal cell layer, pigmentary incontinence in depigmented areas	Often acute onset of anterior or panuveitis occurs Possible retinal detachment, secondary glaucoma, and blindness may occur Depigmentation of eyelids, nose, lips, footpads, scrotum, and (sometimes) haired areas of the body is seen Oral and cutaneous ulcerations are possible in severe forms Mild cutaneous signs include depigmentation of skin and hair, as well as mild scaling and erythema of affected areas Generalized or focal vitiligo is a classic finding	Prednisone is administered 2 mg/kg PO SID or divided BID initially, then tapered once signs are controlled Azathioprine (1-2 mg/kg PO SID) may be needed in addition to prednisone for difficult to control cases See also Chapter 102

Diagnosis

I. History of acquired depigmentation of one or several macular areas of skin, mucosa, or hair, with no history of previous trauma is highly suggestive.
II. Dermatohistopathologic examination reveals normal skin except for the absence of melanocytes and melanin.

Differential Diagnosis

I. Nasal depigmentation (Dudley nose, snow nose)
II. Uveodermatologic syndrome (Vogt-Koyanagi-Harada–like syndrome)
III. Certain autoimmune diseases: cutaneous lupus erythematosus, pemphigus erythematosus, pemphigus foliaceus
IV. Alopecia areata: leukotrichia possibly seen in resolving lesions
V. Epitheliotropic lymphoma (mycosis fungoides)
VI. Postinflammatory or posttraumatic hypopigmentation

Treatment and Monitoring

I. No known treatment is available.
II. Vitiligo is a cosmetic disorder that does not affect the animal's quality of life.

Postinflammatory Hypopigmentation

Definition and Causes

I. It is an acquired hypopigmentation of previously normal skin and hair after destruction of melanocytes.
II. Potential causes include trauma, burns, and infection.
III. A number of inflammatory diseases may begin with hypopigmentation of the nose and occasionally the lips, such as cutaneous lupus erythematosus, pemphigus erythematosus, pemphigus foliaceus, and uveodermatologic syndrome.

Pathophysiology

I. Selective destruction of melanocytes occurs in skin and hair matrix cells.
II. Secondary leukoderma and leukotrichia develop.

Clinical Signs

I. Leukoderma and/or leukotrichia develop at a site of previous skin trauma.
II. Depigmentation is usually permanent.

Diagnosis

I. Acquired depigmentation occurs at the site of previous trauma, infection, or inflammation.
II. It can occur in any breed of dog or cat.

Differential Diagnosis

I. Vitiligo and other hypopigmenting disorders
II. Epitheliotropic lymphoma (see Chapter 91)

Treatment and Monitoring

I. Repigmentation may occur after treatment of the underlying cause.
II. Sunscreen applied before sun exposure may prevent sunburn in the hypopigmented skin.
III. Depigmented skin may be prone to sunburn and subsequent actinic dermatitis.

MISCELLANEOUS ACQUIRED PIGMENTARY DISORDERS

See Table 92-1.

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CHAPTER 93

Crusting and Scaling Dermatoses

Nicola Williamson

CONGENITAL/DEVELOPMENTAL DISORDERS

Primary Seborrhea

Definition and Causes

I. Primary seborrhea is an inherited hyperproliferative disease in which the epidermal cell turnover time is approximately 8 days instead of the normal 21 days.
II. It may be an autosomal recessive trait in West Highland white terriers and Persian cats.

Pathophysiology

I. It is most commonly seen in the American cocker spaniel, West Highland white terrier, English springer spaniel, and basset hound.
II. Other reported breeds include the Jack Russell terrier, Cavalier King Charles spaniel, Wheaton terrier, Chinese shar-pei, dachshund, Doberman pinscher, German shepherd dog, Irish setter, and Labrador retriever.
III. It may also be seen in Persian, Himalayan, and exotic shorthaired cats.
IV. No sex predilection has been noted.

Clinical Signs

I. Dogs
  A. Pruritus is common.
  B. Dogs develop signs early in life that progress with age.
  C. The American cocker spaniel, West Highland white terrier, English springer spaniel, Chinese shar-pei, basset hound, and Labrador retriever tend to have a greasy seborrhea that involves the ventral neck, face, perineum, and feet.
  D. Doberman pinschers and Irish setters tend to have a dry, flaky hair coat.
  E. Ceruminous hyperplasic otitis externa may be noted.
  F. Greasy, malodorous coat may be present.
  G. Digital hyperkeratosis can be present.
  H. Brittle claws may occur.
  I. Lesions tend to be worse around the mouth, eyes, pinnae, axillae, groin, and feet.
II. Cats
  A. Most cats display clinical signs within the first 2 to 3 days of life.
  B. Less severe cases may become evident at 6 weeks of age.
  C. Hair appears dirty and sticks together.
  D. Over time the whole body becomes greasy, scaly, and alopecic.
  E. Waxy accumulations can occur in the ears and face folds.
  F. Rancid odor is often present.

Diagnosis

I. History of early age of onset
II. Histopathologic changes on skin biopsy
  A. Orthokeratotic or parakeratotic hyperkeratosis
  B. Follicular keratosis with variable dyskeratosis
  C. Hyperplasic, superficial, perivascular dermatitis
  D. Possibly bacteria and yeast within the keratin

Differential Diagnosis

I. Ichthyosis
II. Epidermal dysplasia
III. Vitamin A–responsive dermatitis
IV. Sebaceous adenitis
V. Causes of secondary seborrhea

Treatment

I. Dogs
  A. Institute good nutrition.
  B. Treat secondary bacterial and yeast infections on the skin and in the ears.
  C. Use topical antiseborrheic shampoos and emollients for bathing.
    1. Initially bathing may be required every 2 to 3 days for 2 to 3 weeks, until the seborrhea is controlled.
    2. Bathing can then be decreased to every 7 to 14 days.
  D. Fatty acid supplementation with eicosapentaenoic acid (EPA) 180 mg/5 kg PO SID may help control scaling and associated transepidermal water loss.
  E. Prednisone 1 to 2 mg/kg PO SID may be used for pruritus, then tapered to the lowest possible dose.
  F. Retinoid administration may slow keratinocyte differentiation.
    1. Vitamin A: maximum dose of 400 IU/kg/day PO indefinitely
    2. Etretinate 1 mg/kg PO SID indefinitely
    3. Acitretin 0.5 to 1 mg/kg PO SID indefinitely

G. Vitamin D_3 10 ng/kg PO SID may inhibit keratinocyte proliferation, but calcium levels must be closely monitored.

II. Cats
   A. No effective treatment is known.
   B. Periodic clipping, bathing, and grooming may keep the cat comfortable.
   C. Affected cats are often euthanized.

Monitoring of Animal

I. Prognosis depends on the severity of the seborrhea.
II. Seborrhea is a lifelong condition and is incurable.
III. Animals receiving prednisone are monitored for polydipsia, polyuria, polyphagia, weight gain, panting, dull hair coat, vomiting, diarrhea, pancreatitis, elevated liver enzymes, diabetes mellitus, gastrointestinal (GI) ulcerations, muscle wasting, behavioral changes, and secondary infections.
IV. Animals receiving retinoids are monitored for anorexia, vomiting, diarrhea, polydipsia, joint pain and stiffness, behavioral changes, cracked footpads, cutaneous erythema, swelling of the tongue, and keratoconjunctivitis sicca (KCS).
V. Animals receiving Vitamin D_3 are monitored for hypercalcemia.

Familial Footpad Hyperkeratosis

See Chapter 90.

Miscellaneous Congenital Crusting Disorders

See Table 93-1.

INFLAMMATORY DISORDERS

Secondary Seborrhea

Definition and Causes

I. Secondary seborrhea is a chronic skin disease that manifests as increased scale production, greasy coat or skin, and occasionally inflammation.
II. Potential causes include the following:
   A. Allergic disorders: atopy, food allergy, flea allergic dermatitis, contact allergy
   B. Endocrine disorders: diabetes mellitus, hyperadrenocorticism, hypothyroidism, sex hormone imbalances
   C. Infectious disorders: bacterial pyoderma, *Malassezia* spp. dermatitis, dermatophytosis, leishmaniasis
   D. Immune-mediated disorders: pemphigus foliaceus, pemphigus erythematosus, systemic lupus erythematosus, discoid lupus erythematosus, sebaceous adenitis, cutaneous drug reaction
   E. Nutritional disorders: dietary imbalance, zinc-responsive dermatosis, vitamin A–responsive dermatosis
   F. Parasitic disorders: cheyletiellosis, demodicosis, *Scabies* spp., *Otodectes* spp., pediculosis
   G. Metabolic disorders: superficial necrolytic dermatitis, malabsorption, maldigestion
   H. Neoplastic disorders: cutaneous epitheliotropic lymphoma

Diagnosis

I. Compatible history and signalment
II. Appropriate lab work to evaluate for cutaneous and systemic diseases
III. Histopathologic changes on skin biopsy
   A. Orthokeratotic or parakeratotic hyperkeratosis
   B. Follicular keratosis with variable dyskeratosis
   C. Hyperplasic, superficial, perivascular dermatitis
   D. Possibly bacteria and yeast within the keratin

Differential Diagnosis

I. Primary seborrhea
II. Ichthyosis
III. Epidermal dysplasia
IV. Vitamin A–responsive dermatosis
V. Sebaceous adenitis

Treatment and Monitoring

I. Determine and treat the underlying disorder.
II. See previous discussion of Primary Seborrhea.

IDIOPATHIC DISORDERS

Sebaceous Adenitis

Definition

I. An uncommon, idiopathic disease affecting the sebaceous glands of dogs
II. Rare in cats

Causes and Pathophysiology

I. Four theories exist as to the cause and pathogenesis.
   A. Inherited disease causing the destruction of sebaceous glands
   B. Cell-mediated response directed against the sebaceous gland
   C. Keratinization disorder that causes blockage of the sebaceous ducts, resulting in glandular inflammation
   D. Abnormality in dermal lipid production
II. It is thought to be an autosomal recessive trait in standard poodles.

Clinical Signs

I. Middle-aged dogs of either sex are affected.
II. Breed predilections include the standard poodle, vizsla, Samoyed, Akita, dachshund, German shepherd dog, Belgian shepherd, and mixed-breed dogs.
III. Lesions are usually bilaterally symmetrical and affect the head, face, pinnae, and trunk.
IV. Lesions initially develop on the dorsal surfaces of the previously mentioned areas.
V. Lesions can also develop on the tail and cause a "rat tail" appearance.
VI. Secondary bacterial infections may cause folliculitis and furunculosis.
VII. Short-coated breeds (vizsla, dachshund) demonstrate the following:
   A. Lesions are typically asymptomatic and appear as peripherally expanding areas of alopecia and scale.

Text continued on p. 911.

TABLE 93-1

Miscellaneous Congenital Crusting Disorders

DISORDER	SPECIES/BREED	CAUSE	CLINICAL SIGNS	DIAGNOSIS	TREATMENT/PROGNOSIS
Idiopathic facial dermatitis	Persian, Himalayan cats	Idiopathic keratinization disorder	Median age of appearance is 12 months Black exudates appear on the skin and distal portions of the hair shafts with inflammation of the adjacent skin Black, waxy material is seen in the ears Mucoid ocular discharge is seen Lesions are confined to the head and neck, primarily on the chin, around the mouth, and eyes Variable pruritus, secondary infections, and submandibular lymphadenopathy may develop	Diagnosis is based on compatible signalment and history Biopsy results include the following: (1) orthokeratotic hyperkeratosis and crusting, (2) hyperplasia of the epidermis, (3) superficial to perivascular interface dermatitis, with neutrophils, eosinophils, and mast cells predominating, (4) bacteria and *Malassezia* spp.	Treatment is usually unsuccessful Rare reports have indicated positive response to cyclosporine *(Neoral)* at 6-7 mg/kg/day PO Secondary bacterial and *Malassezia* spp. infections are treated Partial control may be obtained with prednisone 1-3 mg/kg PO SID for 4 weeks, then decreased to 1-3 mg/kg PO QOD, or with methylprednisolone acetate 4 mg/kg SC, infrequently
Ichthyosis	Both dogs and cats: West Highland white terrier, golden retriever, Jack Russell terrier, Yorkshire terrier, Wheaton terrier	Congenital keratinization disorder causing excessive scaling Also called *fish scale disease* Autosomal recessive trait	Most of the body has tight adherent scale that flakes off in large sheets Erythematous, scaly patches may be prominent in flexor and interdigital areas Thickening of footpad margins and nasal planum is common Perioral and periocular hyperkeratosis may occur	Diagnosis is based on compatible signalment and history Biopsy results include the following: (1) orthokeratotic hyperkeratosis with hypergranulosis, (2) often numerous mitotic figures in keratinocytes, (3) follicular plugging and keratosis, (4) reticular degeneration	Condition is chronic, incurable, and difficult to manage No specific treatment exists Frequent bathing with antiseborrheic (salicylic acid or sulfur based) shampoos followed by emollient rinses is recommended Information regarding retinoid therapy is as follows: (1) sotretinoin has been ineffective, (2) acitretin *(Soriatane)* 1-2 mg/kg PO SID has helped some cases, and it may take up to 3 months for remission to occur, with administration then decreased to QOD

TABLE 93-1

Miscellaneous Congenital Crusting Disorders—*cont'd*

DISORDER	SPECIES/BREED	CAUSE	CLINICAL SIGNS	DIAGNOSIS	TREATMENT/PROGNOSIS
Epidermal dysplasia	West Highland white terrier	Keratinization disorder Also called *armadillo skin* Autosomal recessive trait	Greasy coat, with mild to moderate pruritus initially affecting the face, ears, ventrum, limbs, and feet is seen Condition progresses to widespread alopecia, erythema, hyperpigmentation, lichenification, and crusting	Diagnosis is based on compatible signalment and history Biopsy results include the following: (1) epidermal hyperplasia and dysplasia with perivascular dermatitis; (2) excessive mitotic figures in the keratinocytes; (3) crowding of basal cell keratinocytes; (4) loss of polarity; (5) often budding yeast on or in the surface and superficial follicular keratin	No specific treatment exists Secondary infections are treated with systemic antibacterial drugs and then maintained with topical therapy
Exfoliative cutaneous lupus erythematosus	See Chapter 91	See Chapter 91	See Chapter 91	See Chapter 91	See Chapter 91
Jack Russell terrier vasculopathy	Jack Russell terrier	Vascular disorder of genetic origin Few cases occurred within 2-3 weeks of vaccination See Chapter 91	Small vessel vasculitis resulting in alopecic, crusting and ulcerated skin over bony prominences of the head and extremities is seen Punctate ulcers occur on the footpads V-shaped necrotic wedges of the pinnae are reported	Diagnosis is based on compatible signalment and history Biopsy results include the following: (1) cell-poor leukocytoclastic vasculitis; (2) apoptosis of basal cell layer; (3) pigmentary incontinence; (4) ischemic degeneration of hair follicles	The following drugs have been used alone and in conjunction with each other: (1) prednisolone 1 mg/kg PO SID; (2) dapsone 1 mg/kg PO TID; (3) vitamin E 200-400 IU PO SID NOTE: Relapses are common with drug withdrawal

Continued

TABLE 93-1

Miscellaneous Congenital Crusting Disorders—*cont'd*

DISORDER	SPECIES/BREED	CAUSE	CLINICAL SIGNS	DIAGNOSIS	TREATMENT/PROGNOSIS
Acrodermatitis	Bull terrier	Inherited autosomal recessive lethal disease of white bull terriers (rare) Abnormalities in zinc and copper metabolism	No sex predilection exists Condition is seen shortly after birth At birth the skin color is lighter than normal Usually by 6-8 weeks, an erythematous, exfoliative, papulopustular dermatitis is present at mucocutaneous junctions and the distal extremities Ulcers and crusts are usually prominent on the pinnae and muzzle Feet are splayed, with abnormal cornification of the pads (exfoliation, villous hypertrophy, and fissures) Claws may be dystrophic and paronychia is usually present Hard palate may be abnormally arched Secondary pyodermas, *Malassezia* spp. dermatitis, candidiasis, and otitis can occur Other signs include growth retardation, abnormal behavior, bronchopneumonia, and diarrhea Average lifespan is 7-8 months, although some affected animals may live up to 3 years	Diagnosis is based on compatible signalment and history Biopsy results include the following: (1) diffuse compact layers of massive parakeratosis; (2) focal crusting; (3) possible laminar pallor	No cure exists Secondary infections are treated Zinc supplementation is usually ineffective Parents of affected dogs should not be bred because they are carriers; littermates should not be bred Normal littermates may experience zinc-responsive dermatosis

B. Scale is typically nonadherent and fine.
C. Swelling of the eyelids, muzzle, and lips can occur.

VIII. In the standard poodle, lesions start as hyperkeratosis and progress to alopecia.
A. Silver-white scale is present along with a dull, dry coat.
B. Follicular casts are common.
C. In some cases the initial signs may be changing of hair coat color and straightening of the hair.
D. Lesions typically are on the head, pinnae, and eventually involve the neck and dorsal trunk.

IX. Akitas usually have generalized, erythematous, and greasy changes to their coats.
A. Matting of the hair, scale, yellow-brown greasy keratosebaceous debris, papules, pustules, and hair casts are common.
B. Undercoat may be lost.
C. Secondary pyoderma is common.
D. Fever, malaise, and weight loss can occur.

X. German shepherd dogs have lesions that usually start on the tail and advance cranially.

XI. Samoyeds have dull, brittle, and broken hairs.
A. Follicular casts are common.
B. Moderate to severe truncal scaling and alopecia may occur.

XII. Most dogs are not pruritic unless a secondary bacterial infection occurs.

XIII. Nonpredisposed breeds may have an acute onset of intense pruritus and generalized exfoliative erythroderma that progresses to nonpruritic alopecia.

XIV. No breed, age, or sex predilection exists in the cat.
A. Lesions typically begin on the head, neck and pinnae and progress caudally over the body.
B. Lesions are comprised of broken hairs, alopecia, scales, crusts, and hair casts.

Diagnosis

I. Suggestive history and signalment in a predisposed breed

II. Diagnosis confirmed with skin biopsy
A. Early lesions
1. Varying degrees of granulomatous or pyogranulomatous sebaceous adenitis are seen.
2. Usually sebocytes are no longer visible.
3. The disease is diagnosed by identifying discrete perifollicular granulomas in an area where a sebaceous gland would normally be found.
4. Early involvement of adnexa is not seen.
B. Chronic lesions
1. Sebaceous glands are absent and replaced by fibrosis.
2. Orthokeratotic hyperkeratosis of the epidermis and hair follicles is common.
3. Hair follicles are often atrophied.

Differential Diagnosis

I. Bacterial pyoderma

II. Causes of secondary seborrhea

III. Demodicosis

IV. Dermatophytosis

V. Follicular dysplasia

VI. Vitamin A–responsive dermatitis

VII. Endocrinopathies, especially hypothyroidism

Treatment

I. Secondary infections are treated.

II. Mild cases may respond to keratolytic shampoos and emollient rinses.
A. Propylene glycol 50% to 75% rinses are used initially SID, then reduced to every 2 to 3 days once clinical signs are controlled.
B. Baby oil solution (1:1 mixture with water) can be applied to the skin for several hours, then washed off with shampoo.

III. Combination of tetracycline and niacinamide is an option.
A. Dogs <10 kg
1. Tetracycline 250 mg and niacinamide 250 mg PO TID or
2. Tetracycline 500 mg and niacinamide 250 mg PO in the morning; tetracycline 250 mg and niacinamide 500 mg PO in the evening
B. Dogs >10 kg
1. Tetracycline 500 mg and niacinamide 500 mg PO TID or
2. Tetracycline 1000 mg and niacinamide 500 mg PO in the morning; tetracycline 500 mg and niacinamide 1000 mg PO in the evening

IV. Some dogs respond to omega-3 and omega-6 fatty acid supplementation.

V. Corticosteroid therapy is of no benefit.

VI. Severe cases may warrant systemic retinoid administration.
A. Etretinate 1 to 2 mg/kg PO SID
B. Acitretin 0.5 to 1.0 mg/kg PO SID

VII. Cyclosporine 5 mg/kg PO BID may help when retinoid administration fails.

VIII. Spontaneous remission is rare.

IX. In cats, one report suggests the of use of cyclosporine 5 mg/kg PO SID initially, then tapered to 5 mg/kg PO QOD (Noli and Thomas, 2006).

Monitoring of Animal

I. Because inflammation of the sebaceous glands cannot be stopped, treatment is aimed at controlling the signs.

II. Animals receiving retinoid therapy are monitored for anorexia, vomiting, diarrhea, polydipsia, joint pain and stiffness, behavioral changes, cracked footpads, cutaneous erythema, swollen tongue, and KCS.

III. Animals receiving cyclosporine are monitored for anorexia, vomiting, diarrhea, weight loss, myelosuppression, and elevations in liver enzymes, blood urea nitrogen (BUN), and creatinine.

Pinnal Seborrhea

Definition and Causes

I. Seborrheic disorder of the ear margins

II. Dachshunds possibly predisposed

III. Occurs in dogs with pendulous ears
IV. Pathophysiology unknown

Clinical Signs

I. Ear margins are the only site affected.
II. Keratinous debris is initially noted along the ear margins.
III. Ear margins can develop alopecia, crusting, fissures, and ulcerations.
IV. Condition is exacerbated by dry heat.

Diagnosis

I. Compatible signalment, history, and clinical signs
II. Orthokeratotic and/or parakeratotic hyperkeratosis and follicular keratosis on biopsy of affected areas

Differential Diagnosis

I. Vasculitis (see Chapter 91)
II. Sarcoptic mange (see Chapter 85)
III. Causes of secondary seborrhea

Treatment

I. No specific therapy known
II. Symptomatic care
  A. Wash ear margins with salicylic acid, sulfur, or benzoyl peroxide–containing shampoos SID to QID until all debris is removed.
  B. Once debris is removed, wash areas with shampoo as needed.
  C. Moisturizer is applied after shampooing.
III. Possible helpful measures
  A. Pentoxifylline 10 to 15 mg/kg PO BID to TID
  B. Topical retinoid therapy
  C. Essential fatty acid supplementation
IV. Severe cases: topical or systemic steroids, surgical excision of affected areas

Monitoring of Animal

I. Initial improvement may be noted 4 to 6 weeks after initiation of symptomatic treatment.
II. If topical therapy does not reduce the amount of scale, then pentoxifylline may be considered.
III. One month after starting pentoxifylline, decreased ulceration and/or scale may be noted.
IV. Once the pinnae have normalized (may take 4 to 12 months) pentoxifylline can be decreased to SID, then QOD, and eventually stopped if the condition does not worsen.

INFECTIOUS DISORDERS

Leishmaniasis

See Chapter 89.

PARASITIC DISORDERS

See Chapter 85.

NUTRITIONAL DISORDERS

Zinc-Responsive Dermatosis

Definition and Causes

I. Zinc-responsive dermatosis is hyperkeratosis of the skin as a result of zinc deficiency.
II. Syndrome I occurs in Alaskan malamutes and Siberian huskies.
III. Syndrome II arises from a zinc-deficient diet, interference of zinc absorption from excessive calcium or phytates in the diet, or essential fatty acid deficiency (generic dog food disease).
IV. Any breed may be affected, and lesions may vary within a litter.

Pathophysiology

I. Syndrome I: genetic defect resulting in decreased intestinal zinc absorption
  A. Lesions usually develop during puberty but may be exacerbated with illness, estrus, or pregnancy.
  B. Age of onset varies from 0.5 to 10.5 years, with 41% developing clinical signs before 2 years of age (Columbini, 1999).
  C. Lesions often develop between September and April.
  D. No sex predilection has been identified.
II. Syndrome II: zinc-deficient diet

Clinical Signs

I. General signs
  A. Anorexia, growth retardation, poor wound healing
  B. Reproductive disorders
  C. Lethargy, pyrexia, lymphadenopathy, cutaneous lesions
II. Cutaneous lesions of syndrome I
  A. Focal alopecia and erythema occur early and progress to scaling and crusting.
  B. Lesions are typically seen around the eyes, mouth, footpads, perianal region, and at pressure points.
  C. Hair coat may be dull and dry, with excessive sebum production.
  D. Secondary bacterial and/or *Malassezia* spp. infections are common.
  E. Pruritus is common.
III. Cutaneous lesions of syndrome II
  A. Lesions are similar to syndrome I.
  B. Lesions primarily occur on the head and pressure points of the extremities.

Diagnosis

I. Compatible history, signalment, and clinical signs
II. Skin biopsy
  A. Severe, diffuse epidermal and follicular parakeratosis, superficial perivascular dermatitis
  B. Secondary infections common

Differential Diagnosis

I. Autoimmune diseases: pemphigus complex, discoid or systemic lupus erythematosus

II. Bacterial pyoderma
III. Demodicosis
IV. Dermatophytosis
V. Metabolic epidermal necrosis

Treatment and Monitoring

I. Syndrome I requires lifelong elemental zinc supplementation.
   A. Zinc sulfate 10 mg/kg/day PO; crush tablets and mix with food to enhance absorption
   B. Zinc gluconate 5 mg/kg/day PO
   C. Zinc methionine 1.7 mg/kg/day PO
II. Syndrome II requires correction of nutritional imbalances.
   A. Zinc supplementation (previously discussed) speeds resolution of symptoms.
   B. Once resolution of clinical signs occurs, discontinue zinc supplementation.
III. If no response to treatment is seen within 4 weeks, then the zinc dose is increased by 50% and/or low-dose prednisone may be started at 0.5 mg/kg/day PO to enhance zinc absorption.
IV. Adding an essential fatty acid supplement also helps zinc metabolism.
V. Dogs that do not respond to these therapies may need injectable zinc sulfate (10 to 15 mg/kg IV).
   A. Injections are given weekly for a minimum of 4 weeks.
   B. Maintenance injections may be needed every 1 to 6 months to prevent relapses.
VI. Treat secondary bacterial infections.

Vitamin A–Responsive Dermatosis

Definition and Causes

I. Rare disease affecting cornification
II. Most commonly seen in American cocker spaniels
III. Possible hereditary origin

Clinical Signs

I. Adult-onset disorder
II. Lesions most commonly on lateral and ventral chest and abdomen
III. Mild to moderate pruritus
IV. Dull, dry, disheveled hair coat
V. Easily epilated hair
VI. Alopecia, papules, crusts, scale
VII. Severe follicular plugging, with follicular fronds or casts
VIII. Concurrent ceruminous otitis

Diagnosis

I. Adult age of onset
II. Skin biopsy
   A. Severe follicular keratosis
   B. Follicular fronds
   C. Furunculosis

Differential Diagnosis

I. Primary seborrhea
II. Sebaceous adenitis
III. Zinc-responsive dermatosis
IV. Causes of secondary seborrhea

Treatment and Monitoring

I. Administer Vitamin A 10,000 IU PO SID with a fatty meal.
   A. Improvement may take 4 to 6 weeks, and remission may require 8 to 10 weeks of therapy.
   B. Lifelong therapy is usually needed to maintain remission.
II. Antiseborrheic shampoos and emollients may be used several times weekly until remission, then 2 to 4 times monthly for maintenance.

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CHAPTER 94

Introduction

Rachel D. Ring

GENERAL CONSIDERATIONS

I. Ocular discomfort or vision loss in animals often evokes emotional responses in owners and prompts presentation to the veterinarian.
II. Common presenting complaints include loss of vision, ocular discomfort or discharge, and/or changes in the appearance of the eye.
III. Presenting complaints can be restricted to the eye or include systemic manifestations.
IV. Common clinical signs are exhibited for both minor and potentially blinding ocular disorders.

EXAMINATION PROCEDURES

I. Obtain a pertinent history.
  A. Animal signalment
  B. Onset and duration of problem
  C. Any concurrent systemic signs or illness
  D. Current and previous environment
  E. Current and/or previous therapy and response
  F. Preventative health status
II. Observe the animal in the examination room.
  A. Initial assessment of vision
  B. Ability to negotiate room and objects
  C. Assessment of adnexal and ocular positioning before handling
  D. Determination of behavioral, neurological, or other impairments that may contribute to or imply visual disorders
III. Perform an adnexal examination.
  A. Direct visual examination with penlight or transilluminator
  B. Palpation of lids, orbital rim, and globe positioning in orbit (retropulsion)
  C. Examination under magnification with slit lamp biomicroscopy or otoscope lens (or magnifying glass)
IV. Assess cranial nerve reflexes (see Chapter 105).
  A. Pupillary light response (PLR)
    1. Assesses retina and optic nerve and tracts, as well as oculomotor nerve and iris pupillary musculature
    2. Subcortical, does not determine vision
    3. Requires bright penlight or transilluminator
  B. Dazzle response
    1. Retina and optic nerve and tracts assessed, as well as facial nerve and lid musculature
    2. Subcortical, does not determine vision
    3. Can provide basic assessment of retinal function when unable to visualize or elicit PLR
  C. Menace response
    1. Retina, optic nerve and tracts, and visual cortex assessed, as well as facial nerve and lid musculature
    2. False-positive test when tactile air currents created
    3. Learned reflex: absent in young animals
V. Consider other routine testing.
  A. Schirmer's tear test (STT) (see Chapter 97)
    1. Filter paper measurement of tear production in millimeters per minute (mm/min)
    2. Important test to determine borderline to low tear production
  B. Fluorescein dye test (see Chapter 98)
    1. Corneal epithelium is hydrophobic, whereas the stroma is hydrophilic.
    2. Stain retention by exposed stroma indicates corneal erosion or ulceration.
  C. Tonometry (see Chapter 100)
    1. Measurement of intraocular pressure in millimeters of mercury (mm Hg)
    2. Indentation or applanation methods
    3. Important in diagnosis of glaucoma and uveitis.
VI. Perform an intraocular examination.
  A. Direct visual examination with penlight or transilluminator
  B. Magnified examination with slit lamp biomicroscopy

C. Funduscopy
   1. Examination with a direct ophthalmoscope provides the most magnification.
   2. Indirect examination with a light source and indirect lens provides the best panoramic view.

ANCILLARY DIAGNOSTIC TESTS

I. Maze testing (obstacle course)
   A. Observed ability to negotiate obstacles
   B. Dimmed and normal lighting
   C. Each eye patched, if necessary
II. Laboratory diagnostics
   A. Indicated for suspected systemic involvement or preanesthetic workup
   B. Complete blood count and serum chemistries as appropriate for problem and age
   C. Serological testing for regional infectious organisms
   D. Bacterial and/or fungal cultures
   E. Cytological and/or histopathologic examination
III. Electrodiagnostics
   A. Electroretinogram
      1. Used to evaluate retinal function
      2. Important for diagnosis of retinal disease and preoperative workup before cataract surgery (see Chapters 101 and 102)
   B. Visual evoked potential
      1. Used to evaluate optic nerve, optic tract, and occipital cortex
      2. Distinguishes between visual problems of ocular versus visual pathway origin (see Chapter 105)
IV. Ocular and orbital imaging
   A. Radiography
      1. Plain films are helpful for evaluation of orbit and sinuses.
      2. Contrast radiography is performed for nasolacrimal, orbital, and fistulous and cystic disorders.
   B. Ultrasonography
      1. A-scan, B-scan, or color Doppler techniques
      2. B-scan most useful in opaque eyes and for evaluation of orbital soft tissues
   C. Computed tomography (CT)
      1. Often used with orbital or visual pathway disorders
      2. Provides good imaging of orbital soft tissue and bony structures
   D. Magnetic resonance imaging
      1. Application similar to CT
      2. Excellent imaging of intraocular and extraocular soft tissue structures
      3. Less precise resolution of bony structures

CHAPTER 95

Diseases of Eyelids

Stacy E. Andrew

CONGENITAL/DEVELOPMENTAL DISORDERS

Dermoid

Definition and Causes

I. Dermoid is a congenital mass with normal epidermal components located in an abnormal place.
II. It is usually an incidental finding.
III. The condition is heritable in some breeds of dog (Dalmatian, German shepherd dog, Saint Bernard) (Bedford, 1999).
IV. It can result from inclusion or arrest of epidermal and connective tissues during fetal cleft closure (Cook, 1999).

Pathophysiology

I. Can include stratified squamous epithelium, hair follicles, sebaceous glands, adipose tissue, sweat glands, and (rarely) cartilage or bone
II. Unilateral or bilateral, and may be multiple in number
III. May involve the eyelid, conjunctiva, and/or cornea
IV. Variable irritation depending on the size of lesion and the component tissues

Clinical Signs

I. Clinical signs are associated mainly with corneal and conjunctival irritation from hairs.
   A. Blepharospasm
   B. Epiphora
   C. Conjunctival hyperemia
   D. Corneal ulceration
II. Normal blinking may be disrupted.

Diagnosis

I. Complete ophthalmic examination reveals presence of abnormally located epidermal tissue.
II. Excisional biopsy and histopathologic examination of submitted tissue are conclusive.

Differential Diagnosis

I. Scar tissue
II. Neoplasia

Treatment

I. If the lesion is small and no clinical signs exist, then no treatment is necessary.
II. Small eyelid lesions (less than one fourth the length of the palpebral fissure) are removed by wedge resection.
III. Larger lesions often require sliding skin grafts or skin transposition techniques (Bedford, 1999).

Monitoring of Animal

I. If surgery is performed, sutures are removed in 10 to 14 days.
II. Stain the cornea with fluorescein to ensure that corneal ulceration has not occurred.

Eyelid Agenesis

Definition

I. Also referred to as *eyelid coloboma*
II. Failure of development of the eyelid, with focal absence of skin, conjunctiva, and fornix

Causes

I. The cause is unknown.
II. It is much more common in cats than dogs.
III. Ventromedial eyelid agenesis may be related to failure of optic fissure closure.

Pathophysiology

I. Upper eyelids develop from the frontonasal process (Cook, 1999).
II. Eyelid epidermis, cilia, and conjunctiva arise from surface ectoderm; the dermis and tarsus arise from neural crest mesenchyme.
III. The condition is usually bilateral, involving the lateral portion of the upper eyelid; however, it may be unilateral.
IV. Other ocular tissues (iris, sclera, optic nerve) can also be involved.

Clinical Signs

I. Proportional to amount of eyelid missing
II. Related to inability to cover the cornea or to contact from trichiasis hairs touching the cornea
III. Possibly asymptomatic
IV. Epiphora, blepharospasm
V. Exposure keratitis: vascularization, ulceration, scarring, pigmentation
VI. Visual deficits if other ocular defects present

Diagnosis

I. Diagnosis is based on the absence of eyelid tissue.
II. Rule out concurrent ocular anomalies.
  A. Iris, scleral, and/or optic nerve colobomas
  B. Keratoconjunctivitis sicca or lacrimal gland deficiency

Differential Diagnosis

I. Entropion
II. Corneal ulceration
III. Symblepharon

Treatment

I. Very young kittens and mature animals with small lesions that are asymptomatic need periodic monitoring for corneal irritation.
II. Topical lubricating ointment is used as needed in animals with only minor clinical signs (e.g., epiphora).
III. Carbon dioxide laser therapy or cryotherapy is useful to remove trichiasis hairs.
IV. Reconstructive blepharoplasty (surgical reconstruction of the eyelid margin and upper eyelid) is indicated for larger defects with keratitis.
  A. Primary goals are to provide a cosmetic, functional upper eyelid and corneal protection (Glaze and Gelatt, 1999).
  B. One technique (Roberts and Bistner, 1968) involves rotating a pedicle of skin and muscle from the lower eyelid to the defect and suturing conjunctiva to the ventral margin.
  C. Trichiasis from the resulting misdirected lower lid hairs is treated (see discussion under Trichiasis).
  D. Techniques can also be performed using conjunctiva transposed from the palpebral side of the third eyelid (Dziezyc and Millichamp, 1989).
  E. H-Plasty using skin from above the lesion is another surgical option.

Monitoring of Animal

I. Asymptomatic animals or those treated medically are monitored periodically to ensure that corneal irritation and keratitis are not developing.
II. Sutures are removed 10 to 14 days after surgery, and additional surgical procedures for trichiasis may be scheduled several weeks to months later.
III. Animals are reevaluated immediately if they exhibit squinting, tearing, or discomfort.

Entropion

Definition

I. Inward rolling of a portion or the entire eyelid
II. Two categories of entropion
  A. Developmental
  B. Acquired
    1. Spastic: resulting from ocular pain
    2. Cicatricial: resulting from trauma or chronic inflammation

Causes

I. Genetic basis of developmental entropion is not understood.
II. In some dogs, developmental entropion is likely inherited in a simple dominant mode with complete penetrance (Bedford, 1999).
III. Breed predispositions include the American cocker spaniel, bullmastiff, chow chow, Clumber spaniel, English bulldog, Great Dane, Labrador retriever, miniature and toy poodles, rottweiler, shar-pei, and Saint Bernard.
IV. Cicatricial entropion is acquired after chronic inflammation or trauma.
V. Squinting as a result of ocular irritation causes spastic entropion (e.g., ulcerative keratitis, anterior uveitis, trichiasis, foreign body).

Pathophysiology

I. Developmental entropion is related to globe size, eyelid muscle tone (often lax), and palpebral fissure length (often excessive).
II. Chronic blepharitis or eyelid trauma can cause fibrosis of the eyelid and secondary cicatricial entropion.
III. Ocular irritation causes squinting via increased orbicularis oculi muscle tone and concurrent enophthalmos from retractor bulbi muscle activity.

Clinical Signs

I. Clinical signs range from absent to severe.
II. Signs are based on the degree and type of entropion, amount of associated trichiasis, and presence of corneal ulceration.
III. Signs include blepharospasm, epiphora, and corneal disease (e.g., pigmentation, vascularization, ulceration).

Diagnosis and Differential Diagnosis

I. Diagnosis is usually straightforward.
  A. Eyelid margin is not discernible in the resting position.
  B. Eyelid hairs (trichiasis) are usually seen in contact with the cornea.
II. Developmental entropion is differentiated from spastic entropion by placing topical anesthetic on the eye, which resolves any spastic component.
III. The cornea is fluorescein stained to rule out corneal ulceration or keratitis.
IV. Other causes of ocular irritation and pain are also ruled out.
  A. Primary trichiasis, ectropion, ectopic cilia
  B. Primary ulcerative keratitis, corneal foreign body
  C. Anterior uveitis, glaucoma

Treatment

I. Medical treatment
  A. Treat causes of spastic entropion.
  B. Treat superficial corneal ulceration with broad-spectrum topical antibiotic agents ± atropine (for cycloplegia).
  C. Use topical lubricating ointment to provide temporary corneal protection before surgery.
II. Temporary tacking: animals <6 months old

A. Use 3-0 or 4-0 nonabsorbable suture material in a vertical mattress pattern.
B. First bite is taken 1 to 2 mm from the eyelid margin, and the second bite is taken through the skin over the orbital rim.
C. Sutures are left in place for 2 to 3 weeks.
D. Alternatively, use skin staples or skin glue.
E. Temporary lateral tarsorrhaphy may also be used for lower eyelid entropion in young dogs (Bedford, 2000).

III. Permanent procedures for mature animals
A. Many surgical procedures are available to correct entropion, and the choice is determined by the cause, location, and extent of the entropion.
B. The most useful surgical procedure is a modified Hotz-Celsus procedure (Figure 95-1).
C. Other entropion procedures to consider are as follows:
1. Arrowhead modification of Hotz-Celsus procedure for lateral canthal eversion
2. Medial canthal V-plasty for medial canthal entropion correction
3. Fornix-based suture placement (Williams, 2004) for lower-eyelid entropion
4. Stades procedure for excessive upper-eyelid skin and sagging brow (Stades, 1987)
5. Brow suspension (Willis et al., 1999), stellate rhytidectomy (Stuhr et al., 1997), or coronal rhydectomy (McCallum, 2004) for entropion and redundant skinfolds
6. Y-V plasty for cicatricial entropion correction (Bedford, 1999)

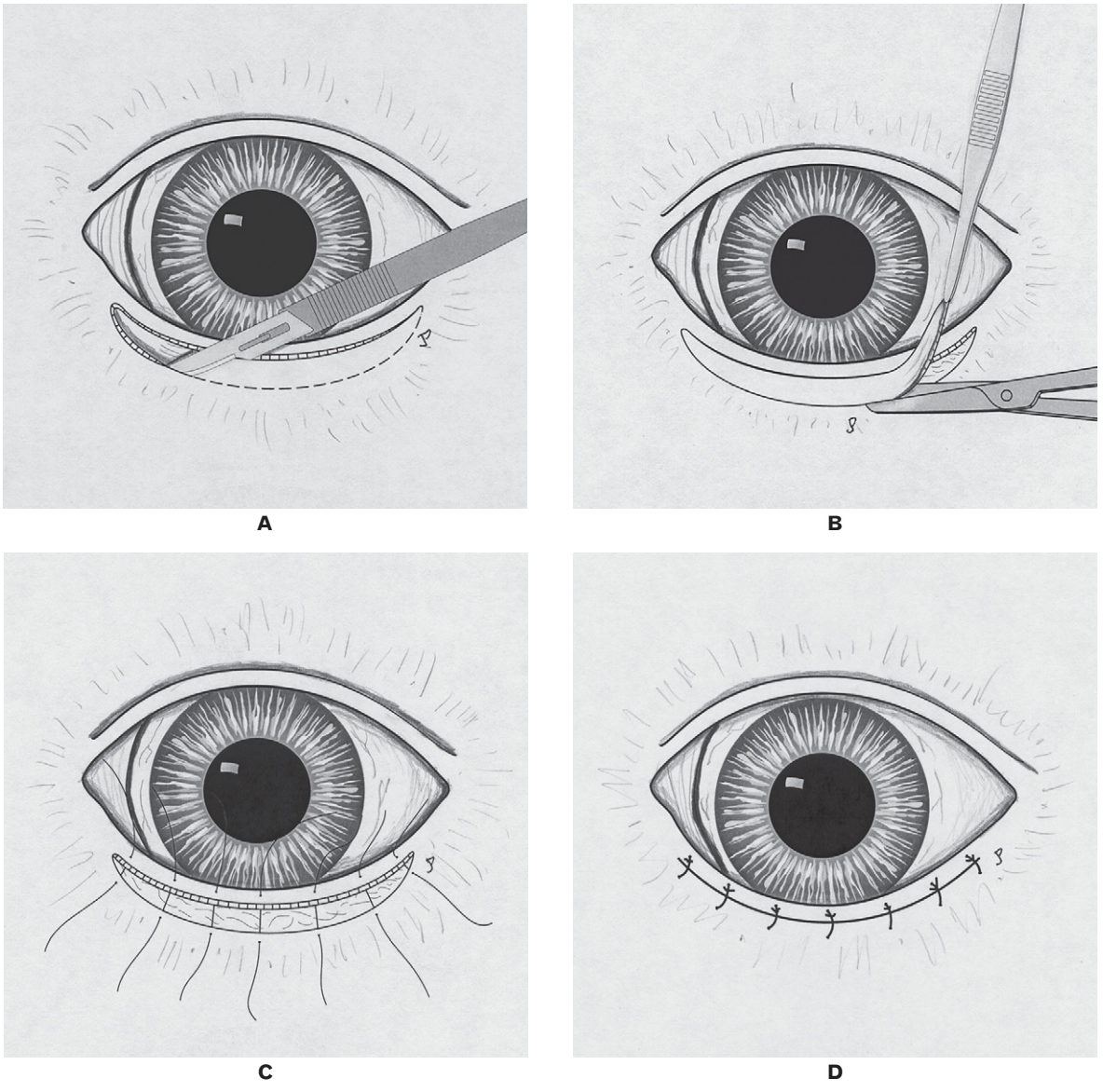


FIGURE 95-1 Modified Hotz-Celsus procedure for entropion of the lower central eyelid. **A,** The first incision is parallel to and 2 mm away from the eyelid margin. A second incision is made, distal to the first one, and incorporates enough skin to correct the entropion. **B,** The tissue is then removed using small tissue scissors. **C,** Simple interrupted, 5-0 or 6-0, nonabsorbable skin sutures are placed to oppose the skin edges. **D,** The first suture is placed in the midpoint of the incision and subsequent sutures are placed to halve the remaining distances. *From Gelatt KN, Gelatt JP: Small Animal Ophthalmic Surgery. Butterworth-Heinemann, Oxford, 2001; with permission.*

Monitoring of Animal

I. Topical ophthalmic antibiotic agent BID to TID
II. Elizabethan collar until suture removal
III. Suture removal in 10 to 14 days
IV. Fluorescein staining to ensure a suture-induced corneal ulcer has not occurred if blepharospasm noted

Ectropion

Definition

I. Outward rolling of a portion or the entire eyelid
II. Occurs most frequently in the lower eyelid

Causes

I. Developmental
   A. Often congenital
   B. Common breeds: American cocker spaniel, basset hound, bloodhound, Clumber spaniel, Great Dane, mastiffs, Newfoundland, Saint Bernard
II. Acquired
   A. Cicatricial: from previous eyelid damage or surgery
   B. Senile: from decreased orbicularis oculi muscle tone
   C. Physiological: from facial muscle fatigue after exercise in hunting breeds
   D. Paralytic: after damage to the branches of cranial nerve VII

Pathophysiology

I. May or may not be clinically significant
II. Desired trait or breed standard in many breeds of dog

Clinical Signs

I. Animals may be asymptomatic.
II. Clinical signs vary with the extent of ectropion.
   A. Conjunctivitis
   B. Epiphora
   C. Debris accumulation in the lower fornix
   D. Keratitis if severe
III. It may be combined with entropion.

Diagnosis

I. Complete ophthalmic examination, including fluorescein staining of the cornea
II. Breed predisposition

Differential Diagnosis

I. Other eyelid diseases: entropion, distichiasis, trichiasis, blepharitis
II. Corneal and conjunctival disease: conjunctivitis, corneal ulcer
III. Nasolacrimal system obstruction

Treatment

I. Medical treatment
   A. Clean accumulated discharge daily.
   B. Apply topical lubricant ointment to exposed conjunctiva and/or cornea BID to TID.
II. Surgical treatment is necessary only if keratitis or severe conjunctivitis is present.
   A. Full-thickness wedge resection at the lateral canthus for cases of excessive laxity (Bedford, 1999)
   B. Kuhnt-Szymanowski technique to shorten the lower eyelid and increase lateral canthal stability (Bedford, 1999)
   C. Kuhnt-Hembolt technique to shorten the lower eyelid (Bedford, 1999)
   D. Wharton-Jones or V-Y plasty (Donaldson, 2005) and other tissue-relaxing procedures for cicatricial ectropion correction (Hamilton et al., 1998)

Monitoring of Animal

I. Postoperative topical antibiotic ointment BID to TID
II. Elizabethan collar until suture removal
III. Suture removal in 10 to 14 days
IV. Fluorescein staining of the cornea if blepharospasm or epiphora occurs

Macropalpebral Fissure

Definition

I. An abnormally large palpebral fissure
II. Also called *euryblepharon* and *macroblepharon*

Causes

I. Brachycephalic conformation in both dogs and cats results in a relative exophthalmos, with a breed predisposition in the Boston terrier, Lhasa apso, pug, and shih tzu.
II. Excessive eyelid length and poor support of eyelids by the globe are often a cause in the bloodhound, Clumber spaniel, and Saint Bernard.
III. It may be accompanied by lagophthalmos.

Pathophysiology

I. The shallow orbit causes protrusion of the eye through the palpebral fissure, and predisposes to proptosis.
II. Excessive lid length and lack of support of the palpebral fissure are accompanied by entropion, ectropion, and/or excessive facial folds.
III. Abnormal precorneal tear film dynamics may result in corneal and conjunctival signs.

Clinical Signs

I. In brachycephalic breeds
   A. Visible sclera around the entire eye
   B. Keratitis: pigmentary or ulcerative
   C. Failure to close eyelids completely while blinking or sleeping
II. In dogs with excessive lid length
   A. Exposure conjunctivitis or keratitis
   B. Mucoid or mucopurulent ocular discharge
   C. Failure to close eyelids completely while blinking or sleeping

Diagnosis

I. Visualization of large palpebral fissure
II. Signalment

III. Complete ophthalmic examination: Schirmer tear test (STT), fluorescein staining, testing of blink reflexes

Differential Diagnosis

I. Acquired exophthalmos (see Chapter 103)
   A. Orbital neoplasia
   B. Orbital cellulitis and abscessation
II. Other eyelid diseases
   A. Entropion
   B. Ectropion
   C. Combination entropion and ectropion
III. Buphthalmos
IV. Cranial nerve VII paralysis

Treatment

I. Medical therapy: topical lubricating ointment TID to QID
II. Surgical therapy (Bedford, 1999)
   A. Lateral permanent tarsorrhaphy (Figure 95-2)
   B. Roberts-Jensen pocket technique (Jensen, 1979)
   C. Wyman and Kaswan lateral canthoplasty (Gelatt and Gelatt, 1994)
   D. Modified Fuchs lateral canthoplasty (Gelatt and Gelatt, 1994)
   E. Bedford lateral canthoplasty (Bedford, 1998)
   F. Combination procedures (van der Woerdt, 2004)

Monitoring of Animal

I. Postoperative topical antibiotic ointment BID to TID
II. Elizabethan collar until suture removal
III. Suture removal in 10 to 14 days
IV. Fluorescein staining of cornea if blepharospasm or epiphora occurs

Distichiasis

Definition

I. Cilia that arise from undifferentiated meibomian gland tissue and exit from the normal meibomian gland opening at the lid margin
II. May occur on both upper and lower eyelids

Causes and Pathophysiology

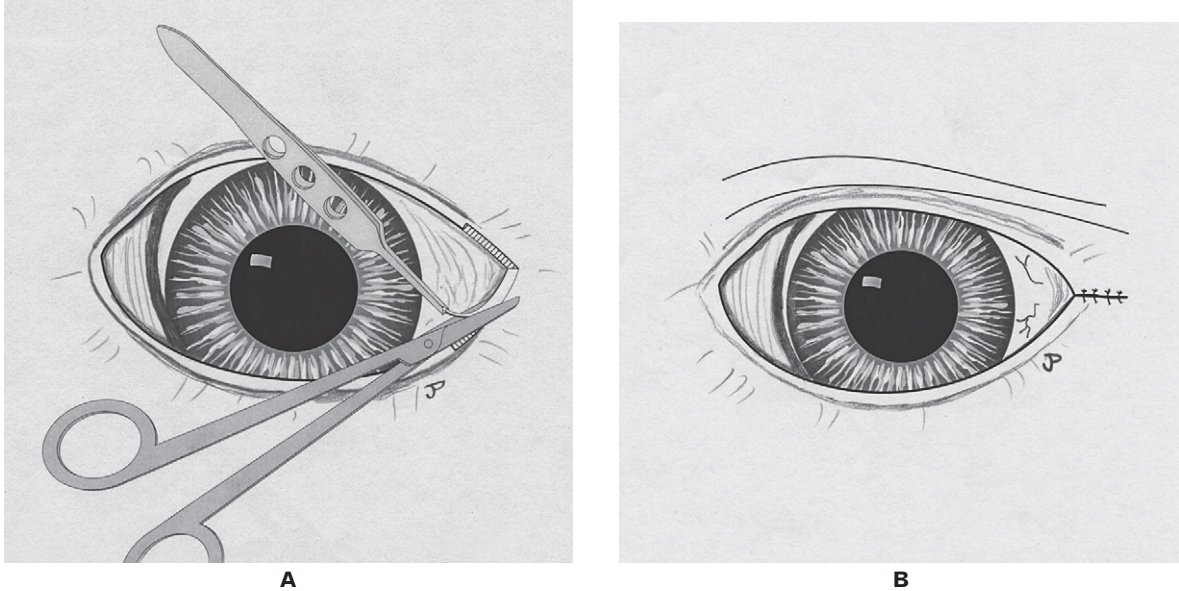
I. Genetic causes have not been determined, but it is probably a heritable trait.
II. Breeds commonly affected include the American cocker spaniel, Bedlington terrier, boxer, golden retriever, miniature longhaired dachshund, miniature and toy poodles, Pekingese, Saint Bernard, Shetland sheepdog, and Yorkshire terrier.
III. Distichiasis may be congenital or secondary to chronic meibomitis that results in glandular metaplasia.
IV. Misdirected hairs can cause corneal irritation and possibly ulceration.

Clinical Signs

I. Asymptomatic, especially American cocker spaniels
II. Symptomatic in some dogs
   A. Epiphora
   B. Blepharospasm
   C. Conjunctivitis
   D. Mucus accumulation
   E. Possible keratitis: ulcerative, pigmentary, vascular

Diagnosis

I. Direct visualization of hairs exiting the meibomian gland openings (easier to visualize with focal illumination and magnification)



A B

FIGURE 95-2 Permanent lateral canthoplasty to reduce the size of the palpebral fissure. **A,** The lower and upper eyelid margins and the lateral canthal margins are excised. **B,** A two-layer closure is used. The tarsoconjunctiva is apposed using 6-0 absorbable suture, and the skin and muscle layer is then apposed using 5-0 or 6-0 nonabsorbable suture material. The canthal margin is closed first using a figure-eight suture (see Figure 95-3, *C*). *From Gelatt KN, Gelatt JP: Small Animal Ophthalmic Surgery. Butterworth-Heinemann, Oxford, 2001; with permission.*

II. Disturbance of tear film at the eyelid margin (Bedford, 1999)
III. Removal of hairs (epilation) to determine if clinical signs resolve
IV. STT and fluorescein staining

Differential Diagnosis

I. Other eyelash or eyelid abnormalities: trichiasis, ectopic cilia, entropion, ectropion
II. Other causes of conjunctivitis or keratitis: keratoconjunctivitis sicca, allergies

Treatment

I. None in asymptomatic animals
II. Medical treatment
  A. If only a few distichia present, if problem is minor, or if animal is poor surgical candidate
  B. Topical lubricant ointment TID to QID
  C. Epilation of hairs with topical anesthesia and cilia forceps for temporary relief
III. Surgical treatment
  A. Cryosurgery (double freeze-thaw) works well, but usually results in transient depigmentation of the lid margins.
  B. Basal meibomian gland cautery destroys the base of the meibomian glands and the germinal hair bulb of the distichia.
  C. Partial tarsal plate resection is used to remove a wedge of tissue containing the affected glands and hairs.
  D. Electrolysis involves inserting a fine needle along the hair shaft to the root and using heat to destroy the follicle, but it is not recommended if distichia are numerous, because of the secondary damage it creates.

Monitoring of Animal

I. Postoperative complications include recurrence of distichia and scarring of the eyelid, with or without cicatricial entropion.
II. Use topical ophthalmic antibiotics postoperatively BID to TID.
III. Apply an Elizabethan collar for the first 5 to 7 days postoperatively.
IV. Stain the cornea with fluorescein if blepharospasm or epiphora occurs.
V. After cryotherapy, lid depigmentation may last as long as 6 months and may be permanent.
VI. Hair regrowth is possible with most procedures, and new hairs can erupt at any time.

Trichiasis

Definition and Causes

I. It is defined as normal eyelid or facial hairs that come into contact with the cornea and conjunctiva.
II. Primary forms are as follows:
  A. Brachycephalic breeds of dogs and cats with medial canthal entropion and nasal fold trichiasis
  B. Genetics undetermined
III. Secondary forms arise from the following:
  A. Entropion
  B. Eyelid agenesis
  C. Dermoid
  D. Previous injury and scar formation

Pathophysiology

I. Hairs from normally located follicles are directed toward and contact the eye.
II. These hairs can induce corneal or conjunctival irritation with resulting clinical signs.

Clinical Signs

I. May be asymptomatic
II. Epiphora and chronic moist dermatitis of nasal folds or affected areas
III. Conjunctivitis and possibly mucoid discharge
IV. Pigmentary keratitis

Diagnosis

I. Visualization of hairs contacting cornea
II. Remainder of ophthalmic examination normal

Differential Diagnosis

I. Keratoconjunctivitis sicca
II. Entropion, ectropion
III. Distichiasis, ectopic cilia
IV. Corneal ulceration

Treatment

I. None for asymptomatic animals
II. Medical therapy
  A. To temporarily relieve clinical signs
  B. Trimming of facial hairs
  C. Application of mustache wax or petroleum jelly to force hairs to lay in proper direction
  D. Use of topical lubricating ointment to temporarily decrease corneal irritation
III. Surgical therapy
  A. Various surgical procedures depending on the area affected
  B. Hotz-Celsus resection (see Figure 95-1)
  C. Stades procedure (Stades, 1987) and brow suspension (Willis et al., 1999), especially for shar-peis
  D. Medial canthoplasty (Yi et al., 2006; see Figure 95-2)
  E. Nasal fold resection (Gelatt and Gelatt, 1994)

Monitoring of Animal

I. Postoperative topical antibiotics BID to TID
II. Elizabethan collar until suture removal
III. Suture removal in 10 to 14 days
IV. Fluorescein staining if blepharospasm or epiphora occurs

Ectopic Cilia

Definition and Cause

I. Cilia grow from the meibomian gland but exit through the palpebral conjunctiva.
II. Cause is unknown, but probably similar to those for distichiasis.

Pathophysiology

I. Corneal irritation from hair rubbing
II. May be single or multiple
III. May be unilateral or bilateral

Clinical Signs

I. Ocular (corneal) pain: squinting, tearing
II. Chronic or recurrent erosions in the central, dorsal cornea

Diagnosis

I. Evert the eyelid.
II. Use magnification to visualize cilia coming through the conjunctiva.
III. Cilia are usually located at the 12 o'clock position in the center of the upper eyelid.
   A. Found several millimeters from lid margin
   B. Often emerge from nonpigmented island in pigmented conjunctiva or from a pigmented island in nonpigmented conjunctiva

Differential Diagnosis

I. Foreign body: corneal, conjunctival, third eyelid
II. Blepharitis
III. Conjunctivitis
IV. Refractory corneal ulcer

Treatment

I. Tarsoconjunctival resection is preferred.
II. Ectopic cilia recur frequently after electroepilation.

Monitoring of Animal

I. If concurrent corneal ulceration is present, then the animal is treated appropriately with topical antibiotic agent BID to TID ± atropine.
II. Reevaluate the animal if blepharospasm or epiphora occurs.
   A. Additional cilia can erupt from the same or additional sites.
   B. Fluorescein stain is applied to the cornea to rule out a corneal ulcer.

INFLAMMATORY DISORDERS

Symblepharon

See Chapter 96.

Neonatal Ophthalmia

Definition

I. An infection that occurs under the totally or partially closed eyelids of neonatal animals
II. Bilateral or unilateral

Causes

I. Cat
   A. Feline herpesvirus 1
   B. *Chlamydia psittaci (Chlamydophila felis)*
   C. *Mycoplasma felis* and *Mycoplasma gatae*
   D. Other miscellaneous causes of conjunctivitis
II. Dog: *Staphylococcus* spp. or other normal adnexal flora

Pathophysiology

I. Normally the eyelids in puppies and kittens remain closed until 10 to 14 days after birth (ankyloblepharon).
II. Conjunctival infection results in the production of ocular discharge, which accumulates under the closed palpebral fissure.

Clinical Signs

I. Distended eyelids
II. Ocular discharge (mucopurulent)

Diagnosis and Differential Diagnosis

I. Based on clinical signs in a neonatal animal
II. Other congenital eyelid conditions ruled out
III. Culture and sensitivity of discharge

Treatment

I. Warm compress applied to area will soften adherent exudate.
II. Open the palpebral fissure with traction or small, dull scissors (Glaze and Gelatt, 1999) to allow drainage.
III. Flush fornices with saline.
IV. Apply topical antimicrobials TID to QID for 7 to 10 days.
   A. Neomycin-polymyxin-bacitracin for puppies
   B. Oxytetracycline or erythromycin for kittens

Monitoring of Animal

I. Resolution of the problem usually occurs after treatment.
II. Evaluate corneas (fluorescein stain) after eyelid opening.
III. Affected animals can develop globe rupture and other serious consequences.
IV. Reevaluate 6 to 8 weeks posttherapy (external examination with focal light source and STT) to ensure that secondary complications such as symblepharon, corneal scars, and keratoconjunctivitis sicca have not occurred.

Blepharitis

Definition

I. Inflammation of the eyelids
II. Granulomatous inflammation of the meibomian glands: chalazion or internal hordeolum
III. Inflammation of the glands of Zeis and Moll: stye or external hordeolum

Causes

I. Blepharitis can be focal or diffuse, unilateral or bilateral, and can affect any or all eyelids.
II. Blepharitis may be a component of or the presenting complaint with many disorders (Table 95-1).

Pathophysiology

I. With parasitic, fungal, bacterial, and viral forms, the animal is exposed to the organism and an infection is established.

TABLE 95-1

Causes of Blepharitis

DISEASE TYPE	DOG	CAT
Parasitic	Localized *Demodex canis* *Sarcoptes scabiei* var. *canis* *Onchocerca* spp. Insect bite	*Demodex cati* and *Demodex gatoi* *Notoedres cati* *Cuterebra* spp. Insect bite
Fungal	*Microsporum canis, Microsporum gypseum* *Trichophyton mentagrophytes* Dermatophytosis *Malassezia* spp. Systemic blastomycosis, cryptococcosis, histoplasmosis, aspergillosis	*M. canis, M. gypseum* *T. mentagrophytes* Dermatophytosis Histoplasmosis
Bacterial	Bacterial folliculitis (*Staphylococcus* spp.) Juvenile cellulitis (puppy "strangles") Cervicofacial *Actinomyces viscosus*	Tuberculosis
Protozoal	Neosporosis Leishmaniasis	Leishmaniasis
Viral	Canine distemper virus	Cat pox Feline herpesvirus 1
Immune-mediated	Bullous pemphigoid Pemphigus foliaceus Pemphigus vulgaris Pemphigus erythematosus Discoid lupus erythematosus Systemic lupus erythematosus Vitiligo Uveodermatologic syndrome Canine familial dermatomyositis Vasculitis Erythema multiforme Canine necrolytic migratory erythema	Pemphigus vulgaris Pemphigus erythematosus Systemic lupus erythematosus Erythema multiforme
Idiopathic	Seborrhea and bacterial folliculitis Chronic ulcerative medial canthal blepharitis Hypereosinophilic syndrome Idiopathic periocular alopecia Topical-steroid alopecia	Facial dermatitis: Persian, Himalayan Periocular leukotrichia: Siamese Hypereosinophilic syndrome
Allergic	Atopy Contact allergies Food hypersensitivity	Atopy Contact allergies Food hypersensitivity
Miscellaneous	Self-trauma Food hypersensitivity Zinc-responsive dermatosis Solar dermatitis Topical steroid–related alopecia	Self-trauma Eosinophilic plaques Hypereosinophilic syndrome
Neoplastic form	Epitheliotropic lymphoma	

Data from Donaldson D, Day MJ: Epitheliotropic lymphoma (mycosis fungoides) presenting as blepharoconjunctivitis in an Irish setter. J Small Anim Pract 41:317, 2000; Donohue DE, Brightman AH: Cervicofacial *Actinomyces viscosus* infection in a Brazilian Fila: a case report and literature review. J Am Anim Hosp Assoc 31:501, 1995; Scott DW, Miller WH Jr, Griffin CE (eds): Muller & Kirk's Small Animal Dermatology. 6th Ed. WB Saunders, Philadelphia, 2001.

A. Often toxin production results in inflammation.
B. Young animals are predisposed, and genetic influences are possible in the cat (Scott et al., 2001).

II. With immune-mediated diseases, autoantibodies or immune complex deposition leads to cutaneous changes.

Clinical Signs

I. Any combination of signs possible
   A. Mucoid discharge
   B. Erythema
   C. Pruritus
   D. Hair loss
   E. Change in pigmentation
II. Often concurrent systemic dermatoses
III. Types of signs with specific disorders
   A. Parasitic
      1. Small, circumscribed, scaly alopecic areas
      2. Possible pruritus, especially with secondary bacterial infection, demodicosis
   B. Fungal
      1. Patchy alopecia and variable scaling
      2. Minimal pruritus
      3. Folliculitis and furunculosis mimicking pemphigus
   C. Bacterial
      1. Alopecia
      2. Eyelid thickening or swelling
      3. Pustules, crusts, ± fistulas
      4. Juvenile cellulitis
         a. Young dog, ± febrile
         b. Regional lymphadenopathy
         c. Eyelid, muzzle, and ear alopecia
         d. Crusts, erythema
         e. Possibly painful, self-trauma
   D. Viral
      1. Alopecia
      2. Pustules and erosions
      3. Ocular discharge, especially with canine distemper virus
   E. Immune-mediated
      1. Pemphigus group: pustular dermatitis, crusts, ulceration, inflammation, depigmentation of the eyelids
      2. Lupus group: alopecia, erythema, vesicles, ulcers
      3. Dermatomyositis: alopecia, scaling, ulceration
   F. Idiopathic
      1. Feline facial dermatitis manifests with inflammation, pruritus, and accumulated black debris around the eyelids.
      2. Periocular leukotrichia includes lightening of hair around the eyes.
      3. Eosinophilic blepharitis manifests with focal masses and erythema of the eyelids.
   G. Allergic
      1. Contact allergies can manifest as acute-onset edema and hyperemia.
      2. Eyelid swelling is common with insect bites.
      3. Atopic dogs demonstrate facial pruritus and periocular hyperemia.
      4. Food-allergic animals exhibit facial and ear pruritus.
   H. Self-trauma: excoriations, thickening, erythema
   I. Drug eruption
      1. Especially with sulfonamides and cephalosporins
      2. Drug-induced pemphigus
      3. Alopecia, crusting, ulceration of eyelids
      4. More severe signs with erythema multiforme
   J. Nutritional
      1. Young dogs: oversupplementation with zinc in large-breed, fast-growing dogs
      2. Zinc-responsive dermatosis in Siberian husky and Alaskan malamute: middle-aged dogs with zinc deficiency
      3. Crusting and erythema
      4. Scaling, alopecia, and hypo- or hyperpigmentation
   K. Epitheliotropic lymphoma (mycosis fungoides)
      1. Recurrent conjunctivitis
      2. Mucoid ocular discharge
      3. Depigmentation of eyelid margins

Diagnosis

I. History, clinical signs, concurrent drug administration, and seasonality are very important to the diagnosis.
II. Stain the cornea with fluorescein to rule out corneal ulceration before use of topical corticosteroid medications.
III. Perform a Wood's lamp examination and fungal cultures to rule out dermatophytes.
IV. Skin scraping and trichograms may identify parasitic causes.
V. Cytological analysis and culture/sensitivity are indicated for possible bacterial and fungal causes.
VI. Skin biopsy and histopathologic examination help confirm immune-mediated, nutritional, neoplastic, and idiopathic causes.
VII. Intradermal skin testing and food trials are helpful with atopic and food-allergic animals.

Differential Diagnosis

I. Conjunctivitis
II. Neoplasia of eyelids

Treatment

I. With all types of blepharitis: prevention of self-trauma with an Elizabethan collar
II. Parasitic blepharitis
   A. *Demodex* spp.
      1. Most cases of localized demodicosis resolve spontaneously in 6 to 8 weeks.
      2. For persistent cases, use systemic ivermectin 0.2 to 0.4 mg/kg PO once weekly for 3 weeks (not recommended for use in collie-type dogs, Shetland sheepdog–type dogs, or microfilaria-positive dogs).
   B. Sarcoptic mange
      1. Topical selamectin 6 to 12 mg/kg is applied every 2 weeks for 3 treatments.
      2. Milbemycin may also be used at 2 mg/kg PO every 7 to 14 days for three treatments.

3. Unresponsive cases may be treated with the following:
   a. High-dose ivermectin is administered 0.4 to 0.6 mg/kg PO once daily (not recommended for use in collie- or Shetland sheepdog–type dogs).
   b. Milbemycin is administered 2 mg/kg PO SID for 1 to 2 months beyond the point that negative skin scrapings are found.

III. Fungal blepharitis
   A. Clip the hair.
   B. Apply topical antifungal cream (clotrimazole, miconazole).
   C. Institute systemic antifungal therapy for generalized disease (see Chapter 111).

IV. Bacterial blepharitis
   A. Systemic antibiotic therapy is instituted based on culture and sensitivity results.
      1. Lincomycin 20 mg/kg PO BID, cephalexin 22 mg/kg PO BID to TID, or cefpodoxime proxetil 5 to 10 mg/kg SID is administered for a minimum of 3 weeks.
      2. Recurrent cases may require treatment with a broader-spectrum antibiotic.
      3. Some dogs with staphylococcal hypersensitivity also require systemic corticosteroids (prednisone 1 mg/kg PO BID, tapered over 3 to 4 weeks).
   B. Topical antibiotic agents with hydrocortisone are also applied BID.
   C. Systemic corticosteroid and antibiotic drugs are administered for juvenile cellulitis (see Chapter 88).

V. Viral blepharitis
   A. Supportive care of systemically ill animals: fluid therapy ± broad-spectrum antibiotic agents
   B. Topical triple-antibiotic ointment with hydrocortisone BID to TID

VI. Immune-mediated diseases
   A. Topical neomycin-polymyxin B-dexamethasone ointment TID to QID
   B. Immunosuppressive doses of prednisone at 2 to 4 mg/kg PO SID to BID, tapered over 3 to 4 weeks
   C. Azathioprine 2.2 mg/kg SID to QOD for unresponsive cases (dogs only)
   D. No effective treatment for dermatomyositis

VII. Idiopathic diseases
   A. No effective treatment exists for feline facial dermatitis (Scott et al., 2001).
   B. No treatment is required for periocular leukotrichia.
   C. Eosinophilic blepharitis is treated with topical and/or systemic corticosteroids.

VIII. Allergic diseases
   A. Removal of offending allergen, if determined
   B. Topical antibiotic and corticosteroid agent TID to QID for 5 to 7 days in dogs
   C. Hyposensitization and possibly hypoallergenic diet
   D. Systemic antihistamines (e.g., hydroxyzine 2.2 mg/kg PO BID to TID)
   E. Cyclosporine 5 mg/kg SID for 2 to 4 weeks, then tapered

IX. Nutritional disorders
   A. Correct any dietary imbalance.
   B. Supplement with oral zinc (see Chapter 93).

Monitoring of Animal

I. Animals on corticosteroids, especially immunosuppressive doses, are closely monitored for systemic side effects.
II. Many cases of blepharitis take weeks to months to resolve.
III. Some cases need lifelong therapy.

IDIOPATHIC DISEASES

See Table 95-2.

NEOPLASIA

Definition and Causes

I. Progressive multiplication and growth of skin, conjunctiva, or gland of the eyelids
II. Can be benign or malignant
III. Primary, secondary, and metastatic forms

TABLE 95-2

Idiopathic Eyelid Disorders

DISEASE	SPECIES	CLINICAL SIGNS	DIAGNOSIS	TREATMENT
Idiopathic granulomatous disease*	Dog	Multiple, bilateral tan, firm, cutaneous lower eyelid granulomas	Histopathology	Intraperitoneal polyethylene glycol-modified L-asparaginase
Apocrine hidrocystomas†	Cat	Multiple cysts in medial canthus, upper and lower eyelids	Histopathology	Surgical excision Trichloracetic acid
Periorbital epidermal cyst‡	Dog	Slowly enlarging medial canthal mass	Histopathology	Surgical excision

*Collins BK, MacEwen EG, Dubielzig RR et al: Idiopathic granulomatous disease with ocular adnexal and cutaneous involvement in a dog. J Am Vet Med Assoc 201:313, 1992.

†Chaitman J, vanderWoerdt A, Bartick TE: Multiple eyelid cysts resembling apocrine hidrocystomas in three Persian cats and one Himalayan cat. Vet Pathol 36:474, 1999; Yang SH, Lin CH, Hsu CD et al: Use of chemical ablation with trichloracetic acid to treat eyelid apocrine hidrocystomas in a cat. J Am Vet Med Assoc 230: 1170, 2007.

‡Davidson HJ, Blanchard GL: Periorbital epidermoid cyst in the medial canthus of three dogs. J Am Vet Med Assoc 198:271, 1991.

Pathophysiology

I. Most canine eyelid tumors are benign (Table 95-3).
II. Tumors in dogs that appear histologically malignant tend to be infiltrative but rarely metastasize.
III. Eyelid tumors in cats are far less common than in dogs, but they are much more likely to be malignant.
IV. Eyelid neoplasms destroy normal eyelid tissue at varying rates and degrees.
V. Secondary effects can occur with all types of tumors.
   A. Extension into orbit
   B. Ocular discharge
   C. Hemorrhage from mass

TABLE 95-3

Classification of Eyelid Tumors in the Dog and Cat

TUMOR TYPE	CLINICAL FEATURE
Dog	
Sebaceous gland adenoma (meibomian gland adenoma)	Most common eyelid tumor Usually occurs in older dogs Slow-growing mass at or near lid margin Visible through conjunctival surface, extends onto the eyelid margin
Papilloma	Usually occurs in young dogs May be associated with oral papillomas Viral forms regress over time
Sebaceous adenocarcinoma	Usually occurs in older dogs Locally invasive, slow-growing mass at or near lid margin Rare
Melanoma (benign or malignant)	Dark, superficial, well-demarcated nodules Tend to occur at eyelid margin
Histiocytoma	Usually seen in young dogs Raised, hairless, pink nodules that often regress over time
Mast cell tumor (mastocytoma)	See Chapter 89
Basal cell carcinoma	Ulcerative, invasive mass
Squamous cell carcinoma	Rare in the dog Rapidly growing, ulcerative, invasive mass
Fibrosarcoma	Aggressive, invasive mass
Apocrine gland adenocarcinoma	Very invasive
Lobular orbital adenoma	Swollen, hyperemic eyelids
Cat	
Squamous cell carcinoma	Most common eyelid tumor Slightly raised or depressed ulcerated lesion On or adjacent to eyelid margin Locally invasive, malignant
Lymphosarcoma	Conjunctival invasion Primary or multisystemic manifestations
Fibrosarcoma	Focal, nodular, ulcerated Aggressive, invasive
Basal cell carcinoma	Round, well-circumscribed, ulcerated lesion Generally benign
Mast cell tumor (mastocytoma)	Single or multiple Dermal, epidermal, or subcutaneous Variable appearance See Chapter 89
Adenoma/adenocarcinoma	Rare in the cat
Melanoma	Often darkly pigmented (but not always)

Data from Glaze MB, Gelatt KN: Feline ophthalmology. p. 997. In Gelatt KN (ed): Veterinary Ophthalmology. 3rd Ed. Lippincott Williams & Wilkins, Philadelphia, 1999; Headrick JF, Bentley E, Dubielzig RR: Canine lobular adenoma: a report of 15 cases with distinctive features. Vet Ophthalmol 7:47, 2004; Hirai T, Mubarak M, Kimura T et al: Apocrine gland tumor of the eyelid in a dog. Vet Pathol 34:232, 1997; Krehbiel JD, Langham RF: Eyelid neoplasms of dogs. Am J Vet Res 36:115, 1975; McLaughlin SA, Whitley RD, Gilger BC et al: Eyelid neoplasms in cats: a review of demographic data (1979-1989). J Am Anim Hosp Assoc 29:63, 1993; Moore CP, Constantinescu GM: Surgery of the adnexa. Vet Clin North Am Small Anim Pract 27:1011, 1997; Roberts SM, Severin GA, Lavach JD: Prevalence and treatment of palpebral neoplasms in the dog: 200 cases (1975-1983). J Am Vet Med Assoc 189:1355, 1986.

D. Eyelid deformation
E. Corneal ulceration and irritation

Clinical Signs

I. A mass-type lesion is present on the eyelid margin or eyelid skin.
II. Appearance of the various tumors is listed in Table 95-3.
III. Ulcerative keratitis occurs, depending on the tumor size and location.

Diagnosis

I. Signalment and clinical signs
II. Thorough ocular examination
III. Cytological examination of fine-needle aspirate or impression smears
IV. Histopathologic examination: essential
V. Lymph node aspiration and thoracic radiography: recommended with some malignant tumors

Differential Diagnosis

I. Granulation tissue
II. Chalazion
III. Foreign body
IV. Ulcerative blepharitis
V. Trauma
VI. Eosinophilic granuloma in Siberian huskies (Vercelli et al., 2005)

Treatment

I. Wedge resection (Figure 95-3)
A. For removal of neoplasms that are less than one third the length of the eyelid margin

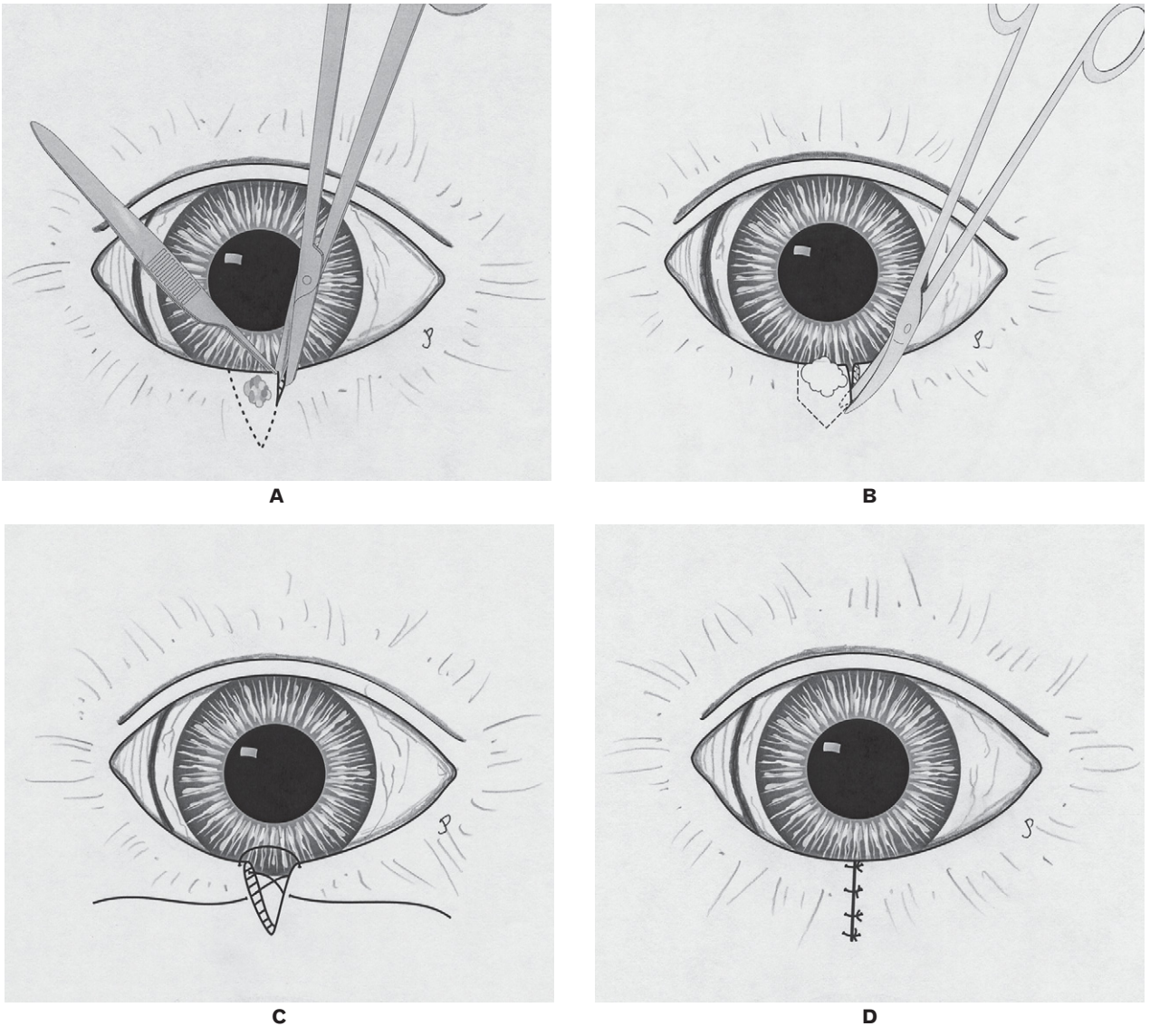


FIGURE 95-3 Full-thickness wedge excision for eyelid tumor removal. **A,** A V-shaped wedge of tissue is excised. The clinician should ensure that the sides of the incision are of equal length and can be full or partial thickness. **B,** For slightly larger lesions, a four-sided incision is recommended. **C,** A two-layer closure is used. The tarsoconjunctiva is apposed using 6-0 absorbable suture, and the skin and muscle layer is then apposed using 5-0 or 6-0 nonabsorbable suture material, starting at the eyelid margin using a figure-eight suture. **D,** The remainder of the incision is closed with simple interrupted sutures. *From Gelatt KN, Gelatt JP: Small Animal Ophthalmic Surgery. Butterworth-Heinemann, Oxford, 2001; with permission.*

B. Precise alignment of the eyelid margin, skin, and conjunctiva (essential)
C. Postoperative care
1. Topical cold compress during recovery ± warm compresses for 2 to 4 days postoperatively
2. Elizabethan collar until suture removal in 10 to 14 days
3. Broad-spectrum topical antibiotic agent BID to TID for 5 to 7 days

II. Split-thickness or full-thickness sliding skin graft (Figure 95-4)
A. Used for lesions that encompass more than one third of the eyelid margin.
B. Precise alignment of the eyelid margin, skin, and conjunctiva is essential.
C. Postoperative care is the same as for wedge resection.

III. Multiple other pedicle and rotating grafts for large lesions (Bedford, 1999; Schmidt, 2005)

IV. Carbon dioxide laser ablation (Bussieres et al., 2005)
A. Uses a defocused beam for adnexal tumors
B. May be cost prohibitive

V. Diode laser ablation: useful for pigmented masses

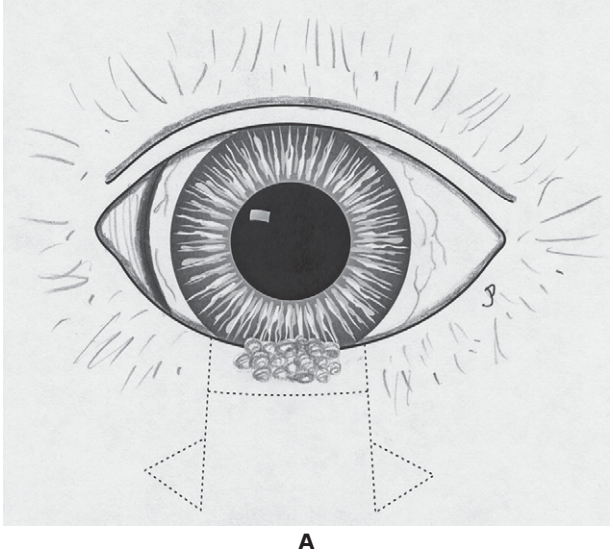
VI. Cryotherapy
A. Used as adjunctive or primary therapy for some eyelid masses (e.g., squamous cell carcinoma).
B. Especially useful for tumors that are too large for resection.

VII. Chemotherapy
A. Rarely used for eyelid neoplasms
B. May be of benefit for mast cell tumors or lymphosarcoma
C. May be useful to reduce mass size before other therapies are conducted (e.g., surgical resection)

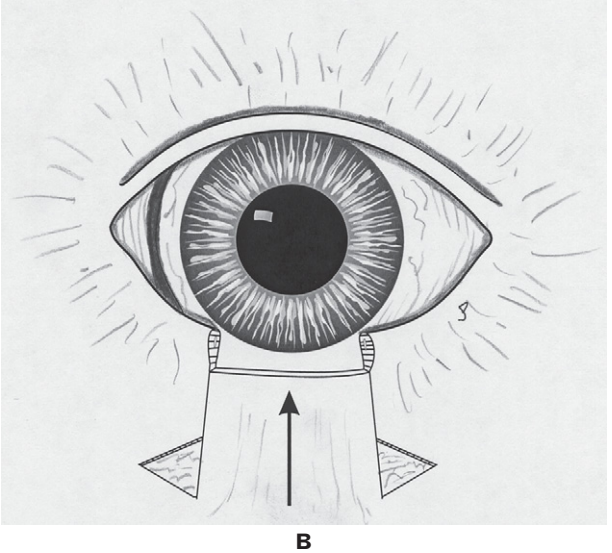
VIII. Radiation therapy
A. It is most useful for squamous cell carcinoma.
B. Reducing the tumor burden via surgical debulking increases the effectiveness of radiation.

Monitoring of Animal

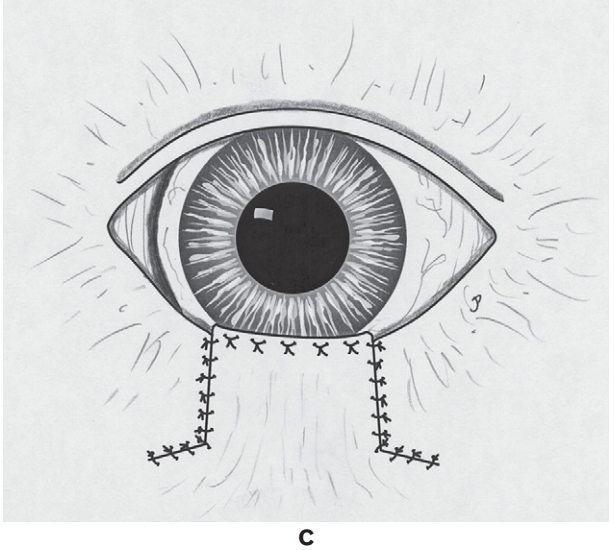
I. Most canine lid tumors are cured by local excision.
A. Skin sutures are removed in 10 to 14 days.



A



B



C

FIGURE 95-4 H-plasty or sliding skin graft for treatment of large eyelid margin lesions. **A,** Two slightly diverging incisions are made in the skin. A third incision is made parallel to the eyelid margin and serves as the distal margin of the mass removal. The length of the diverging incisions is twice the height of the tissue to be excised. A Burow's triangle of skin is excised from each side of the distal incision. **B,** The lid mass is excised and the skin flap is dissected from underlying subcutaneous tissues and advanced into the defect. The posterior aspect of the graft must be lined with mucosa. **C,** The leading edge of the graft is positioned 0.5 to 1.0 mm above the adjacent normal eyelid margin. Nonabsorbable 5-0 to 6-0 simple interrupted sutures are placed first at the junction of the graft with the eyelid margin, then at the edges of the previous Burow's triangles. The conjunctival tissue is attached to the edge of the skin using simple interrupted sutures that do not contact the cornea. *From Gelatt KN, Gelatt JP: Small Animal Ophthalmic Surgery. Butterworth-Heinemann, Oxford, 2001; with permission.*

B. Animals are evaluated sooner if the owner reports excessive squinting or tearing that could indicate a suture-induced corneal ulcer.

II. Malignant tumors are likely to recur and may eventually metastasize.

III. Monitoring frequency depends on the histological diagnosis.

TRAUMA

Eyelid Laceration

Definition and Causes

I. A partial-thickness or full-thickness tear in the eyelid

II. Most commonly traumatic: associated with bite wounds or other traumatic events

Pathophysiology

I. Sharp or blunt wound to the eyelid causes skin, muscle, tarsal plate, and/or conjunctiva to be torn.

II. Ineffective blink and corneal exposure can result.

III. Keratitis ensues, especially if the eyelid margin is disrupted.

Clinical Signs

I. Tear in the upper or lower eyelid: partial or full thickness

II. Associated hemorrhage and swelling

III. Epiphora, especially with injury to ventral lacrimal punctum or canaliculus

IV. Granulation tissue formation: possible in chronic wounds

V. Keratitis from ineffective blink or from causative agent

Diagnosis

I. Complete physical and ophthalmic examinations are performed to evaluate for other injuries.
   A. Animal is examined for globe rupture, proptosis, pneumothorax, or additional bite wounds.
   B. Cornea is fluorescein stained to evaluate the integrity of the corneal epithelium.

II. Nasolacrimal system is also evaluated for damage, especially with medial canthal injuries.

Differential Diagnosis

I. Dehiscence of eyelid surgery repair

II. Neoplasia: similar in appearance to chronic lacerations that have granulated closed

III. Eyelid or eyelash abnormalities: entropion, ectropion, trichiasis

Treatment

I. Eyelids are highly vascular and have a great capacity to heal and resist infection.

II. Partial-thickness lacerations may be treated medically or surgically.
   A. Wound is cleaned and topical antibiotic ointment is applied.
   B. Tissue is kept moist before surgical repair.
   C. Gentle cleansing with dilute povidone-iodine (1:50 *Betadine* in saline) is performed.

III. With surgical repair, minimal debridement is needed because of the good vascular supply.
   A. Do not excise eyelid tissue flaps.
   B. Direct closure and healing by primary intention provide the best results.

IV. It is imperative to precisely align the eyelid margin, skin, and conjunctiva.
   A. Two-layer closure is stronger than one layer.
   B. Tarsal plate and conjunctiva are closed starting at the lid margin with a buried mattress suture (5-0 or 6-0 absorbable suture).
   C. Remainder of the conjunctiva and muscle layer is closed in a partial-thickness, buried, simple continuous pattern, ensuring that suture is not rubbing on the cornea.
   D. Eyelid margin skin is apposed and sutured in a figure-eight fashion with monofilament material (5-0 or 6-0 nonabsorbable) (see Figure 95-3, *C*).
   E. Remainder of the skin is closed with simple interrupted or cruciate sutures.

V. Postoperative care includes the following:
   A. Topical ice packs during recovery ± warm compresses for 2 to 4 days postoperatively
   B. Elizabethan collar until suture removal
   C. Broad-spectrum topical and systemic antibiotics for 5 to 7 days

Monitoring of Animal

I. Skin sutures are removed in 10 to 14 days.

II. Animal is evaluated sooner if excessive squinting or tearing occurs, which could indicate a suture-induced corneal ulcer.

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CHAPTER 96

Disorders of the Conjunctiva and Third Eyelid

Harriet J. Davidson

CONGENITAL/DEVELOPMENTAL DISORDERS

Encircling Third Eyelid

Definition and Cause

I. The lateral edge of the third eyelid extends dorsotemporally around the eye.
II. Genetic predisposition exists in American cocker spaniels.

Clinical Signs

I. Eye and conjunctival tissues are normal, with the exception of the extra layer of tissue surrounding the eye.
II. The leading edge of the third eyelid is frequently pigmented.

Diagnosis

I. Clinical appearance is pathognomic.
II. Movement of the third eyelid using a cotton-tipped applicator after the application of topical anesthetic helps to identify the eyelid margin as normal.
III. Cytology of the eyelid margin reveals normal epithelial cells, with or without melanin granules.

Differential Diagnosis

I. Conjunctivitis
II. Melanoma

Treatment and Monitoring

I. Therapy is not necessary.
II. This condition has no effect on the third eyelid movement or gland function.

Dermoid and Choristoma

Definition

Dermoid or choristoma is a growth of normal epithelial cells (most often skin) in an abnormal location, in this case the conjunctiva.

Causes

I. It may occur as an unusual finding in any breed.
II. Breed predisposition is as follows:
   A. Dogs: dachshund, Dalmatian, Doberman pinscher, German shepherd dog, Saint Bernard
   B. Cats: Birman (Hendy-Ibbs, 1985)

Clinical Signs

I. The abnormal tissue has the appearance of hairy or nonhairy skin.
II. It is raised and irregular.
III. The most common locations are at the temporal or dorsal conjunctiva.
IV. It may grow over the corneal surface.

Diagnosis and Differential Diagnosis

I. Biopsy of the tissue reveals normal epithelial layers and/or components of skin and hair.
II. The primary differential consideration is neoplasia.

Treatment and Monitoring

I. Complete surgical resection of the dermoid is usually curative.
II. Sharp dissection of the surface of the dermoid is completed with a scalpel blade, whereas blunt dissection of the deeper tissues is accomplished with a blade or scissors.
III. Closure of the conjunctival tissues may not be necessary for a small dermoid, but large wounds are closed with a continuous pattern of 6-0 absorbable suture.
IV. Treat postoperatively with ophthalmic steroid and antibiotics TID for 2 weeks.
V. Ophthalmic antibiotic agents are used alone if a corneal ulcer has been created from the surgery.
VI. Examine the animal 2 to 6 weeks postoperatively to confirm there is no recurrence.
VII. Failure to remove all the tissue may result in regrowth at the same location.

Prominent Third Eyelid

Definition

I. The third eyelid protrudes across the surface of the eye, altering the normal appearance.
II. The third eyelid itself is not inflamed.

Causes

I. Neurological diseases
   A. Horner's syndrome: loss of sympathetic innervation

B. Haw's syndrome (Muir et al., 1990)
   1. Seen in cats
   2. Specific cause unknown
   3. Possibly diarrhea as an accompanying clinical sign

II. Pain or malaise
   A. Ocular pain: corneal ulcer, uveitis, glaucoma
   B. Systemic illness or malaise

III. Loss of orbital tissue
   A. Dehydration
   B. Fat or muscle atrophy
   C. Microphthalmia or phthisis bulbi

IV. Orbital space–occupying mass
   A. Neoplasia
   B. Orbital abscess, cellulitis

V. Tetanus

Pathophysiology

I. Passive upward movement of the third eyelid when the eye moves deeper into the orbit
   A. Loss of sympathetic innervation (Horner's syndrome)
   B. Contraction of the extraocular muscles
      1. Pain from ocular disease results in contraction of the extraocular muscles, pulling the globe deeper into the orbit in an effort to protect the eye.
      2. Overstimulation of the extraocular muscles can occur, as with tetanus.
   C. Loss of orbital structures allowing the globe to fall deeper into the orbit
      1. Microphthalmic globe: congenitally abnormal small eye, often nonvisual
      2. Phthisical globe: shrunken in size, acquired, usually nonvisual
      3. Loss of fat or muscle within the orbit

II. Physical displacement by a space-occupying mass or inflammation within the orbit

Clinical Signs

I. The condition may be uni- or bilateral.
II. The third eyelid is usually physically normal.

Diagnosis and Differential Diagnosis

I. Bilateral condition: dehydration, fat or muscle atrophy, generalized pain or malaise, tetanus, haws
II. Unilateral condition: orbital neoplasia or infection, ocular pain, Horner's syndrome
III. Complete physical examination
IV. Examination of the face for evidence of a symmetry
V. Thorough ophthalmic examination: pupillary light reflexes, Schirmer's tear test (STT), fluorescein stain, intraocular pressure, retropulsion of globe to evaluate the orbit
VI. Possibly pharmacologic testing to determine the cause of Horner's syndrome (see Chapter 105)

Treatment and Monitoring

I. Treat any underlying condition.
II. No treatment may be required; the presence of the third eyelid across the eye is not detrimental to the animal.
III. Topical application of 1% to 5% phenylephrine or 0.1% to 0.5% epinephrine ophthalmic solution may be applied as needed to cause retraction of the eyelid.
IV. The leading edge of the eyelid can be tattooed to make the eyelid less noticeable.

Prolapsed Gland of the Third Eyelid

Definition

I. The gland of the third eyelid prolapses and is no longer lying in the normal position.
II. The gland is exposed while still under the conjunctiva and the third eyelid is folded over.

Causes

I. The ligament that holds the gland in place breaks and allows the distal end of the gland to slip forward while still remaining under the conjunctival tissue.
II. Subsequent exposure results in swelling and inflammation of the glandular tissue.
III. Some breeds are predisposed.
   A. Dogs: American cocker spaniel, basset hound, beagle, English bulldog, Lhasa apso, poodle, and brachycephalic breeds in general
   B. Cats: Burmese (Koch, 1979)
IV. It may also be associated with an everted third eyelid cartilage.

Clinical Signs

I. Smooth, rounded, soft mass under the conjunctiva on the third eyelid
II. Possibly mucoid discharge
III. Unilateral or bilateral
IV. Predominantly in dogs <1 year of age

Diagnosis

I. Clinical appearance is usually diagnostic.
II. Palpate the third eyelid to rule out everted cartilage.
III. The mass can often be gently pushed back into place (transiently), behind the third eyelid.
IV. Consider fine-needle aspiration with cytological examination to rule out neoplasia, proliferative conjunctivitis, or episcleritis.

Differential Diagnosis

I. Neoplasia
II. Proliferative conjunctivitis: plasmacytic conjunctivitis (PC), ligneous conjunctivitis (LC) (see Inflammatory Disorders, later in this chapter)
III. Everted third eyelid cartilage
IV. Prominent third eyelid
V. Subconjunctival cyst
VI. Episcleritis (see Chapter 98)

Treatment

I. Surgical restoration of the normal gland position.
   A. Administer topical ophthalmic antibiotic and steroid preparations TID 1 week before surgery and ophthalmic

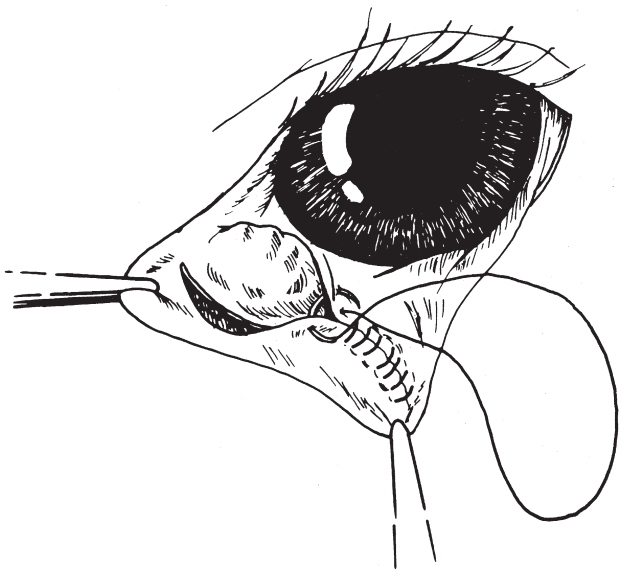

FIGURE 96-1 Repair of a prolapsed third eyelid gland using a pocket technique. One-centimeter incisions are made on the posterior surface of the third eyelid on either side of the prolapsed gland parallel to the free margin. The far sides of each incision are sutured together with 6-0 absorbable suture. *From Morgan RV, Duddy JM, McClurg K: Prolapse of the gland of the third eyelid in dogs: a retrospective study of 89 cases (1980-1990). J Am Anim Hosp Assoc 29:56, 1993; with permission.*

antibiotic alone TID for 2 weeks after surgery to help decrease inflammation and improve surgical success.

B. With a unilateral prolapse, consider surgery of the opposite eye to prevent future prolapse.

C. A pocket, imbrication technique may be performed (Figure 96-1).
   1. The third eyelid is pulled forward, exposing the bulbar surface.
   2. One-centimeter incisions are made on either side of the gland parallel with the free edge.
   3. The far edges of the two incisions are sutured together using an absorbable 6-0 suture in a continuous pattern.
   4. The gland is tucked down into the pocket as the suture line is closed.

D. A modified orbital rim tacking technique may be considered (Figure 96-2).
   1. Double-armed, nonabsorbable 2-0 to 4-0 suture is used.
   2. A 5-mm skin incision is made along the ventral orbital rim.
   3. A 5-mm conjunctival incision is made inside the eyelid, matching the skin incision.
   4. Suture is passed through the skin incision and the periosteal orbital rim and exits the conjunctival incision.
   5. The same suture is then passed through the conjunctiva and exits the dorsal surface of the gland.
   6. The same suture is then passed back into the dorsal surface of the gland and exits the conjunctiva close to the original position.
   7. The second arm of the suture is passed through the skin incision and the periosteal orbital rim, and exits the conjunctival incision (same as the first suture arm).
   8. The two arms of the suture are tied together, pulling the gland downward and anchoring it to the orbital rim.

E. A modified purse-string procedure is used in selected cases (Figure 96-3).
   1. It is recommended for puppies with acute prolapse of the gland.
   2. Absorbable 6-0 suture is used.
   3. Initially the suture is inserted in the bulbar conjunctiva within the ventral fornix (between the gland and the limbus).
   4. Then the suture is passed between the free edge of the third eyelid and the gland.
   5. Finally, the suture is passed into the bulbar conjunctiva of the ventral fornix.
   6. The suture is tied together, drawing the gland downward as the purse string is closed.

II. Surgical removal of the gland is considered only as a last resort.
   A. It is not an ideal therapy because removal of the lacrimal gland tissue predisposes the dog to development of keratoconjunctivitis sicca (KCS) (Morgan et al., 1993).
   B. Amputation of the exposed portion of the prolapsed gland can be completed with mild sedation and a topical or short-acting anesthetic.
   C. Sharp dissection of the gland is used, with no closure of the conjunctival tissues.

Monitoring of Animal

I. Reexamine the affected eye in 1 to 2 weeks.
   A. To ensure no corneal damage has resulted from surgical trauma or exposure
   B. To ensure proper healing of the incision

II. Reexamine the animal again in 1 to 3 months.
   A. To ensure proper position of the gland
   B. To ensure normal tear production (see Chapter 97)

Everted Third Eyelid Cartilage

Definition

I. The base of the T-shaped cartilage curls and protrudes anteriorly.

II. The rest of the third eyelid is usually normal with primary eversion of the cartilage.

Causes

I. Genetic predisposition in large-breed dogs

II. Genetic predisposition in German shorthaired pointers (Martin and Leach, 1970)

III. Reported in conjunction with prolapsed gland of the third eyelid in a Burmese cat (Albert et al., 1982)

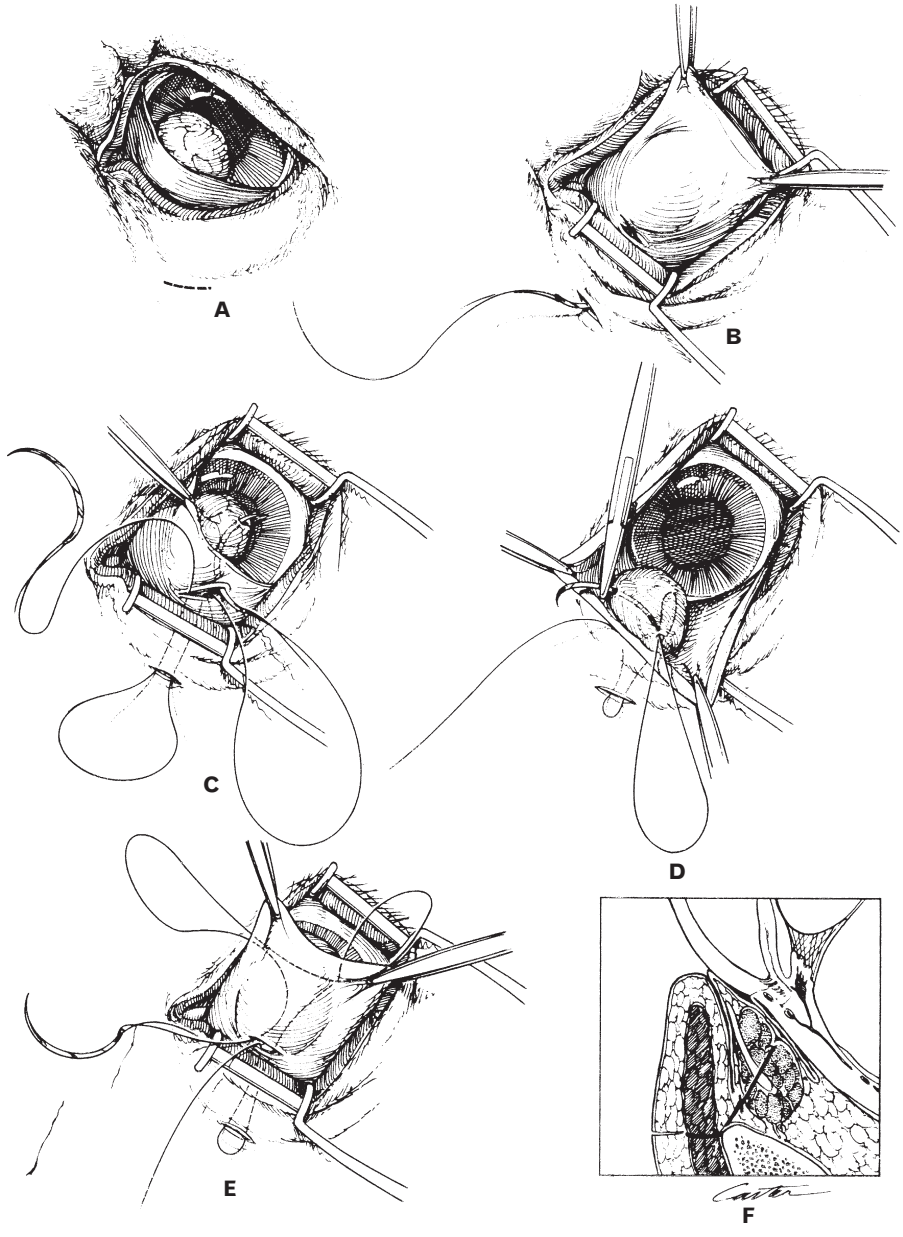

FIGURE 96-2 Diagram of a modification of the orbital rim anchorage method for surgical replacement of the gland of the third eyelid in dogs. A 5-mm skin incision is made parallel and subjacent to the ventral periorbital rim (**A**). A second incision is made parallel to the skin incision in the ventral conjunctival fornix. Nonabsorbable, monofilament suture (2-0 to 4-0 nylon, depending on the size of the dog) on a 3/8 circle cutting needle is passed through the skin, the periosteal rim, and the conjunctival incision (**B**). This is repeated with a second needle attached to the other end of the same suture. The first needle is passed through the conjunctiva and emerges through the dorsal gland (**C**). The needle is passed back through the gland (**D**) and then back out the conjunctival incision (**E**). A knot is tied securing the repair (**F**). Neither conjunctiva nor skin is sutured. *From Stanley RG, Kaswan RL: Modification of the orbital rim anchorage method for surgical replacement of the gland of the third eyelid in dogs. J Am Vet Med Assoc 205:1412, 1994; with permission.*

Pathophysiology

I. It is believed to result from rapid growth of the posterior portion of the cartilage compared with the anterior portion (Martin and Leach, 1970).
II. It may occur secondary to chronic prolapse of the gland of the third eyelid, which may weaken the cartilage.

Clinical Signs

I. Appearance of the third eyelid may change acutely.
II. Firm, thin, linear scroll of tissue is present on the palpebral surface of the free margin of the third eyelid.
III. Palpation of the third eyelid allows identification of the cartilage borders.

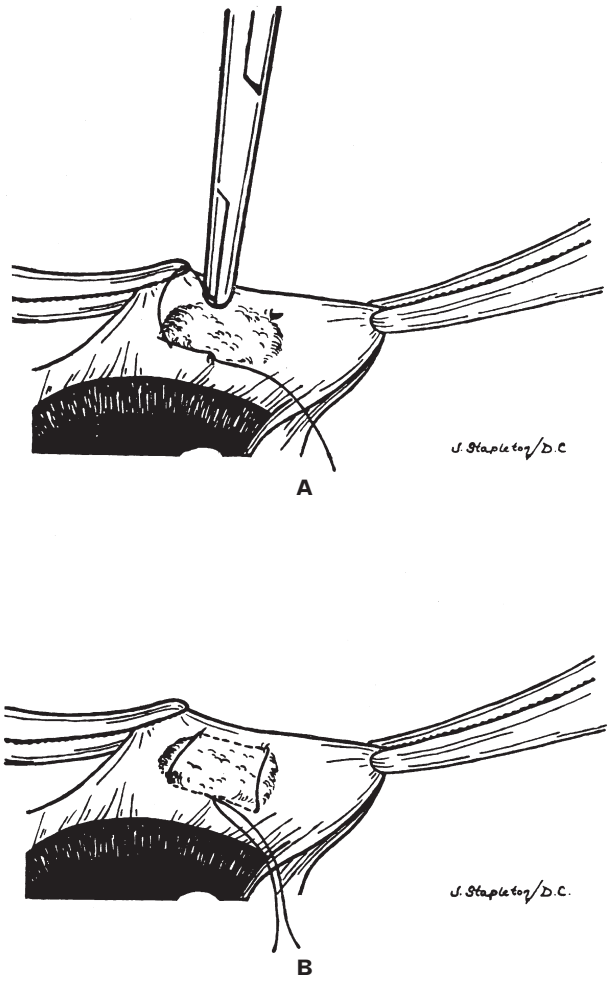

FIGURE 96-3 Placement of a modified purse-string suture around the prolapsed third eyelid gland. The initial bite is taken in the ventral fornix at the base of the third eyelid, and the second bite is taken between the body of the gland and the free margin of the third eyelid **(A).** The modified purse-string is completed when that final bite is placed back into the fornix to exit near the point of initial entry, drawn together, and tied **(B).** To stimulate adequate adhesion, the conjunctiva over the prolapsed gland is scarified before suture placement. *From Moore CP: Imbrication technique for replacement of prolapsed third eyelid gland. p. 126. In Bojrab MJ (ed): Current Techniques in Veterinary Surgery. 3rd Ed. Lea & Febiger, Philadelphia, 1990; with permission.*

IV. It is not usually painful, but mild conjunctivitis may develop.

Differential Diagnosis

I. Prolapsed gland of the third eyelid
II. Prominent third eyelid
III. Neoplasia of the third eyelid

Treatment

I. Surgical removal of the everted portion of the cartilage may be performed if the eye is symptomatic.
II. A single incision is made on the bulbar surface of the third eyelid conjunctiva.
III. The curled portion of the cartilage is bluntly dissected from the surrounding tissue using scissors or scalpel blade.
IV. Conjunctiva does not usually require closure.
V. In breeds that are predisposed to prolapse of the gland of the third eyelid, closure of the incision with 6-0 absorbable suture in a continuous pattern may prevent prolapse of the gland.
VI. After surgery a topical ophthalmic antibiotic is applied TID for 2 weeks.

Monitoring of Animal

I. Reexamine the animal in 1 to 2 weeks to ensure normal healing and no corneal ulceration secondary to surgical manipulation.
II. Reexamine the animal in 2 months to ensure normal position of gland of the third eyelid.

DEGENERATIVE DISORDERS

Subconjunctival Cyst

Definition

An epithelial cell-lined, fluid-filled sac forms as a result of an abnormal accumulation of glandular cells beneath the conjunctival surface.

Causes

I. Congenital abnormal location of glandular tissue
II. Chronic conjunctivitis
III. Trauma
IV. Surgical malpositioning of a prolapsed gland of the third eyelid

Clinical Signs

I. Soft, pliable swelling beneath the conjunctiva
II. Minimal discomfort

Diagnosis

I. Fine-needle aspiration of the mass reveals clear to golden, acellular, proteinaceous fluid.
II. Lacrimal duct flushing confirms no connection exists with the lacrimal canaliculus or sac.
III. Ultrasonography reveals a circumscribed mass with a hypoechoic center.

Differential Diagnosis

I. Neoplasia
II. Prolapse of the gland of the third eyelid
III. Prolapsed orbital fat
IV. Foreign body granuloma
V. Dacryoadenitis

Treatment and Monitoring

I. Surgical removal of the entire cyst
   A. Enlarged area of the conjunctiva is incised along one edge of the structure, followed by blunt dissection and removal of the entire cyst.
   B. If the cyst is ruptured, then identifying all the tissues is difficult; however, every effort is made to remove all the glandular tissue.

C. Conjunctival tissue is closed over the wound using 6-0 absorbable suture in a continuous pattern.
D. Failure to completely remove the cyst may result in local recurrence.

II. Ophthalmic antibiotics TID for 2 weeks to prevent infection

III. Reexamination postoperatively
A. At 1 to 2 weeks to ensure no corneal damage occurred secondary to surgical trauma and to ensure proper healing of the conjunctival wound
B. At 3 to 6 months to ensure no recurrence of the cyst

INFLAMMATORY DISORDERS

Conjunctivitis

Definition

I. Inflammation of the conjunctival tissues

II. May involve bulbar conjunctiva overlying the globe and on the posterior surface of the third eyelid

III. May affect palpebral conjunctiva lining the external eyelid and on the anterior surface of the third eyelid

Causes

I. Infectious agents
A. Bacteria and other organisms
1. *Chlamydia psittaci (Chlamydophila felis):* common in cats
2. *Mycoplasma felis:* common in cats, frequently accompanies viral respiratory disease
3. Gram-positive bacteria: *Staphylococcus* spp., *Bacillus* spp., *Corynebacterium* spp.
B. Viruses
1. Feline herpesvirus 1: chronic or recurrent conjunctivitis, with or without concurrent corneal ulceration
2. Calicivirus: frequently associated with signs of upper respiratory infections and oral ulceration in cats
3. Canine distemper: nonspecific conjunctivitis during acute disease
C. Parasites
1. Uncommon
2. *Thelazia* spp.
3. *Cuterebra* spp.
4. *Dirofilaria* spp. larvae
D. Systemic infections
1. *Blastomyces dermatitidis*
2. *Histoplasma capsulatum*
3. *Borrelia burgdorferi*

II. Immune-mediated disorders
A. Atopy, type I hypersensitivity
B. Cell-mediated inflammation
1. Eosinophilic conjunctivitis (EC): cats
2. Ligneous conjunctivitis (LC): dogs
3. PC (or pannus-associated conjunctivitis): dogs, most common in German shepherd dogs or related breeds

III. Irritative conditions
A. Drying of tissue from exposure or KCS (see Chapter 97)
B. Abnormal hairs: distichia, ectopic cilia, entropion, or trichiasis rubbing on the conjunctival surface
C. Environmental irritants: chemicals, smoke, dust, foreign bodies, others

IV. Trauma

V. Conditions accompanying other ocular diseases: uveitis, episcleritis, glaucoma, or corneal ulceration

Pathophysiology

I. Vasodilation occurs from any of the nonspecific causes, resulting in edema and inflammatory cell infiltration.

II. Chemotaxins stimulate increased inflammatory cell migration in the tissues, and these inflammatory cells increase the inflammatory cascade.

III. Specific causes of EC, LC, and PC are unknown.
A. EC has been associated with feline herpesvirus (Larocca, 2000).
B. LC may result from excessive vascular permeability that arises from an immune-mediated condition (Ramsey et al., 1996).
C. PC may be a hypersensitivity reaction and is related to excessive ultraviolet light stimulation (Eichenbaum et al., 1986).

Clinical Signs

I. Discharge
A. Epiphora: overflow of tears from increased lacrimation
B. Mucoid: from increased stimulation of goblet cells
C. Purulent: bacterial infections resulting in degenerate neutrophils

II. Chemosis: swelling of the conjunctiva

III. Hyperemia (engorgement of vessels)
A. Conjunctival vessels lie on the surface of the globe, can easily be moved across the globe, and blanch with topical ophthalmic epinephrine.
B. Scleral vessels are deep, usually a darker color, and move with the globe beneath the conjunctiva.
C. Hemorrhaging may also occur beneath the conjunctiva.

IV. Possible blepharospasm

V. Proliferative changes
A. Swelling of conjunctival lymphoid follicles: pink to clear, smooth swellings with a cobblestone appearance
B. EC: white to pink to red, raised, irregular tissue
C. LC: membranous white to pink tissue that may encircle the entire eye and obscure the cornea
D. PC: most often involving the third eyelid or the lateral aspect of the globe, producing a raised, red, cobblestone or "hamburger meat" appearance

Diagnosis

I. Complete ophthalmic examination to determine causes or rule out other conditions
A. Diagnostic tests
1. STT
2. Fluorescein stain
3. Intraocular pressure

B. Areas to examine
1. Eyelids for entropion, distichiasis, ectopic cilia, trichiasis, and foreign bodies
2. Cornea for evidence of keratitis or ulceration
3. Anterior chamber and iris for signs of intraocular inflammation or glaucoma

II. Cytology
A. Technique
1. Apply topical ophthalmic anesthetic to the conjunctival surface.
2. Retract the eyelid to expose the inflamed surface.
3. Use a blunt instrument (e.g., Kimura spatula, blunt edge of a scalpel blade) to scrape the surface several times.
4. Transfer cells to a glass slide; dry and stain the cells.
B. Normal cytology
1. Cell types: epithelial cells, melanin granules, mucin strands, blood cells
2. Bacteria: variable depending on the type of animal; mainly gram-positive such as *Staphylococcus* spp., *Bacillus* spp., and *Corynebacterium* spp. (in the dog)
C. Abnormal cytology
1. Degenerative and nondegenerative neutrophils with abundant bacteria suggest infections.
2. Intracytoplasmic inclusion bodies suggest *Chlamydophila* spp. or *Mycoplasma* spp.
3. Eosinophils (especially if more present than would be seen in a normal peripheral blood smear) and/or mast cells are suggestive of EC.
4. Amorphous, fibrillar hyaline-like material is a common finding in LC.
5. Abundant plasma cells are a prominent feature of PC.

III. Identification of organisms
A. Culture
1. Bacteria: aerobic culture
2. Mycoplasma: requires special media and growth conditions
B. Immunofluorescent antibody testing: herpesvirus and chlamydophilia
1. False positives may occur when fluorescein stain has been used before sample collection.
2. False negative occurs when an adequate sample is not obtained.
C. Polymerase chain reaction: herpesvirus, chlamydial or mycoplasmal agents

IV. Biopsy
A. Reserved for severe or unresolved conjunctivitis
B. Technique
1. Topical ophthalmic anesthetic is applied to the conjunctival surface.
2. Excise the most severely affected tissues with scissors.
3. Stop any bleeding with gentle pressure or application of topical ophthalmic epinephrine or phenylephrine.

Differential Diagnosis

I. Keratitis and corneal ulcers
A. Examine cornea to ensure it is clear and healthy.
B. Stain cornea to rule out ulcers (see Chapter 98).

II. Scleritis
A. Inflammation of the tissue beneath the conjunctiva confirms diagnosis.
B. Moving the conjunctiva across the surface of the inflamed tissue can help to localize it.

III. Uveitis
A. Measure intraocular pressure because it may be low with acute uveitis.
B. Examine the anterior chamber, iris, lens, and fundus for signs of inflammation (see Chapter 99).

IV. Glaucoma
A. Vascular engorgement often accompanies glaucoma.
B. Measure the intraocular pressure because it will be elevated with glaucoma (see Chapter 100).

Treatment

I. Infection (Table 96-1)
A. *Chlamydophila* spp. and *Mycoplasma* spp.: topical ophthalmic chloramphenicol, tetracycline, or erythromycin QID until resolution of clinical signs
B. Gram-positive bacteria: broad-spectrum topical ophthalmic antibiotic agent QID until resolution of clinical signs
C. Herpesvirus
1. Topical antiviral medications
a. Initial treatment must be five or more times daily.
b. Frequency is decreased as the clinical signs regress.
c. Choices include trifluorothymidine, idoxuridine, and vidarabine.
2. Oral L-lysine
a. Dose variable: 250 to 500 mg PO SID to BID
b. Used to decrease clinical signs and prevent recurrence
c. Unproven clinical efficacy
D. Parasites
1. Systemic therapy for the specific condition
2. Topical ophthalmic steroids BID to QID for inflammation (see Table 96-1)

II. Immune-mediated diseases
A. Atopy
1. Isolate and remove the cause, if possible.
2. Rinse eyes with sterile eyewash.
3. Administer topical steroids BID to QID (see Table 96-1).
4. Consider ophthalmic antihistamines (see Table 96-1) BID to QID in place of, or in conjunction with, ophthalmic steroid.
B. Eosinophilic conjunctivitis
1. Ophthalmic steroidal preparations (see Table 96-1)
a. Administer BID to QID depending on severity of the condition.
b. Decrease frequency as the condition improves.
c. Low-level topical steroid therapy (SID, QOD, or once weekly) is often required for life to prevent recurrence.
2. Megestrol acetate
a. Used specifically for EC in the cat.

TABLE 96-1

Medications Available for the Treatment of Conjunctivitis

DRUG	BRAND NAME (MANUFACTURER)	ROUTE	RECOMMENDED DOSE	MECHANISM AND USE
Antiviral Drugs				
Vidarabine (adenine arabinoside)	*Vira-A* (Monarch)	Ointment	5-8 times daily	All three products inhibit viral replication of herpesvirus
Idoxuridine	*Herplex* (Allergan)	Solution	5-8 times daily	
Trifluorothymidine	*Viroptic* (Burroughs Wellcome)	Solution	5-8 times daily	
Topical Steroidal Drugs				
Prednisolone acetate 1% Prednisolone $NaPO_4$ 1% Dexamethasone 0.1% Hydrocortisone 1% Betamethasone 0.1%	Multiple manufacturers	Solution and ointment	BID-QID	These drugs suppress inflammatory responses: EC, LC, PC, atopy, irritative, noninfectious, and nonulcerative conjunctivitis
Antiinflammatory Drugs				
Ketorolac 0.5%	*Acular* (Allergan)	Solution	BID-QID	Inhibits prostaglandin synthesis: atopy
Naphazoline 0.027%/ pheniramine 0.315%	*Opcon-A* (Bausch & Lomb)	Solution	BID-QID	Causes vasoconstriction, antihistamine
Cyclosporine 0.2%	*Optimmune* (Schering)	Ointment	BID	Causes T-cell suppression: LC
Olopatadine 0.1% Ketotifen fumarate 0.025%	*Patanol* (Alcon) *Zaditor* (Ciba Vision)	Solution Solution	BID-TID BID-TID	These drugs are H_1-receptor antagonists, prevent mast cell degeneration
Antibiotic Drugs				
Chloramphenicol 1%	Multiple manufacturers	Solution and ointment	TID-QID	These four drugs are bacteriostatic: *Chlamydophila* spp. and *Mycoplasma* spp.
Erythromycin 0.5%	Multiple manufacturers	Ointment	TID-QID	
Tetracycline	*Achromycin* (Storz/Lederle)	Ointment	TID-QID	
Oxytetracycline-polymyxin	*Terramycin* (Pfizer)	Ointment	BID-TID	
Bacitracin-neomycin-gramicidin and bacitracin-neomycin-polymyxin	Multiple manufacturers	Solution and ointment	TID-QID	Broad-spectrum antibiotic drugs
Antibiotic-Steroid Combinations				
Neomycin-polymyxin-dexamethasone	Multiple manufacturers	Solution and ointment	TID-QID	These drugs are broad-spectrum antibiotic-steroid combinations: prevent infection and inflammation
Bacitracin-neomycin-polymyxin-hydrocortisone	Multiple manufacturers	Ointment	SID-QID	
Gentamicin-betamethasone	*Durafilm* (Schering)	Solution	SID-QID	

EC, Eosinophillic conjunctivitis; *LC,* ligneous conjunctivitis; *PC,* plasmacytic conjunctivitis; H_1, histamine$_1$.

b. Although topical ophthalmic steroidal preparations are effective in the treatment of EC, such preparations may aggravate a concurrent viral infection (Larocca, 2000).
c. The mechanism of action in the resolution of this disease is unknown.
d. Use of megestrol acetate is controversial because of known side effects, including diabetes, adrenocortical suppression, and mammary neoplasia, and is considered a treatment of last resort.

C. Ligneous conjunctivitis (Ramsey et al. 1996)
1. No single therapy is effective in all cases.
2. Surgical debulking of membranes is combined with topical steroid or oral antiinflammatory medications to prevent recurrence.
3. Prednisolone may be given at an initial dose of 2 mg/kg PO SID, then decreased to 0.5 mg/kg PO SID to QOD.
a. Systemic side effects, including hyperadrenocorticism, pancreatitis, and diarrhea, may occur.
b. Low dose of prednisolone may be needed for life to maintain remission of the disease.
4. Azathioprine is given at an initial dose of 2 mg/kg PO SID and then decreased to 0.5 to 1.0 mg/kg PO QOD.
a. This is an immunosuppressive drug, and the dog must be systemically evaluated with a complete blood and platelet count to look for bone marrow suppression, as well as urinalysis to test for secondary infection.
b. Therapy may be needed for the lifetime of the animal to maintain remission of the disease.
5. Topical ophthalmic medications may be tried.
a. Prednisolone 1% BID to TID may be used in conjunction with other therapies.
b. Cyclosporine 2% solution or 0.2% cyclosporine ointment may be used BID in conjunction with other therapies.

D. Plasmacytic conjunctivitis
1. Ophthalmic steroidal preparations (see Table 96-1)
a. Apply these medications BID to QID, depending on severity of clinical signs.
b. Dose is decreased as condition improves.
c. Low level of therapy may be necessary for life to keep the condition from progressing to involve the cornea.
2. Ophthalmic cyclosporine (0.2% to 2.0%) BID alone or in conjunction with topical steroidal preparations
3. Ophthalmic tacrolimus (0.02% to 0.03%) BID alone or in conjunction with topical steroids

III. Irritative conditions
A. Remove or treat the source of the irritation.
B. Use topical steroidal preparations BID to QID until condition is resolved.

IV. Trauma: topical steroidal preparations BID to QID until conjunctivitis is resolved

V. Primary ocular diseases
A. Treat the specific underlying ocular disease.
B. Ophthalmic steroids may be used as needed BID to QID.
C. Treatment of conjunctivitis is not necessary if corneal ulceration (see Chapter 98) is the primary disease.

Monitoring of Animal

I. Monitor the animal biweekly until complete resolution of signs.
II. If clinical signs do not regress or if they return rapidly after discontinuation of therapy, perform a complete ophthalmic examination to ensure other ocular diseases are not present.
III. Chronic conjunctivitis may require a biopsy to rule out uncommon forms of the disease or hidden neoplasia.

Symblepharon

Definition

I. Symblepharon is the development of adhesions between apposing epithelial surfaces.
II. It most often involves the bulbar and palpebral surfaces, but can involve the cornea or the third eyelid (adhering to the cornea and/or eyelid).
III. Cats are affected more frequently than dogs.

Causes

I. Herpesvirus infection in kittens is the most common cause.
II. Conjunctival surface trauma from chemical irritants or severe abrasion may also result in symblepharon.

Pathophysiology

I. Abrasion of the epithelial surface results in fibrosis and adhesion of the conjunctiva to the conjunctiva, eyelids, or the cornea.
II. Adhesion of the conjunctival surfaces may cause damage to lacrimal tissues, with a loss of normal tear function.
III. Normal movement of the eyelids may be impaired.
IV. Vision may be obscured from decreased palpebral fissure size, conjunctival tissue covering the cornea, or secondary keratitis.

Clinical Signs

I. It may appear similar to conjunctivitis.
II. Epiphora or mucopurulent discharge is common.
III. Eyelid movements may be decreased.
IV. Corneal opacification or ulceration may also be present.

Diagnosis

I. Physical examination reveals the conjunctival surfaces are adherent to themselves, the eyelids, or cornea.
II. Apply a topical ophthalmic anesthetic and then use a cotton-tipped applicator to move the conjunctival surfaces.
A. Normal conjunctiva is easily moved in multiple directions.
B. With symblepharon, a loss of tissue mobility occurs.

III. Stain the cornea with fluorescein to identify corneal ulceration, especially if herpesvirus infection is suspected.

Treatment and Monitoring

I. Treat any underlying active condition.
   A. Herpesvirus is treated with antiviral medications.
   B. Chemical irritants are rinsed with copious amounts of sterile eyewash followed by antibiotic agents to prevent secondary bacterial infections and steroidal preparations to decrease further inflammation.
II. Corneal opacities are treated as follows:
   A. Corneal ulcers (stain fluorescein positive) are treated with topical antibiotics QID to prevent secondary bacterial infections (see Chapter 98).
   B. Scars (stain fluorescein negative) may be treated with topical steroids BID to TID to attempt to decrease the opacification.
III. Decreased tear production requires specific therapy.
   A. Topical cyclosporine BID may be beneficial in improving natural tear production and decreasing corneal vascularization.
   B. Artificial tear solutions BID to QID are used to supplement natural tears.
   C. If KCS results in chronic corneal disease, then further treatment may be necessary (see Chapter 97).
IV. Surgical intervention is necessary to break down the adhesions.
   A. Although several techniques have been described, a high rate of readhesion exists (Gelatt and Gelatt, 1994).
   B. Results of surgery are often disappointing.

NEOPLASIA

Definition

I. Primary growth of neoplastic cells in the conjunctiva, third eyelid, or both
II. Invasion of secondary neoplasia
   A. Spread of local neoplasia from adjacent tissues (eyelid or orbit) into the conjunctiva
   B. Metastatic spread of neoplastic cells (rare)
III. Uncommon

Causes

I. Cellular origin of primary neoplasia
   A. Epithelial: squamous cell carcinoma, papilloma
   B. Melanocytic: melanoma, amelanotic melanoma
   C. Vascular: hemangioma, hemangiosarcoma, angiokeratoma
   D. Glandular: adenoma, adenocarcinoma
   E. Round cell origin: histiocytoma, mastocytoma, lymphosarcoma
II. Secondary neoplasia
   A. Adenocarcinoma: local invasion from the lacrimal glands
   B. Melanoma: local invasion from limbal neoplasia
   C. Lymphosarcoma: often multifocal disease

Clinical Signs

I. Appearance of the tissues varies depending on the type of neoplasm.
II. Tumors of the conjunctiva and third eyelid are raised, irregular, and often develop rapidly.
III. Concurrent conjunctivitis may be present.

Diagnosis

I. Cytological examination
   A. After application of proparacaine, a blunt instrument (Kimura spatula or the blunt end of a scalpel blade) is used to scrape the surface several times.
   B. Cells are transferred to a glass slide, dried, and stained.
II. Biopsy under topical anesthesia
III. Excisional biopsy under general anesthesia

Treatment

I. Surgical resection of entire mass with clean margins
II. Diode laser ablation for melanoma
III. Adjunctive therapy
   A. Cryotherapy: squamous cell carcinoma, papilloma, melanoma, adenoma, adenocarcinoma
   B. Radiation therapy: squamous cell carcinoma, melanoma, hemangiosarcoma
   C. Hyperthermia: squamous cell carcinoma
IV. Concurrent treatment of systemic neoplasia
V. Topical antibiotic-steroid combinations TID for 2 weeks to prevent secondary infection and inflammation postoperatively

Monitoring of Animal

I. Reexamine the animal in 2 weeks to ensure proper healing of surgical site.
II. Failure to remove all neoplastic cells may result in local recurrence.
   A. Malignant melanoma
      1. High rate of local recurrence
      2. Guarded to poor prognosis
   B. Papilloma
      1. Self-limiting
      2. Good prognosis
   C. Squamous cell carcinoma
      1. Focal mass: good prognosis
      2. Extensive masses: poor prognosis
   D. Hemangioma and angiokeratoma: good prognosis
   E. Hemangiosarcoma: guarded to poor prognosis unless small and completely excised
   F. Adenoma: good prognosis
   G. Adenocarcinoma: guarded to poor prognosis
   H. Histiocytoma and mastocytoma: good prognosis
III. Metastatic spread of conjunctival neoplasia is rare.
   A. Melanomas may metastasize.
   B. Secondary conjunctival neoplasia may be associated with metastatic disease elsewhere.
IV. Reexamine in 2 to 3 months to ensure no recurrence of the tumor.

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CHAPTER 97

Disorders of the Lacrimal and Nasolacrimal System

Robert J. Munger

CONGENITAL/DEVELOPMENTAL DISORDERS

See Table 97-1.

DEGENERATIVE DISORDERS

Keratoconjunctivitis Sicca

Definition

I. Keratoconjunctivitis sicca (KCS) is an ocular surface disorder arising from a deficiency of aqueous tear secretion.
   A. Primary KCS: results from failure of lacrimal secretion
   B. Secondary KCS: results from obstruction of ductules from the lacrimal glands and failure of tears to reach the eye
II. Deficiency of aqueous tears causes desiccation and inflammation of the cornea and conjunctiva.

Causes

I. Primary KCS
   A. Immune-mediated inflammation of the lacrimal glands and the ocular surface
      1. Possible genetic influences and breed-related predisposition
         a. Includes the American cocker spaniel, English bulldog, Lhasa apso, shih tzu, West Highland white terrier, Cavalier King Charles spaniel, and others (Moore, 1999)
         b. Breeds similar to those with atopic disease
      2. Lymphocytic infiltrates in lacrimal glands and conjunctiva
      3. Positive response to topical cyclosporine (T-cell suppressor)
   B. Neurohormonal factors
      1. Age and neutering predispose to KCS.
      2. Spayed females may predominate.
   C. Drug toxicity
      1. Sulfonamides: including trimethoprim and sulfa combinations
      2. Phenazopyridine
      3. Atropine: topical or parenteral (Hollingsworth et al., 1992)
      4. Anesthesia-induced (Herring et al., 2000)
      5. 5-Aminosalicylic acid
      6. Etodolac *(EtoGesic)*
   D. Excision of prolapsed gland of third eyelid
      1. Especially in canine breeds predisposed to KCS
      2. Burmese cats
   E. Neurogenic: decreased secretion associated with loss of parasympathetic stimulus of the lacrimal glands
   F. Trauma
      1. Damage to lacrimal glands or their innervation
      2. Orbital damage or proptosis with exposure of globe
   G. Infectious diseases
      1. Canine distemper virus may affect the lacrimal glands.
      2. Feline herpesvirus 1 is incriminated in most cases of feline KCS, but the mechanism is unclear and may be secondary to scarring of ductules.
   H. Radiation-induced damage to the lacrimal glands
      1. Especially during cancer treatment for neoplasia of the head
      2. Becoming more common with advances in oncology
   I. Congenital alacrima (see Table 97-1)
II. Secondary KCS
   A. Severe and/or chronic conjunctivitis causes scarring and occlusion of the ductules leading from the lacrimal glands to the conjunctival sac.
   B. Causes include infections (bacterial, chlamydial, viral), allergy, and chemical irritation.
   C. Obstruction can be permanent with severe scarring.

Pathophysiology

I. Hypersensitivity and altered ocular surface immunity contribute to inflammation of the ocular surface and lacrimal glands (Kaswan et al, 1985; Bistner, 1994; English, 1999).
   A. Accumulation of lymphocytes in glands and the subepithelial layer of the conjunctiva alters glandular and conjunctival cellular architecture and physiology, thereby adversely affecting lacrimal secretions.
   B. Altered corneal epithelium participates in antigen presentation to T-helper cells and recruitment of immune cells.
   C. Release of inflammatory mediators adds to the process.
      1. Diffuse infiltration of subconjunctival tissues with neutrophils and lymphocytes
      2. Keratitis
         a. Superficial inflammation progressing to deep stromal inflammation

TABLE 97-1

Congenital/Developmental Disorders of the Nasolacrimal System

DISORDER	DEFINITION	CAUSES	CLINICAL FEATURES	DIAGNOSIS	DIFFERENTIAL DIAGNOSIS	TREATMENT
Congenital alacrima	Congenital absence of tearing from lacrimal gland from hypoplasia or agenesis	Breed related: pug, Yorkshire terrier (Aquirre et al., 1971; Grahn, 1999); or anomalous development	Severe drying of ocular surface with corneal scarring/pigmentation, conjunctival hyperemia Copious mucopurulent discharge Usually unilateral	Clinical signs typical of neonatal KCS Confirmed by low Schirmer tear test	KCS from neonatal ophthalmia with secondary damage to lacrimal gland	Tear replacements: lacrimal stimulation not effective Topical antibiotics Parotid duct transposition if salivary production is normal
Lacrimal cysts	Rare, fluid-filled cystic swelling originating from orbital lacrimal gland or nictitans gland	Congenital or developmental defect of the glands or their ductules, or acquired from duct obstruction arising from trauma and/or inflammation Secretory stasis leads to dilated acini and ductules with epithelial atrophy Cyst wall lined with flattened cuboidal epithelium ± inflammation	Soft, fluctuant swelling within orbit or at medial canthus Possible distention of conjunctiva with protrusion into palpebral fissure Possible displacement of globe, third eyelid, and orbital structures Epiphora or impaired secretion of tears may be present	Based on: identification of orbital and/or subconjunctival cyst with orbital ultrasound or MRI	Orbital cellulitis: swelling is usually painful and responsive to antibiotics Orbital neoplasm	Surgical excision usually curative Topical and systemic antibiotics to prevent postoperative infection Monitor tear production with Schimer tear test
Imperforate puncta	Lacrimal punctal aplasia: a congenital absence of the opening of the upper and/or lower lacrimal punctae Usually presents as membrane over the position of the punctum	Genetic or breed related factors: most commonly seen in American cocker spaniel, Bedlington terrier, golden retriever, miniature and toy poodles, and Samoyed (Rubin, 1989)	Epiphora from impaired drainage into NLD with wetting and reddish brown staining of periocular hair Secondary dermatitis with bacterial infection when wetting is severe Stasis of tears in NLD may lead to dacryocystitis Epiphora may be absent if only upper punctum involved	Examination with magnification to visualize site of punctae Failure of fluorescein passage to nares is not diagnostic Flushing nasolacrimal system (19-gauge or smaller canula) usually results in bulging of the membrane occluding the punctum	Epiphora from any impaired drainage: 1. Scarring of punctae or NLD 2. NLD atresia or attenuation 3. Dacryocystitis or acquired obstruction from foreign body or infection 4. Micropunctum or punctal malposition (congenital or with entropion or ectropion)	Surgical opening of punctum: best performed under anesthesia with tenting of the occluding conjunctival veil by NLD flushing or passage of pigtail probe or lacrimal duct probe Topical antibiotic-steroid drops TID-QID for 2-3 weeks

KCS, Keratoconjunctivitis sicca; *MRI,* magnetic resonance imaging; *NLD,* nasolacrimal duct.

TABLE 97-1

Congenital/Developmental Disorders of the Nasolacrimal System—*cont'd*

DISORDER	DEFINITION	CAUSES	CLINICAL FEATURES	DIAGNOSIS	DIFFERENTIAL DIAGNOSIS	TREATMENT
					Diverted drainage or overflow of tears from trichiasis, distichiasis, entropion, shallow or scarred lacrimal lake Excessive lacrimation from ocular disease	Prevent closure by cannulation of duct with monofilament flexible tubing, such as silastic, polyethylene, or polyvinyl tubing (Slatter, 2006b)
Micropunctum	Incomplete development or stricture of the lacrimal punctum	Congenital malformation or cicatricial stenosis	Epiphora and stasis of tear flow, as for imperforate lacrimal punctum	The presence of epiphora and identification of small, punctal opening confirm the diagnosis	As for imperforate lacrimal punctae (see earlier)	Enlarge punctum with punctal dilator or by incision/excision of surrounding conjunctiva and maintain opening with cannulation as described earlier (Grahn, 1999)
Malpositioned punctae and canaliculi	Congenital misplacement of the lower punctum and canaliculus or displacement of the punctum by medial lower lid entropion	Congenital development of the punctum and canaliculus in an abnormal position Displacement occurs commonly in toy and brachycephalic breeds in association with tight medial canthal ligaments and/or medial entropion and trichiasis	May be asymptomatic Chronic epiphora and periocular staining Medial canthal trichiasis may be present	Direct examination of punctal position With medial entropion, eversion of the lid will rotate the punctum into a normal position	Same as for imperforate punctum and micropunctum	None if asymptomatic Cannulation, dissection, and repositioning of the punctum and canaliculus after careful incision and dissection of the surrounding conjunctiva (Grahn, 1999) Correction of medial lower lid entropion

Continued

TABLE 97-1

Congenital/Developmental Disorders of the Nasolacrimal System—*cont'd*

DISORDER	DEFINITION	CAUSES	CLINICAL FEATURES	DIAGNOSIS	DIFFERENTIAL DIAGNOSIS	TREATMENT
Dacryoma	A cyst formed by the accumulation of tears in an obstructed canaliculus or NLD Sometimes confused in the literature with dacryops, which refers to a constant presence of an excess of tears in the eye owing to narrowing of the lacrimal punctum	Embryonic malformation of the canaliculus or NLD can cause obstruction and dilation of the ductular structures Acquired obstruction of NLD or canaliculus may occur secondary to trauma of inflammation	Epiphora varies depending on degree of obstruction Fluctuant medial canthal swelling that may distort the medial canthus Cysts are lined by epithelium	Impaired flow of tears to nares NLD flushing: obstruction varies from none to complete, and cyst swelling may increase if NLD communicates with cyst Skull radiographs may reveal nasal or sinus cavity cysts, bony changes from pressure on adjacent bone, or other primary diseases blocking NLD (e.g., abscessed teeth, foreign body, neoplasm) Positive contrast dacryocystorhinography may reveal ductule abnormalities or communication with sinuses or adjacent cysts Other modalities include ultrasonography and MRI	Structural abnormalities including dacryocystitis, acquired stenosis, adjacent orbital disease (cellulitis, zygomatic mucocele or adenitis, myositis, neoplasia), other congenital anomalies (see earlier) Functional impairment of tear drainage (see earlier) Excessive lacrimation from extraocular or intraocular or irritation	Surgical excision or marsupialization of the cyst is done, with careful dissection from the duct and cannulation if possible during closure to prevent stenosis of the duct; curettage may be adequate if removal is not possible Complications include scarring with permanent obstruction and epiphora, and recurrence of the cyst Creation of new drainage route may be required in the event of scarring (dacryocystorhinostomy or conjunctival buccostomy)

b. Superficial corneal vascularization and pigmentation
c. Neutrophilic and lymphocytic cellular corneal infiltration

II. Loss of lacrimal secretions leads to pathologic changes.
A. Commingling of lipid and mucoid layers of the tear film
1. Hypertonicity of the tear film
2. Accumulation of mucopurulent discharge (worse with chronicity)
B. Altered cleansing, lubrication, and nutrition of the ocular surfaces
1. Accumulation of environmental irritants
2. Accumulation of bacteria and cellular debris
3. Altered gas and nutrient exchange
C. Acute decline in tear production often leading to corneal ulceration and secondary bacterial infection
1. Keratomalacia
2. Descemetocele
3. Corneal perforation

III. Chronicity produces secondary surface changes.
A. Pigmentation and scarring of cornea
B. Conjunctival hypertrophy and goblet cell proliferation
C. Irregular corneal surface and altered wettability

Clinical Signs

I. Acute KCS
A. Blepharospasm, intense conjunctival hyperemia, protrusion of the third eyelid, dull and/or irregular corneal surface
B. Exudates: mucoid to mucopurulent (mild to moderate)
C. Corneal ulceration
1. May progress rapidly to keratomalacia
2. Possible perforation of the cornea, with secondary uveitis
D. Early corneal vascularization: more severe if decline in tear secretion is preceded by other causes of keratoconjunctivitis

II. Chronic KCS
A. Conjunctival hyperemia, thickening (hypertrophy), chemosis
B. Exudates: copious, ropy mucopurulent
1. Yellow to green in color
2. Heavy accumulations in conjunctival sac and on lids: may interfere with lid opening after periods of sleep
3. Often confused with primary infection
C. Corneal changes
1. Corneal vascularization and scarring progressing to corneal opacification (deep and superficial)
2. Corneal pigmentation that progresses with time
3. Irregular corneal surface, ± dried exudates on the surface
4. Corneal ulcers: less common than with acute KCS
D. Decreased vision secondary to severe corneal changes
E. Blepharitis: variable incidence
F. Less ocular pain
G. Lagophthalmos, especially in brachycephalic breeds
H. Cats: clinical signs less severe, little discharge

III. Unilateral versus bilateral disease
A. Usually bilateral
B. Unilateral: particularly in early stages of primary KCS, any time with secondary KCS

IV. Dry nares and nostril (xeromycteria)
A. May occur on affected side(s)
B. Possibly from concurrent involvement of nasal glands (Slatter, 2006b) and/or pterygopalatine nerve damage (Scagliotti, 1999)
C. Dried exudate in nostril, occluding nostril in severe cases

Diagnosis

I. Based on clinical signs
A. Some animals with borderline KCS appear normal.
B. Discharge and ocular irritation warrant Schirmer tear test (STT) evaluation.

II. Schirmer tear test
A. Standard method for quantifying aqueous tear production
B. Normal values
1. Dog: ≥15 mm/min (19.8 ± 5.3 mm/min) (Slatter, 2006a)
2. Cat: 16.9 ± 5.7 mm/min (Slatter, 2006a)
a. Marked variation in tear production depending on stress
b. Interpretation difficult and closely linked to clinical signs
C. Abnormal values
1. Marginal or early subclinical KCS: clinical signs minimal or absent
a. Dog: 11 to 14 mm/min
b. Cat: 5 to 11 mm/min
2. Mild to moderate KCS
a. Dog: 6 to 10 mm/min
b. Cat: 5 to 11 mm/min
3. Severe KCS
a. Dog: <5 mm/min
b. Cat: <5 mm/min
c. Both species: 0 to 2 mm/min, associated with guarded prognosis
D. Technique and materials
1. Commercially available test strips may vary in absorbency.
a. Use same brand for repeated measurements in same animal.
b. Color-impregnated strips are available with calibrations for easy reading of results.
2. Strip is bent at notch and placed over lower lid (preferably laterally).
3. Remove excessive mucopurulent discharge before testing.
4. Perform test before instillation of other solutions or medications (e.g., local anesthetics, mydriatics).
5. Repeated testing is indicated for evaluation of transient versus permanent KCS.

III. Phenol red thread tear test (Brown et al., 1997)

IV. Ancillary testing
  A. Conjunctival bacterial culture and sensitivity testing
  B. Fluorescein staining for erosions and ulceration of cornea
  C. Polymerase chain reaction testing for feline herpesvirus 1
  D. Rose bengal staining
    1. For detection of devitalized epithelial cells
    2. May have a toxic effect on the epithelial cells with repeated use

Differential Diagnosis

I. Primary conjunctivitis and keratoconjunctivitis: allergic, bacterial, viral, traumatic
II. Dacryocystitis
  A. Mucoid to mucopurulent discharge in medial canthus
  B. STT normal
  C. Nasolacrimal duct flushing: discharge flushed from punctae and nares
III. Facial and lid paralysis and lagophthalmos
IV. Trigeminal nerve dysfunction
  A. Low STT from loss of reflex stimulation, without significant conjunctivitis or discharge
  B. Loss of palpebral and corneal blink responses
V. Idiopathic, low STT in cats associated with stress or unknown factors

Treatment

I. Tear replacement and lubrication
  A. Applied pending recovery of normal tear secretion
  B. Designed to replace one or more of the tear film components (mucin, aqueous, and/or lipid layers)
    1. May be combined with electrolytes and other medications
    2. Applied 4 to 12 times daily as needed
    3. Single-dose preparations, preservative free to reduce toxicity to the cornea
  C. Various types of tear replacements (Table 97-2).
II. Tear stimulation
  A. Topical cyclosporine A
    1. Lacrimogenic action incompletely understood
      a. Inhibits T-helper cells in lacrimal tissue
      b. Restores dominance of T-suppressor cells in sustaining normal lacrimal function
      c. Influences prolactin production and neurohormonal control of lacrimal secretion
    2. Antiinflammatory and immunomodulating effects
      a. Decreases cytokine production
      b. Decreases recruitment of immune cells and release of inflammatory mediators
      c. Preserves normal cellular architecture and function of both the lacrimal glands and the ocular surface
    3. Preparations
      a. Cyclosporine 0.2% ointment *(Optimmune)*
      b. Cyclosporine 1% to 2% solution in corn, mineral oil, or medium-chain triglyceride solution
    4. Therapeutic use
      a. Recommended BID (TID in severe cases)
      b. May require 6 to 12 weeks for response, especially in severe cases
      c. Therapy usually lifelong: 85% recurrence when discontinued (Moore, 1999; Slatter, 2006b)
      d. Controlled studies lacking for indications and safety in cats

TABLE 97-2

Types of Tear Replacement Preparations

CLASS	PROPERTIES	ACTION	EXAMPLES
Carboxycellulose and methylcellulose preparations	Water soluble and viscous	Prolonged contact time and increased surface wettability	*Celluvisc, Biovy Tears, Tears Naturale, Refresh*
Polyvinyl alcohol	Less viscous than methylcellulose but good corneal adhesion	Increased adhesion and contact with cornea, with increased wettability	*AKWA Tears, Artificial Tears,* other generics
Prolonged contact polymers (e.g., dextran, polyvinylpyrrolidine, carbopol)	Mucinous	Combined with aqueous preparations to replace mucin and aqueous tears and increase contact time	*Genteal Gel, Refresh Liquigel, Lubrithal*
Viscoelastics (methylcellulose, glycosaminoglycans—sodium hyaluronate and chondroitin sulfate)	Mucinous and viscous	Increase tear viscosity Prolong tear retention Enhance lubrication and comfort Protect corneal surface	*UltraTears, I-Med Plus, Hyoptic, Blink*
Ophthalmic lubricating ointments (petrolatum)	Mimic action of lipids from meibomian glands	Prevent tear evaporation Prolong contact time for medications Sustained release of medication	*Lacrilube, Refresh PM, Genteal PM, Puralube,* other generics

B. Tacrolimus 0.02% to 0.03% ointment or solution BID to TID (Chambers et al., 2002; Berdoulay et al., 2005)
1. Action and efficacy similar to topical cyclosporine
2. Anecdotal reports of efficacy when topical cyclosporine fails

C. Pilocarpine 1% to 2% ophthalmic solution
1. Administration of one to four drops on food PO BID to TID has been used for its parasympathomimetic action on lacrimal glands.
2. Efficacy is questionable; best indication for use is neurogenic KCS (Smith et al., 1994).

III. Antimicrobial therapy to prevent secondary infections

IV. Antiinflammatory therapy
A. Topical corticosteroids and nonsteroidal antiinflammatory drugs
B. Possibly systemic corticosteroids: severe inflammation, allergic keratoconjunctivitis

V. Mucinolytic and anticollagenase therapy
A. Formulations
1. Acetylcysteine 5% to 10% applied topically BID to QID
2. Acetylcysteine added to Severin's KCS solution: artificial tears, pilocarpine, antibiotics (Severin, 1996)

B. Actions
1. Break down and remove excess mucus
2. Anticollagenase activity to prevent enzymatic degradation of the corneal stroma

C. Disadvantages
1. May be irritating, especially with prolonged use
2. Expensive, degrades rapidly

VI. Surgical therapy
A. Parotid duct transposition
1. When tear stimulation fails and tear replacement therapy is inadequate
2. Case selection critical
a. Functional parotid gland and duct must be present; check for adequate salivation.
b. Corneal and conjunctival infection and ulceration must be controlled before surgery.
c. Normal lid structure and function are essential.

B. Punctal occlusion via implants or cauterization
1. Act to retard drainage of tears from lacrimal sac
2. Efficacy in animals unproven
3. Require basal tear production for adequate benefit
4. Cautery of punctae irreversible: last resort therapy

Monitoring of Animal

I. Medical therapy
A. Prognosis after treatment with cyclosporine and tacrolimus
1. Good in dogs when treatment is initiated early (66% to 75% improvement) (Moore, 1999; Slatter, 2001b)
2. Poor when STT is 0 to 2 mm/min, especially if duration prolonged

B. Complications and side effects rare
1. Cyclosporine 2% solution in corn oil can affect systemic cellular immunity (Gilger et al., 1995, 1996).
2. Occasional blepharoconjunctivitis can occur in dogs with either formulation.
3. Compounded corn oil solutions are easily contaminated by bacteria.
4. Compounded tacrolimus has similar complications and side effects to cyclosporine.

II. Surgical therapy: parotid duct transposition
A. Postoperative care
1. Administer topical antibiotic and steroidal medications, ± systemic antibiotic agents.
2. Stimulate salivation frequently with food treats.
3. Monitor for corneal irritation and ulcers from sutures.

B. Postoperative complications
1. Excessive wetting of face and lids from saliva
a. It may lead to bacterial dermatitis and blepharitis.
b. Frequent cleansing helps to reduce bacteria.
c. Possible resolution is achieved with partial ligation of the duct to reduce secretion.
2. Salivary and mineral precipitates on lids and ocular surface
a. Possible irritation, pain, blurred vision
b. Topical 1% disodium ethylenediamine tetraacetic acid (NaEDTA) in artificial tears BID to QID to reduce precipitates
c. Frequent cleansing: possibly as demanding as tear replacement therapy
3. Corneal ulceration with delayed healing

Qualitative Tear Film Abnormalities

Definition

I. Abnormalities in the quality and/or volume of the mucin or lipid layers of the tear film

II. Result in tear film instability with inadequate distribution and adherence of tear film over the cornea despite sufficient aqueous secretion

Causes

I. Lipid abnormalities
A. Inflammation of the meibomian glands and lid margin
1. Marginal blepharitis, blepharoconjunctivitis, and meibomian gland adenitis cause deficient production of lipids and production of abnormal lipids (Moore, 1999; Moore and Collier, 1990).
a. Bacterial infections: *Staphylococcus* spp. most common
b. Yeast infections: *Candida* spp., *Malassezia* spp.
2. Lipid secretions from damaged glands are released into lid tissues, causing further inflammation.

B. Autoimmune diseases affecting lid margins and lipid secretion

C. Generalized seborrhea in dogs, with altered meibomian gland secretions

II. Mucin abnormalities (Moore and Collier, 1990; Davidson and Kuonen, 2004)
A. Loss of conjunctival goblet cells with chronic inflammation from infectious and immune-mediated diseases

B. Severe ulceration and scarring of the conjunctiva with goblet cell loss
C. Vitamin A deficiency, with squamous metaplasia and keratinization of the conjunctiva (experimental)

Pathophysiology

I. Lipid deficiency and lipid abnormalities
  A. Altered distribution of tear film over the eye
  B. Increased evaporation and premature dispersion of aqueous tears
  C. Increased friction between ocular surface and abnormal lid margins during blinking
  D. Corneal and conjunctival toxicity from abnormal lipids and inflammatory products
II. Mucin deficiency
  A. Premature breakup of tear film from altered distribution and binding of tears over cornea
    1. Tear film breakup time is decreased.
    2. Dry spots appear on cornea from a relative deficiency of aqueous tears despite normal production and volume.
  B. Progressively altered conjunctival architecture and differentiation of goblet cells leading to progressive mucin deficiency

Clinical Signs

I. Many similarities regardless of type of abnormality
  A. Keratitis and keratoconjunctivitis with superficial vascularization and scarring of cornea
  B. STT normal unless chronicity has affected lacrimal glands
II. Lipid abnormalities
  A. Hyperemic swollen lid margins with prominent openings of meibomian glands; openings plugged
  B. Lipid granulomas, multiple chalazia
  C. Dried exudates on lids
  D. Perimarginal lid ulceration and fistulation
  E. Corneal epithelial irregularities, ± fluorescein retention
III. Mucin abnormalities
  A. Relative absence of discharge
  B. Corneal ulceration: multifocal erosions or deep ulcers, variable severity and duration
  C. Multifocal corneal desiccation and opacities: lackluster appearance to cornea
  D. Conjunctival thickening

Diagnosis

I. Lipid disorders
  A. Eyelid examination for typical changes
  B. Evaluation of meibomian gland secretions
    1. Culture and sensitivity
    2. Cytology: bacteria, inflammatory cells
    3. Secretions thick, opaque, inspissated, cream-cheese consistency
II. Mucin deficiency
  A. Tear film breakup time
    1. Instill one to two drops of fluorescein in conjunctival sac, blink lids once, then hold lids open to prevent blinking.
    2. Record time from last blink to appearance of first dry (dark) spot in fluorescein film.
    3. Normal is 19 ± 5 seconds.
    4. Irregularity of corneal surface, tractability of the animal, and other factors disrupting the tear film affect reliability.
  B. Conjunctival biopsy to confirm deficiency or absence of goblet cells
    1. Under topical local anesthesia, obtain sample from ventral conjunctival fornix anterior to base of the third eyelid.
    2. Normal ratio of goblet cells to epithelial cells in this area is 0.3.

Differential Diagnosis

I. Keratoconjunctivitis sicca
II. Keratoconjunctivitis: infectious, allergic, traumatic

Treatment

I. Lipid abnormalities
  A. Ocular lubricating ointments: reduce friction between lids and cornea, decrease evaporation of tears
  B. Topical antibiotic/steroid therapy for infection and inflammation (in absence of corneal ulceration), ± systemic antibiotics
  C. Possible surgical curettage of chalazia
  D. Warm compresses and lid washing with soaps formulated for the eye to remove crusts, exudates, and bacteria
  E. Cyclosporine ointment
    1. Petrolatum and corn oil base: lubricates and decreases evaporation of aqueous tears
    2. Stimulates tearing: improves health of ocular surfaces
    3. Antiinflammatory effects
II. Mucin deficiency
  A. Topical artificial tear solutions with mucinous and/or viscoelastic properties
  B. Control of infection and inflammation with topical antibiotic and corticosteroid drugs
  C. Cyclosporine ointment as for lipid abnormalities

Monitoring of Animal

I. Long-term therapy and monitoring are required if permanent loss or impairment of tear film components exists.
II. Reexamine SID to QOD in acute or severe cases (especially with corneal ulceration) until stable.
III. Educate owner regarding importance of treatment compliance in chronic cases.

INFLAMMATORY DISORDERS

Dacryocystitis

Definition and Causes

I. Dacryocystitis is inflammation of the lacrimal sac and nasolacrimal duct.

II. Causes are varied.
  A. Infection
    1. Primary: bacteria (most common), fungi (rare)
    2. Secondary: dental (tooth root abscesses) or nasal diseases
  B. Foreign bodies lodged in nasolacrimal duct: seeds, grass awns, other plant material
  C. Trauma
  D. Stasis of tear flow through duct: stenosis, adhesions, cysts

Pathophysiology

I. Abnormalities of the punctae, canaliculi, and/or nasolacrimal duct (congenital or acquired) impair tear flow and allow microbial proliferation.
II. Foreign bodies provide nidus for infection and inflammation.

Clinical Signs

I. Unilateral or bilateral involvement
II. Epiphora ± medial canthal dermatitis
III. Conjunctivitis: usually mild, ± recurrent
IV. Mucoid to mucopurulent discharge
  A. Discharge accumulates in the medial canthus.
  B. Discharge is expressed from punctae with pressure at medial canthus or after nasolacrimal irrigation.
V. Local pain: especially with medial canthal abscess (rare) or cyst formation

Diagnosis

I. Typical clinical signs
II. Expression or flushing of exudates and/or foreign bodies from punctae
III. Dacryocystorhinography using a positive contrast agent
  A. Demonstrates sites of stenosis and cyst formation; may outline foreign bodies
  B. Recommended in recurrent cases before surgical intervention
IV. Computerized tomography (CT) and magnetic resonance imaging (MRI) (Giuliano et al., 2006)

Differential Diagnosis

I. Keratoconjunctivitis sicca
II. Conjunctivitis
III. Epiphora from functional impairment of drainage, medial canthal excoriation
IV. Dental disease with fistula formation near medial canthus

Treatment

I. Flushing of nasolacrimal duct to remove foreign bodies and improve patency
  A. Sterile saline or water flushed through nasolacrimal cannula
    1. Dogs: 23-gauge lacrimal cannula
    2. Cats: 27-gauge lacrimal or air injection cannula
  B. Occlude opposite punctum while flushing
  C. Retrograde flushing from nose also possible
  D. May require anesthesia
    1. Especially with difficult obstructions requiring repeated flushing to dislodge foreign material
    2. When animal is in pain
  E. Bacterial culture and sensitivity testing on effluent flushed from duct
II. Broad-spectrum topical antibiotic or antibiotic/steroid therapy
  A. Based on results of culture and sensitivity testing
  B. Solutions preferred for optimal access to duct system
  C. Frequent applications (every 4 to 6 hours) for several weeks
III. Systemic antibiotics for nasolacrimal and dental abscesses, severe dermatitis, fistulous tracts
IV. Systemic antifungal therapy when mycotic disease confirmed
V. Indwelling nasolacrimal catheterization (Slatter, 2006b) in recurrent or persistent cases
  A. Polypropylene or nylon sutures (2-0 or 3-0)
  B. Polyethylene, polyvinyl, or silastic tubing
  C. Sutured to skin below medial canthus and near the nares
  D. Left in place for 2 to 3 weeks
VI. Dacryocystotomy to remove foreign bodies or explore lacrimal sac swelling (Grahn, 1999; Slatter, 2006b)
  A. Skin incision over the lacrimal bone and lacrimal sac adjacent to medial canthus and parallel to the lower lid
  B. Incision into the lacrimal sac parallel to the lumen for removal of foreign material and inspissated pus
  C. Silastic tubing cannulation of duct
VII. Dacryocystorhinostomy (Giuliano et al., 2006)
  A. Skin incision (3.5 cm) is made from level of infraorbital foramen dorsocaudally over the lacrimal and maxillary bones toward the medial canthus.
  B. Maxillary bone is exposed with sharp dissection and opened with an air drill.
  C. Nasolacrimal sac is sharply incised and evacuated.
  D. Silicone stent is passed from superior lacrimal punctum to lacrimal sac and into nasal cavity.
  E. Soft tissue and skin are closed over the opened nasolacrimal sac.
VIII. Adjunctive procedures: dental extractions for tooth root abscesses

Monitoring of Animal

I. Repeat nasolacrimal flushing and cytology every 1 to 2 weeks until cytology and/or culture are normal.
II. Continue antimicrobial therapy for 1 to 2 weeks past resolution of clinical signs and demonstration of normal nasolacrimal flushing.
III. Warn owners that recurrences (early or late) are common.

NEOPLASIA

Definition and Causes

I. New and uncontrolled growth of abnormal and/or undifferentiated cells derived from the lacrimal glands

(primary), or by extension or metastasis from other sites (secondary).

II. Primary tumors are as follows:
  A. Lacrimal gland: adenoma, adenocarcinomas (Rebuhn and Edwards, 1977; Wilcock and Peiffer, 1988)
  B. Third eyelid gland (see Chapter 96)

III. Primary neoplasia of the nasolacrimal duct has not been documented, but metastasis from distant sites and by local extension from adjacent sites may compress or obliterate the duct.

Pathophysiology

I. May decrease aqueous tear production
II. May displace globe and/or third eyelid
III. May extend into other orbital structures
IV. Possible local extension of neoplasia from the orbit, nasal cavity, or paranasal sinuses, with compression or invasion of the nasolacrimal duct
V. Increasing incidence with age

Clinical Signs

I. Space-occupying, nonpainful mass of orbit, base of third eyelid
  A. Protrusion of third eyelid and enophthalmos when third eyelid gland involved
  B. Superotemporal swelling when orbital lacrimal gland involved
  C. Exophthalmos with retrobulbar tumors

II. Epiphora from compression of lacrimal lake or nasolacrimal duct by the tumor or globe (exophthalmos)
III. KCS in rare cases
IV. Possible ipsilateral involvement of the nasal cavity
  A. Mucoid, mucopurulent, and/or serosanguinous ocular and nasal discharge
  B. Ipsilateral obstruction of airflow through nasal passage

Diagnosis

I. Suspicious ocular and orbital findings
  A. Evidence of an orbital mass (see Chapter 103)
  B. Firm mass at base of third eyelid
  C. Possible palpable orbital rim abnormalities
  D. Possible enlargement of regional lymph nodes or swelling in oral cavity (especially behind last upper molar)

II. Radiography
  A. Plain radiographs of skull usually normal except with extension to bone
  B. Thoracic radiographs to check for metastasis
  C. Ultrasonography
    1. Depiction of mass: location, size, echogenicity
    2. Guidance of percutaneous biopsy or fine-needle aspiration
  D. CT and MRI: provide best resolution and delineation of mass
  E. Contrast studies for involvement of nasolacrimal duct

III. Biopsy and fine-needle aspirates for histopathology and cytology
IV. Orbital exploration and biopsy when previous tests nondiagnostic

Differential Diagnosis

I. Other causes of orbital neoplasia
II. Granulomatous inflammation of orbit from foreign body, mycotic infection, pseudotumor
  A. Chorioretinal granulomas may be found with systemic mycoses.
  B. Radiolucent foreign bodies may be identified with ultrasonography, CT, or MRI.
  C. Fistulous tracts may be present with foreign bodies.

III. Zygomatic adenitis or mucocele (especially dog and ferret)
IV. Orbital cellulitis
V. Orbital lacrimal cysts

Treatment

I. Early excision (treatment of choice)
  A. Early removal of primary third eyelid adenocarcinomas may be curative.
  B. Neoplasia is one of the rare indications for complete excision of the third eyelid.
  C. Orbital exenteration is indicated when tumor extends beyond the third eyelid or when the orbital lacrimal gland is involved.

II. Adjunctive therapy
  A. Radiation for orbital lacrimal adenocarcinomas
  B. Systemic antibiotics for secondary infections
  C. Systemic antiinflammatory therapy
    1. Palliative therapy to reduce inflammation and swelling around the tumor
    2. Piroxicam 0.3 mg/kg PO SID to QOD in dogs
  D. Topical cyclosporine therapy
    1. KCS is present or anticipated from removal of the lacrimal gland.
    2. Lacrimal gland is in the path of the radiation beam or the target radiation therapy.

Monitoring of Animal

I. Neoplasia of the third eyelid gland (see Chapter 96)
II. Primary lacrimal gland adenocarcinomas
  A. Prognosis is usually poor, because tumor has often extended into the orbit.
  B. Local recurrence is common within 3 to 6 months.

III. Neoplasia involving the nasolacrimal duct
  A. Long-term prognosis is usually poor, because tumors are usually carcinomas or adenocarcinomas extending from the nasal cavity or paranasal sinuses.
  B. Recurrence is common within 6 to 18 months after radiation therapy.

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CHAPTER 98

Diseases of the Cornea and Sclera

Ruth Marrion

CONGENITAL DISORDERS

See Table 98-1.

ACQUIRED NONINFLAMMATORY OPACITIES

See Tables 98-2 and 98-3.

INFECTIOUS DISEASES

Feline Herpesvirus Keratitis

Definition and Causes

I. Superficial corneal ulcers caused by infection with feline herpesvirus 1 (FHV)
II. May also produce stromal keratitis without ulceration

Pathophysiology

I. FHV infects cells of corneal and conjunctival epithelium (Nasisse et al., 1989a).
II. Necrosis of corneal epithelium results in superficial corneal ulcers.
   A. Geographic (maplike) corneal ulcers: large, superficial, irregularly shaped areas of ulceration most common
   B. Branching dendritic ulcers: less common
   C. Possibly recurrent from latent infections (Gaskell and Povey, 1979; Gaskell et al., 1985)

Clinical Signs

I. Superficial corneal ulceration in either a geographic or dendritic pattern is a typical finding.
II. Geographic, corneal ulceration appears clinically identical to a canine indolent ulcer, but basement membrane disease does not cause it.
III. Ulcers may be associated with a painful conjunctivitis, producing conjunctival hyperemia and mild chemosis.
IV. Ulcers may become secondarily infected with bacteria and appear identical to other infected ulcers.

Diagnosis

I. Nontraumatic corneal ulcers in a cat are often presumed to be caused by FHV.
II. Polymerase chain reaction (PCR) and virus isolation are the best tests to confirm the presence of FHV.
   A. These tests have a high incidence of false positives and negatives (Maggs et al., 1999).
   B. They are also expensive and not readily available.
III. Immunofluorescent antibody tests are less sensitive than PCR tests.

Differential Diagnosis

I. Ulcers from irritants such as distichia: uncommon in cats
II. Trauma from cat scratches, other exogenous sources
III. Lagophthalmos, medial canthal trichiasis, and entropion in brachycephalic breeds
IV. Dry eye: may be associated with FHV infection

Treatment

I. Antiviral therapy
   A. Antiviral drugs are virustatic and not virucidal; therefore they must be used frequently.
   B. These medications may be toxic to host cells if used long term.
   C. Available drugs cannot eradicate latent infections; therefore owners must be warned of possible recurrences.
II. Specific antiviral medications
   A. Idoxuridine
      1. Not commercially available; may be compounded
      2. Used topically four to six times daily for 1 week past resolution of clinical signs
   B. Trifluridine
      1. Most effective virucidal agent in vitro (Nasisse et al., 1989b)
      2. Commercially available but expensive
      3. May burn or sting upon administration
      4. Used topically four to six times daily for 1 week past resolution of clinical signs
   C. Acyclovir
      1. Dosage: 200 mg PO BID to QID for 2 weeks
      2. *Caution:* not labeled for use in cats; potentially toxic
         a. Check complete blood count and chemistry profile after 1 week of use.
         b. A low incidence of blood dyscrasias and renal problems is associated with this medication.

TABLE 98-1

Congenital Disorders of the Cornea and Sclera

DISORDER	CAUSES	CLINICAL APPEARANCE	DIAGNOSIS	TREATMENT AND PROGNOSIS
Neonatal superficial corneal opacities	Not known; may arise from incomplete development of the corneal epithelium at the time of lid opening or subsequent to metabolic deficiencies of the neonatal cornea	Faint multifocal gray opacities within the superficial cornea, usually in the interpalpebral region	Based on clinical appearance in puppies <4 mo old, the absence of history or signs of prior disease, the absence of pain, and lack of fluorescein uptake	No treatment is indicated; most lesions disappear by 3-6 mo of age
Deep stromal and endothelial opacities	Persistent pupillary membranes (PPMs; see Chapter 99) attach to corneal endothelium, resulting in a gray or pigmented dense plaque; inherited in many dog breeds (e.g., basenji, Australian shepherd dog, Welsh corgi, Yorkshire terrier)	PPMs result in a white, gray, or pigmented opacity usually not involving >25% of the corneal surface	Opacities associated with PPMs often exhibit a strand of tissue originating from the iris collarette	No effective treatment is available Corneal opacities associated with PPMs may appear to get smaller as the eye/cornea grows
	Anterior segment dysgenesis (see Chapter 99) results in disordered development of the mesenchyme destined to form the cornea and anterior uvea; inherited in Doberman pinschers, Saint Bernards (Bergsjo et al., 1984)	Anterior segment dysgenesis may result in a cornea that is focally or diffusely opaque Other abnormalities, including blindness, microphthalmia, glaucoma, and lenticular dysgenesis, may be present	Signs of anterior segment dysgenesis in a young dog	Cases of anterior segment dysgenesis with glaucoma may need enucleation
Dermoid	Breed predisposition in the dachshund, dalmation, Doberman pinscher, German shepherd dog, Saint Bernard; sporadic in other breeds and in cats	An area of the cornea and/or sclera containing tissue covered by keratinized skin, with or without hair	Clinical appearance in a young dog or cat	Superficial keratectomy generally results in resolution; some scarring may remain

D. Famciclovir
   1. Dosage: one fourth of a 125 mg tablet PO BID for 8 days or more
   2. Most information anecdotal (Sapienza, 2002)

E. L-Lysine
   1. Slows replication of the virus by virtue of its chemical similarity to arginine (an amino acid found at high concentration in the virus)
   2. Dosage: 250 to 500 mg PO SID to BID long-term

Bacterial and Fungal Keratitis

Definition

I. Bacterial keratitis: an ulcer that is primarily or secondarily infected with bacteria

II. Fungal keratitis: an ulcer that becomes secondarily infected with fungi (Marlar et al., 1994; Glaze and Gelatt, 1999)

Causes

I. Common bacterial pathogens: *Staphylococcus* spp., *Streptococcus* spp., *Corynebacterium* spp., *Enterococcus* spp., *Pasteurella multocida* (Massa et al., 1999), *Pseudomonas aeruginosa* (Tolar et al., 2006)

II. Fungal pathogens: *Aspergillus* spp. most common (Marlar et al., 1994)

Pathophysiology

I. Usually a primary event results in loss of corneal epithelium (e.g., trauma, exposure, FHV infection).

II. Bacteria or fungi colonize the corneal stroma.

TABLE 98-2

Acquired Noninflammatory Opacities

LESION	CAUSES	CLINICAL SIGNS AND DIAGNOSIS	TREATMENT
Lipid keratopathy	Accumulation of lipid in anterior corneal stroma Inherited (see Table 98-3) Postinflammatory Associated with metabolic diseases causing hypercholesterolemia	White, shiny crystalline infiltrate in superficial corneal stroma Often present as a dense perilimbal infiltrate (arcus lipoides cornea) when associated with hypercholesterolemia and hypothyroidism	None for inherited lipid infiltrates Identify and treat any underlying metabolic disease Lower blood cholesterol with a low-fat diet
Calcium infiltration	Calcium accumulation in the superficial corneal stroma, especially in interpalpebral space May be secondary to chronic keratitis or systemic diseases (e.g., chronic renal disease, hyperadrenocorticism), or following previous corneal trauma	Dense white corneal stromal deposits, often in the axial cornea Disruption of the overlying corneal epithelium may cause chronic and/or recurrent ulceration.	Identify and treat underlying cause, if present Topical 1% NaEDTA solution in artificial tears BID-TID or lubricating ointments may be helpful Superficial keratectomy may be necessary if medical treatment does not alleviate discomfort
Endothelial dystrophies and degenerations	Hereditary endothelial dystrophy: Boston terrier, Chihuahua (Martin and Dice, 1982), Manx cat (Bistner et al., 1976), and domestic shorthair cat (Crispin, 1982) Senile endothelial degeneration Feline bullous keratopathy (Glover et al., 1994)	Endothelial dystrophy: progressive corneal edema that may lead to blindness, corneal bullae and ulceration; occurs in middle-aged to older dogs and as early as 4 mo (Manx) or 3-4 wk (domestic shorthair) in cats Senile endothelial degeneration: appears similar to familial canine endothelial dystrophy Bullous keratopathy: severe corneal edema that may result in bulla formation and subsequent ulceration	Topical hypertonic ointment or solution (5% sodium chloride or 40% glucose) applied 4-6 times daily may reduce bullae formation and subsequent ulceration. Conjunctival flap or thermokeratoplasty may be indicated for cases with recurrent ulceration. Penetrating keratoplasty may be performed for cases of bullous keratopathy or marked opacity.

EDTA, Ethylenediamine tetraacetic acid.

III. Collagenases from bacteria and host leukocytes digest the corneal stroma, resulting in progressively more loss of stroma.
IV. Presence of bacteria stimulates elaboration of inflammatory mediators, resulting in signs of secondary uveitis.
V. Fungal infections are rare and are most likely to occur after use of topical corticosteroid medications, cyclosporine, or antibiotics (Marlar et al., 1994).

Clinical Signs

I. Positive fluorescein stain retention
II. Marked pain with severe epiphora and blepharospasm
III. White stromal infiltrates in area of ulcer from presence of bacteria, leukocytes
IV. Stromal abcessation if epithelialization occurs over the infected area
V. Evidence of secondary uveitis, especially hypopyon
VI. Corneal edema
VII. Peripheral corneal vascularization ("brush border")
VIII. Corneal plaque, ± satellite lesions in cases of fungal keratitis

Diagnosis

I. Cytological examination of corneal scraping
   A. Gram and/or Diff-Quik stain
   B. Bacteria and numerous neutrophils in bacterial keratitis
   C. Fungal elements ± leukocytes in fungal keratitis
II. Aerobic bacterial and fungal culture and sensitivity testing
   A. False-negative culture or cytology occurs in some cases of infected ulcers.
   B. Consider initiating treatment based on finding the previously listed clinical signs.

TABLE 98-3

Canine Corneal Dystrophies

BREED	AGE	LOCATION	APPEARANCE	OTHER DATA
Shetland sheepdog	>4 mo	Epithelial-subepithelial	Multiple small focal spots or rings	Recurrent erosions common; may be associated with distichia, tear film deficiency
Cavalier King Charles spaniel	Any age	Central anterior stroma	Oval gray opacity with "ground glass" appearance	Composed of lipids; no associated systemic disease
Beagle	>3 yr	Central anterior stroma	Solid oval or doughnut-shaped gray opacity	Composed of various lipids; no associated systemic disease
Siberian husky, Samoyed	>6 mo	Anterior, mid, and deep stroma	Gray/tan hazy oval opacity in anterior stroma, or refractile crystals in deep stroma; often clearer centrally	Recessive inheritance; composed of lipids
Airedale terrier	> 6 mo	Starts centrally, progresses toward limbus	Dense milky infiltrate, usually clear at the limbus	Can cause blindness; composed of lipids; no associated systemic disease
American cocker spaniel	>1 yr	Endothelium, Descemet's membrane	Multifocal gray spots, patches, or streaks	May be dominant genetic trait; no associated corneal edema
Boston terrier, Chihuahua	> 5 yr	Starts temporally, progresses nasally	Gray reticulated opacity typical of corneal edema	Severe edema may result in corneal bullae and/or recurrent erosions

From Kirschner SE: Diseases of the cornea and sclera. p. 1007. In Morgan RV (ed): Handbook of Small Animal Practice. 3rd Ed. WB Saunders, Philadelphia, 1997; with permission.

Differential Diagnosis

I. Traumatic, aseptic ulcers
II. Persistent erosions
III. Viral-induced ulcers

Treatment

I. Hospitalization is recommended for the following reasons:
   A. Facilitates frequent application of medications
   B. Allows frequent reevaluation of cornea
   C. Allows rapid surgical intervention as needed
II. Apply topical antibiotic solutions every 2 to 4 hours.
   A. Variety of products are available.
   B. Most isolates are sensitive to ciprofloxacin or a combination of a cephalosporin and tobramycin (Tolar et al., 2006), but topical cephalosporin is not available commercially.
III. Administer topical autologous serum every 2 to 4 hours.
   A. Serum contains numerous protease inhibitors, including α_2-macroglobulin, the universal protease inhibitor (Berman et al., 1975).
   B. Acetylcysteine is an alternative but is expensive and may not be readily available.
IV. Topical atropine is given to effect (every 2 to 4 hours).
   A. Solutions may cause profuse salivation in cats, so consider use of an ointment.
   B. Solutions are preferred for deep stromal lesions.
V. Systemic nonsteroidal antiinflammatory agents are used in dogs for treatment of secondary uveitis.
   A. Aspirin 10 mg/kg PO BID
   B. Carprofen 2 mg/kg PO BID
VI. Systemic antimicrobials are indicated, especially if a penetrating wound is noted or suspected.
   A. Presence of hypopyon does not confirm bacterial endophthalmitis because the hypopyon is generally sterile.
   B. Consider use of amoxicillin 22 mg/kg PO BID.
VII. Subconjunctival antibiotics may be helpful.
   A. Amikacin 25 to 125 mg
   B. Ampicillin 50 to 100 mg
   C. Cefazolin 100 mg
   D. Gentamicin 20 to 40 mg
VIII. Antifungal agents are indicated for fungal keratitis.
   A. Natamycin is the only drug currently approved for ocular use and is effective but expensive.
   B. Nystatin is fungistatic, not fungicidal, and is made by mixing 50,000 U soluble powder in 1 mL saline.
   C. Intravenous fluconazole or miconazole may be used topically.
   D. Itraconazole 1% in dimethyl sulfoxide has been used in horses (Ball et al., 1997).
   E. Miconazole vaginal cream and silver sulfadiazine cream have also been used in horses.
IX. Surgery (placement of a conjunctival flap, corneoscleral transposition, or corneal lamellar graft) is indicated in the following circumstances:
   A. Descemetoceles
   B. Deep stromal ulcers
   C. Rapidly progressive ulcers

Monitoring of Animal

I. Monitor for improvement in clinical signs.
   A. Depth of ulcer
   B. Secondary uveitis: degree of miosis, aqueous flare, hypopyon
II. Consider changing antibiotics and/or increasing frequency of application if signs worsen.
III. Consider surgical intervention if signs worsen.

INFLAMMATORY DISORDERS

Corneal Ulceration

Definition

I. Superficial erosion is a loss of the corneal epithelium only.
II. Stromal ulceration involves loss of both the epithelium and some portion of stroma.
III. With a descemetocele, stroma is lost down to Descemet's membrane.
IV. Perforation is a wound in Descemet's membrane, with leakage of aqueous humor and/or iris prolapse.

Causes

I. Trauma
   A. External sources: cat scratch, foreign body, others
   B. Eyelid disease: distichiasis, ectopic cilia, entropion
II. Tear film disease
   A. Keratoconjunctivitis sicca (KCS)
   B. Goblet cell deficiency
   C. Lipid tear film abnormality from meibomian gland pathology (Moore, 1999)
III. Lagophthalmos
   A. Macropalpebral fissure
   B. Exophthalmos: pathologic or conformational
   C. Buphthalmos
   D. Decreased blink frequency
      1. It may occur from corneal denervation after trigeminal nerve injury.
      2. Brachycephalic dogs have relatively few corneal nerves and often an incomplete blink.
   E. Palpebral nerve palsy
IV. Infections
   A. Bacterial (Tolar et al., 2006; see previous discussion)
   B. Fungal: aspergillosis (Marlar et al., 1994; see previous discussion)
   C. Viral: FHV (see previous discussion)
      1. Infection may be primary or may be a recurrence of latent infection.
      2. Infection may be more common in immunosuppressed or stressed cats.
V. Thermal or chemical burns
   A. Detergent agents
   B. Acids
   C. Alkaline agents
VI. Immune-mediated disease: marginal keratitis (Parshall and Kellum, 1987)
VII. Secondary to other corneal disease
   A. Calcium infiltrates
   B. Edema (especially bullous keratopathy)
   C. Corneal epithelial basement membrane disorder

Pathophysiology

I. One of the causative events results in damage to the corneal epithelium, with focal or widespread loss.
II. In some cases, corneal stroma is lost as well.
III. Epithelial cell mitosis and migration occur, covering the wound in several days.
IV. Continued presence of an inciting cause (e.g., trauma, lagophthalmos) or a secondary factor (e.g., basement membrane disease, secondary bacterial infection, FHV infection) may prevent healing.

Clinical Signs

I. Superficial erosions
   A. Blepharospasm
   B. Epiphora
   C. Congestion of conjunctival vessels
   D. Miosis in some cases
II. Stromal ulcers
   A. All of the signs of superficial erosions
   B. Visible defect in the stroma
   C. Mucopurulent discharge
   D. Aqueous flare, with or without hypopyon
   E. Perilimbal vascularization (brush border)
III. Descemetoceles
   A. All the signs of stromal ulcers are usually present.
   B. Exposed Descemet's membrane is smooth and clear, not edematous like stroma, does not retain fluorescein stain.
IV. Perforated corneal ulcers
   A. All the signs of descemetoceles, plus intense blepharospasm
   B. Fibrin or pigmented mass (iris prolapse) in the ulcer bed
   C. Possibly fluid leaking from the wound
V. Herpesvirus keratitis
   A. Young kittens
      1. Signs of upper respiratory infection
      2. Ocular discharge associated with corneal ulceration
   B. Adult cats
      1. Signs of upper respiratory infection are rarely seen.
      2. Very small epithelial linear or dendritic lesions, or erosions and ulcers of any size and shape may be found.
      3. Secondary KCS may be present.

Diagnosis

I. Stain the cornea with fluorescein to determine the presence of an ulcer (Descemet's membrane will not stain).
II. Test palpebral nerve function and ability to blink completely.
III. Perform a Schirmer tear test (STT) unless obvious epiphora is present.

IV. Carefully examine the adnexa to determine whether the ulcer is from an endogenous or exogenous irritant.

Differential Diagnosis

I. Anterior uveitis may also cause pain, epiphora, miosis, and congestion of episcleral vessels; however, a fluorescein dye test is negative.
II. Glaucoma may cause pain, epiphora, and episcleral vessel congestion; however, the pupil is usually dilated, unresponsive.
  A. Lack of normal menace reflex occurs.
  B. The fluorescein dye test is negative.
III. Entropion, distichiasis, and ectopic cilia may cause pain, epiphora, and conjunctival hyperemia, with or without a concurrent corneal erosion or ulcer.
IV. KCS or conjunctivitis may cause pain and conjunctival hyperemia.
  A. Epiphora is not present in cases of KCS, and the STT is abnormally low.
  B. Fluorescein dye test is negative.

Treatment

I. Topical antibiotics
  A. Apply TID to QID for superficial erosions, 4 to 12 times a day for stromal ulcers.
  B. Stromal ulcers are treated with antibiotics that are bactericidal and broad spectrum.
  C. Neomycin is used with caution in cats because of the potential for anaphylactic reactions (Plunkett, 2000).
  D. Fluoroquinolones and tobramycin should *not* be used prophylactically but are reserved for rapidly progressive ulcers, as discussed previously.
II. Topical atropine
  A. Give to effect.
  B. Usually SID to QID is sufficient, but some cases require a higher frequency.
  C. Also indicated for anterior uveal inflammation as manifested by miosis, aqueous flare, and hypopyon.
III. Systemic nonsteroidal antiinflammatory agents in dogs
  A. Indicated if uveitis is present
  B. Aspirin 10 mg/kg PO BID
  C. Carprofen 2 mg/kg PO BID
IV. Systemic antibiotic medications
  A. Indicated for corneal perforations
  B. Amoxicillin 22 mg/kg PO BID
V. Contact lenses
  A. Soft contact lenses are indicated for superficial nonhealing erosions and are contraindicated in infected corneal ulcers.
  B. Collagen contact lenses can be rehydrated in topical antibiotic solution and used in infected corneal ulcers (last 24 to 72 hours).
VI. Surgical therapy (Table 98-4)
  A. Third eyelid flaps
    1. Useful to protect ulcers secondary to lagophthalmos, decreased blink frequency, poor lid conformation, and KCS
    2. Contraindicated in rapidly progressive ulcers because they prevent monitoring of the condition
  B. Conjunctival flaps
    1. They are indicated for descemetoceles or for deep stromal ulcers.
    2. They act as a graft with an intact blood supply rather than a bandaging effect.
    3. The graft is cut at the base 6 to 8 weeks after surgery to interrupt blood supply and reduce scarring.
  C. Primary closure
    1. It is used for descemetoceles and for ruptured corneal ulcers <2 to 3 mm in diameter.
    2. If performed in larger wounds, it may distort the cornea excessively.
  D. Corneoscleral transposition and lamellar grafts (Brightman et al., 1989)
    1. Used for closure of descemetoceles and perforated corneal ulcers too large to close primarily
    2. Require adjacent healthy cornea to transpose
  E. Swine intestinal submucosa (SIS) (Bussieres et al., 2004)
    1. Has been used for perforated ulcers, deep stromal ulcers, and corneal abscesses
    2. Requires adjacent healthy cornea to which to suture
VII. Therapy of FHV (see previous discussion)
VIII. Therapy of bacterial fungal ulcers (see previous discussion)
IX. Therapy of persistent erosions (see following section)

Monitoring of Animal

I. Recheck visits are important.
  A. Superficial erosions: in 5 to 7 days
  B. Stromal ulcers: every 2 to 3 days until reepithelialized or until no purulent discharge is seen
II. Watch for signs of infection (change from epiphora to purulent discharge, increased depth of the lesion).
  A. Culture the wound.
  B. Increase antibiotic frequency and/or change antibiotics.
  C. Consider surgical intervention.
III. If not healed in 1 to 2 weeks, then a thorough ocular examination is repeated to rule out any previously undiagnosed cause.
IV. Postoperative rechecks are scheduled every 2 to 3 days for a week, then every 1 to 2 weeks until the cornea is healed.
V. Herpesvirus keratitis is controllable but not curable; periodic flare-ups are common.

Persistent Corneal Erosions

Definition

I. A corneal ulcer that does not heal within 2 weeks despite appropriate treatment
II. Also known as *nonhealing ulcer, indolent ulcer, boxer ulcer,* and *spontaneous chronic corneal epithelial defect* (SCCED)

TABLE 98-4

Surgical Therapies for Corneal Ulcers

SURGERY	INDICATIONS	CONTRAINDICATIONS	TECHNIQUE	REFERENCE
Third eyelid flap	Ulcers associated with exposure keratitis or KCS	Rapidly progressive ulcers	Use mattress pattern to suture third eyelid to superior bulbar conjunctiva or to upper lid.	Slatter (1990)
Conjunctival flap	Descemetoceles, deep stromal ulcers, rapidly progressive ulcers	Corneal perforations in which the anterior chamber is difficult to maintain (must use additional means of corneal support)	Use tenotomy scissors to dissect thin flap (pedicle, bridge, 180°, 360°) of conjunctiva from the limbus, based in the fornix. Suture to ulcer wall (pedicle flap), to normal cornea (bridge or 180° flap), or to conjunctiva (360° flap) using 6-0 to 8-0 suture. Reform anterior chamber if necessary.	Hakanson and Merideth (1987)
Corneoscleral transposition, corneal lamellar graft	Descemetoceles, deep stromal ulcers, perforated ulcers	No normal cornea exists	Make partial-thickness corneal flap, free lamellar graft, or corneal flap attached to conjunctival pedicle flap, using a scalpel blade (cornea) and tenotomy scissors (conjunctiva). Slide the prepared graft over the defect and suture in place with 7-0 or 8-0 absorbable suture, thus sealing the wound. Reform the anterior chamber if necessary.	Slatter (1990), Brightman et al. (1989)
SIS graft	Descemetoceles, deep stromal ulcers, perforated ulcers	No normal cornea to which to suture SIS	Use punch biopsy to prepare graft 2.0 mm wider than recipient bed. Rehydrate graft in sterile saline and suture graft onto defect using 8-0 to 10-0 absorbable suture.	Featherstone et al. (2001), Bussieres et al. (2004)
Primary closure	Small decemetoceles and perforations (<3 mm)	Large defects	Close with simple interrupted or mattress sutures of 7-0 to 8-0 absorbable material. Reform anterior chamber if necessary.	Slatter (1990)

KCS, Keratoconjunctivitis sicca; *SIS,* swine intestinal submucosa.

Causes and Pathophysiology

I. Ulcer does not heal because of inadequate adhesion between the corneal epithelium and the stroma (Kirschner et al., 1989).
II. Defects in the epithelial basement membrane are present in some cases.
  A. The basement membrane is thickened and misshapen.
  B. Hemidesmosomes are decreased in number.
  C. An acellular, hyalinized zone may be present in superficial stroma (Bentley, 2005).
III. Endothelial disease is causative in some cases.
  A. Endothelial disease results in stromal edema, and subsequently in epithelial cell and intercellular edema.
  B. Corneal epithelial cells are unable to adhere and migrate normally.

Clinical Signs

I. Occur in middle-aged to older dogs
II. Epiphora, conjunctival hyperemia, variable blepharospasm
III. Superficial erosion with no stromal loss
IV. Pathognomonic: loose epithelium that is easily debrided from the edge of the ulcer
V. Possibly corneal vascularization
VI. Possibly corneal edema
  A. Localized if basement membrane disease is underlying cause
  B. Generalized if endothelial disease is present

Diagnosis

I. Presence of a superficial erosion with loose epithelial margins
II. Exclusion of other causes of corneal erosions

Differential Diagnosis

I. Determine if other causes of corneal ulceration are present, such as trauma, entropion, lagophthalmos, KCS, distichiasis, ectopic cilia.
II. Corneal ulcers caused by FHV appear clinically similar, and indolent erosions from basement membrane disease have not been documented in cats.

Treatment

I. Initial treatment
  A. Debridement is essential.
    1. Under topical anesthesia ± sedation, all loose epithelium is carefully removed with a sterile cotton swab, spatula, or scalpel blade.
    2. This procedure may result in removal of the entire corneal epithelium.
  B. Topical antibiotics are used BID to QID.
  C. Topical atropine is used to effect for blepharospasm and anterior uveitis (miosis, photophobia).
  D. Elizabethan collars are used in all cases.
  E. Many erosions heal within several weeks using this therapeutic regimen.
II. Ancillary therapies
  A. Used if debridement does not result in healing of the ulcer
  B. Superficial punctate keratotomy (Champagne and Munger, 1992)
    1. Debride all loose epithelium as described previously.
    2. Create a series of shallow punctures in the anterior corneal stroma, using a 22- to 25-gauge needle.
    3. Perform the punctures in the ulcerated area and the surrounding normal cornea.
    4. Nearly 90% of persistent erosions heal within 2 weeks of this procedure.
  C. Grid keratotomy (Stanley et al., 1998)
    1. Debride all loose epithelium.
    2. Create a crosshatch pattern in the anterior corneal stroma, using a 22- to 25-gauge needle.
    3. Perform the keratotomy starting in normal cornea, then extending into the ulcerated area and back into normal cornea.
    4. More than 80% of persistent erosions heal within 2 weeks of this procedure.
  D. Superficial stromal keratectomy (Stanley et al., 1998)
  E. Soft contact lenses
    1. They may be applied after debridement, keratotomy, or keratectomy.
    2. Lenses are left in place for 2 to 6 weeks.
  F. Third eyelid flap
    1. Provides a bandage over the cornea
    2. May be placed after debridement, keratotomy, or superficial keratectomy
  G. Hypertonic ophthalmic solutions and ointments
    1. Dose: 5% sodium chloride (NaCl) or 40% glucose SID to TID
    2. Indicated if edema is present
  H. Collagen shields
    1. Provide short-term protection (3 days)
    2. Questionable benefit for indolent ulcers
  I. Chondroitin sulfate and antibiotic solutions (Ledbetter et al., 2006)
    1. Chondroitin sulfate 100 mg/mL and tobramycin 3 mg/mL TID to QID
    2. Chondroitin sulfate 100 mg/mL and ciprofloxacin 3 mg/mL TID to QID
    3. Chondroitin sulfate solutions: possibly beneficial after debridement
  J. Thermokeratoplasty for refracting ulcers in edematous corneas

Monitoring of Animal

I. Recheck 7 to 14 days or sooner if additional signs occur.
II. If not healed in 2 weeks, consider an additional therapy as outlined previously.
III. Many erosions associated with basement membrane disorders heal within 2 to 4 weeks with debridement, application of an Elizabethan collar, and contact lens placement.
IV. Cases with corneal edema or extensive granulation tissue are more refractory.
  A. Ancillary therapy may be needed.
  B. Some cases take ≥10 weeks to heal.

Pannus

Definition

I. Pannus is infiltration of the cornea with lymphocytes, plasma cells, neutrophils, melanocytes, and granulation tissue.
II. It is also known as *chronic superficial keratitis* or *Uberreiter's syndrome*.
III. Atypical pannus, or plasmoma, is a variation of pannus involving the third eyelid (see Plasmacytic Conjunctivitis in Chapter 96).

Causes and Pathophysiology

I. Thought to be immune-mediated
II. Breed predisposition
  A. German shepherd dog (primarily)
  B. Other herding dogs: Belgian Tervuren, border collie, Australian shepherd dog
  C. Golden retriever, greyhound, rottweiler
III. Exacerbated by ultraviolet radiation and pollution (Chavkin et al., 1994)

Clinical Signs

I. A red to grey, irregular infiltrate begins in the inferotemporal and inferonasal cornea.
II. The infiltrate may cover the entire cornea in severe cases.
III. Melanin often accompanies the infiltrate.
IV. The lesion is usually fluorescein negative.
V. Redness, irregular thickening, and focal depigmentation of the third eyelid often occurs.
VI. The condition is often bilaterally symmetrical.

Diagnosis

I. Diagnosis is based primarily on clinical signs, especially in a predisposed breed.

II. Conjunctival or corneal scrapings demonstrating lymphocytes, plasma cells, and neutrophils are confirmatory.
III. Rule out the presence of other ocular diseases with a thorough ocular examination.

Differential Diagnosis

I. Corneal granulation tissue: history of prior trauma, ± obvious cause
II. Pigmentary keratitis: usually in brachycephalic breeds or dogs with underlying eyelid or tear film disease, absence of inflammatory corneal infiltrate
III. Corneal squamous cell carcinoma (SCC): rare in dogs, may be ulcerative, usually unilateral

Treatment

I. Topical corticosteroid medications
   A. Initially, 0.1% dexamethasone or 1% prednisolone acetate is used.
   B. Frequency is based on the severity of the disease (i.e., from once daily in mild cases to six to eight times daily in severe cases).
II. Topical cyclosporine (Williams et al., 1995)
   A. Commercially available 0.2% ointment BID
   B. Used in conjunction with topical steroidal medications
   C. Effective in cases with nictitans involvement (Read, 1995)
III. Subconjunctival corticosteroid medications for severe or refractory cases
   A. Betamethasone 1 to 2 mg
   B. Triamcinolone 4 to 8 mg
   C. Methylprednisolone acetate 4 to 8 mg
IV. Beta radiation and cryosurgery for severe cases (Rickards, 1980; Whitley, 1991)

Monitoring of Animal

I. Warn owners of chronicity and need for lifelong therapy.
II. Exacerbation of signs may occur in the summer or winter.
   A. Frequency of topical steroid treatment may need to be increased to up to six to eight times daily.
   B. Topical cyclosporine ointment may be added to treatment regimen as needed.
   C. Consider subconjunctival steroidal agents for refractory cases.
III. Schedule rechecks every 3 to 4 months, especially in the summer months.

Pigmentary Keratitis

Definition and Causes

I. Accumulation of melanin pigment in the corneal stroma
II. Result of chronic irritation of the cornea
   A. Distichia or trichiasis hairs
   B. Exposure of cornea from lagophthalmos
   C. Keratoconjunctivitis sicca
   D. Exophthalmos
   E. Buphthalmos
   F. Macropalpebral fissure
   G. Decreased blink frequency
   H. Palpebral nerve palsy

Pathophysiology

I. Pigment is produced in the corneal epithelium and superficial stroma in response to chronic irritation.
II. Pigment is often associated with keratitis and vascularization.

Clinical Signs

I. Corneal pigmentation is present and may be accompanied by vascularization.
II. It is not associated with corneal ulceration.
III. In severe cases, dogs are visually impaired from the corneal opacity.
IV. Corneal melanosis is most common in the Pekingese, pug, and other brachycephalic breeds.

Diagnosis

I. Appearance is diagnostic.
II. Location of pigment is often indicative of the source of chronic irritation.
   A. Exposure keratopathy from lagophthalmos results in central horizontal pigmentation.
   B. Irritation from medial canthal or nasal fold trichiasis results in pigmentation of nasal cornea.
III. Thorough ocular examination is performed with emphasis on the following:
   A. Blink frequency (normal, four blinks per minute)
   B. Ability to completely close the lids
   C. Presence of entropion, trichiasis, distichiasis
   D. STT results
   E. Tear film breakup time (normal, 19 ± 5 seconds)

Differential Diagnosis

I. Corneal lamellar scarring and fibrosis
II. Corneal/scleral melanoma

Treatment

I. Correct the underlying contributing cause.
   A. Administer topical cyclosporine BID for KCS.
   B. Topical tacrolimus BID may be more effective than cyclosporine for KCS (Berdoulay et al., 2005).
   C. Protect the cornea with topical lubricants BID to QID indefinitely.
   D. Surgically correct any eyelid abnormalities, and consider performing a medial canthoplasty to narrow the palpebral fissure.
II. Cyclosporine may decrease the amount of corneal pigment.
III. Surgical removal is generally not indicated because an exaggerated inflammatory response occurs postoperatively, with a rapid return of pigment.

Monitoring of Animal

I. Reexamine the animal every 3 to 6 months.
II. If pigmentation progresses, then increase the frequency of medical treatment, reevaluate the underlying cause, and perform a medial canthoplasty.

III. Eventual success of treatment is dependent on correction of the underlying cause; often the condition is incurable, only controllable.
IV. Because long-term topical corticosteroids suppress the adrenocortical axis and carry the risk of corneal ulceration, they must be used cautiously.

Feline Eosinophilic Keratitis

Definition

I. It is an infiltrative disease of the feline cornea, characterized by the presence of lymphocytes, plasma cells, eosinophils, and sometimes neutrophils and mast cells.
II. It may be unilateral or bilateral.

Causes

I. The exact cause of this disorder is unknown.
II. Many affected cats have concurrent FHV infection (Nasisse et al., 1996).
III. The relationship of eosinophilic keratitis to feline dermatologic eosinophilic granuloma complex is unknown.

Clinical Signs

I. Elevated pink or white vascularized lesions occur on the corneal surface, most often located temporally.
II. Often a yellow-white, caseous exudate clings to the surface of the lesion.
III. The condition is often nonpainful, but mild blepharospasm and mucoid discharge may be seen, particularly if the eyelids are abraded or the cornea is ulcerated.
IV. Fluorescein dye tests may reveal patchy ulceration of the surface of the lesion or of the adjacent cornea.

Diagnosis

I. Diagnosis is based on the presence of eosinophils or mast cells in corneal or conjunctival scrapings.
II. In a proliferative variant of the disease, scrapings reveal only lymphocytes or plasma cells.
III. Consider testing for FHV infection.

Differential Diagnosis

I. Feline herpesvirus stromal keratitis
II. Corneal granulation tissue secondary to prior corneal disease
III. Chronic corneal ulceration
IV. Limbal SCC

Treatment

I. Institute therapy with topical corticosteroid medications.
   A. Apply topical dexamethasone or prednisolone acetate two to six times a day until the cornea becomes clear, then as needed to prevent recurrence.
   B. In severe cases, consider subconjunctival corticosteroid administration (see Pannus).
II. Topical antiviral medications are administered for concurrent herpesvirus infection.
III. In refractory cases, consider the following drugs:
   A. Prednisone 5 to 10 mg/day PO for 7 to 14 days
   B. Megestrol acetate 0.5 mg/kg PO SID for up to 2 weeks, then as needed; used with caution and close monitoring for diabetes mellitus

Monitoring of Animal

I. Eosinophilic keratitis is often an incurable condition (only controllable).
II. Recheck the cat every 2 weeks until the cornea is clear, then every 2 to 3 months to monitor for recurrence.
III. If lesions return, then reinitiate or increase the frequency of therapy.

Feline Corneal Sequestration

Definition

I. Coagulative necrosis of the corneal stroma
II. Characteristic brown to black corneal lesion

Causes

I. The cause is multifactorial.
   A. Following corneal ulceration
   B. Secondary to corneal irritation
II. FHV is a potential underlying cause.

Pathophysiology

I. Sequestrum formation is initiated by damage to the cornea.
II. Sequestra occur in areas of chronic corneal ulceration and irritation.
III. Pigment may be absorbed from the tear film by exposed corneal stroma; this may be melanin (Featherstone et al., 2004).

Clinical Signs

I. Brown or black lesion in the cornea, often round and located in the axial cornea
II. May be associated with corneal edema and vascularization
III. Possible corneal ulceration
IV. Possible pain and ocular discharge

Diagnosis

I. Clinical appearance in a cat is diagnostic.
II. Samples may be submitted for detection of herpesvirus via culture or PCR assay; however, false positives and negatives are common (Maggs et al., 1999).
III. Assess tear function with a STT.
IV. Determine if eyelid conformation is a contributing factor.
   A. Brachycephalic cats may be lagophthalmic.
   B. Entropion may be present as a primary or secondary condition.

Differential Diagnosis

I. Pigmentary keratitis (rare in cats)
II. Corneal foreign body
III. Corneal ulceration

Treatment

I. Topical antibiotics are indicated if active ulceration is present.
   A. Use medications TID to QID.
   B. Neomycin-polymyxin-bacitracin ointment is used with caution in cats because it has been associated with fatal anaphylactic reactions (Plunkett, 2000).
II. Antiviral treatment is indicated if FHV is suspected as an underlying cause (see Feline Herpesvirus Keratitis).
III. Some lesions may be superficial and may be manually debrided or slough off of their own accord.
IV. Lubricating ointments may help decrease discomfort.
V. Surgery to remove the sequestrum is considered if the cat is painful or if the lesion persists and enlarges (Whitley, 1989).
   A. Superficial keratectomy is performed to remove the abnormal portion of the cornea.
   B. Adjunctive surgical therapies may be performed to protect the cornea after keratectomy.
      1. Conjunctival graft (Blogg et al., 1989)
      2. Corneoscleral transposition (Andrew et al., 2001)
      3. SIS graft (Featherstone et al., 2001)
      4. Third eyelid flap or contact lens (Morgan, 1994)
VI. Goals of postoperative care are to prevent infection, relieve pain, and prevent recurrence.
   A. Topical antibiotic medications TID to QID
   B. Atropine to effect (usually SID to BID)
   C. Lubricants as needed if tear production is decreased

Monitoring of Animal

I. Schedule recheck examinations every 3 to 4 weeks if surgery is not performed.
   A. The sequestrum may slough of its own accord.
   B. Watch for development of ulcers and treat with topical antibiotics as outlined previously.
II. Correct and/or treat and monitor any underlying problems.
   A. Long-term lubricants may be indicated, especially in brachycephalic, lagophthalmic cats.
   B. Entropion and other conformational problems are corrected if present.
III. Monitor for recurrences and development of new sequestra.
   A. Recurrence develops in a few cases after keratectomy (Morgan, 1994).
   B. Sequestrum formation may also occur in the fellow eye.

Episcleritis

Definition

I. Inflammation of the episcleral tissue ± involvement of the adjacent cornea
II. Occurs in focal and diffuse forms in the dog
III. Also known as *nodular fasciitis, nodular granulomatous episclerokeratitis,* and *fibrous histiocytoma* when a focal mass is produced

Causes and Pathophysiology

I. Idiopathic; possibly immune mediated
II. Proliferation of histiocytes, fibroblasts, lymphocytes, and plasma cells
III. Collies predisposed

Clinical Signs

I. Focal episcleritis
   A. This form is seen in collies, collie-like dogs, and a wide variety of breeds.
   B. Smooth, raised, red to white masses generally occur at the temporal limbus.
   C. Lesions are occasionally found in the conjunctiva, external eyelids, third eyelid, and oral gingiva.
II. Diffuse episcleritis
   A. This variation is most often seen in American cocker spaniels, Airedale terriers, and rottweilers (Slatter, 1990).
   B. Episcleral tissue is diffusely thickened and hyperemic.
   C. The temporal limbus is most often involved.
III. Signs common to both forms
   A. Episcleritis is characterized by lack of pain and ocular discharge.
   B. Corneal edema and vascularization may accompany the lesion.
   C. Corneal stromal lipid deposition may be noted at the leading edge of the lesion.

Diagnosis

I. Clinical findings are suggestive, especially in predisposed breeds.
II. Definitive diagnosis is based on biopsy with characteristic cytological or histopathologic findings.

Differential Diagnosis

I. Neoplasms such as lymphoma, mast cell tumor, SCC, viral papilloma
II. Granuloma
III. Idiopathic granulomatous disease with adnexal and cutaneous involvement (Collins et al., 1992)

Treatment

I. Topical 1% prednisolone or 0.1% dexamethasone is used QID for several weeks beyond resolution of signs.
II. Subconjunctival corticosteroid administration (see Pannus) is often required initially in severe cases.
III. Systemic prednisone (1 to 2 mg/kg/day PO) may be indicated if an adequate response is not noted with topical and subconjunctival steroidal medications.
IV. Oral azathioprine may also be indicated if remission is not achieved with steroidal agents (Latimer et al., 1983).
   A. Dose is 2 mg/kg/day PO for 5 to 30 days, then tapered to three times a week until the lesion has regressed.
   B. Complete blood count and chemistry profile are performed at initiation of therapy, 2 weeks later, and at regular intervals.

1. Azathioprine may cause leukopenia and/or thrombocytopenia.
2. Gastrointestinal disturbances and elevation of liver enzymes may also be noted.

V. Focal lesions may respond to cryotherapy.
VI. Tetracycline and niacinamide may be an alternative treatment (Rothstein et al., 1997).
   A. Dose is 250 mg of each TID for dogs <10 kg; 500 mg of each TID for dogs >10 kg.
   B. It may take up to 8 weeks to observe a response.
   C. Both tetracycline and niacinamide have immunomodulatory properties.
VII. Chronic therapy may be required in refractory or recurrent cases.

Monitoring of Animal

I. Long-term use of topical steroidal agents may be required to keep the lesion in remission.
II. Schedule recheck examinations every 2 to 3 weeks until lesions resolve, then every 4 to 6 months.

NEOPLASIA

Limbal Melanoma (Melanocytoma)

Definition

I. Brown to black, focal raised masses located at the limbus
II. May be locally expansile, but do not tend to metastasize (Wilcock and Peiffer, 1986)

Causes and Pathophysiology

I. Stromal melanocytes located at the limbus are the cell of origin.
II. Cells undergo transformation to a benign neoplasm.
III. The tumor may be aggressive, grow rapidly, and invade the globe in young (<4 years) dogs (Martin, 1981).
IV. Tumors are generally slow growing in older (>8 years) dogs and cats (Martin, 1981; Harling et al., 1986).

Clinical Signs

I. Smooth, black, raised mass located at the limbus, often temporally
II. Seen most commonly in the German shepherd dog, Labrador retriever, and golden retriever (Martin, 1981; Sullivan et al., 1996; Donaldson et al., 2006)
III. Possible corneal stromal lipid or neoplastic infiltrates at the leading edge of the lesion

Diagnosis

I. The clinical appearance is highly suggestive, especially in a German shepherd dog.
II. It must be differentiated from the scleral extension of a uveal neoplasm by thorough ocular examination with gonioscopy.
III. Diagnosis is based on biopsy and histopathologic examination.

Differential Diagnosis

I. Outward growth of an anterior uveal melanoma through the sclera
II. Limbal staphyloma

Treatment

I. Surgical removal or cryotherapy is indicated in young dogs with progressive lesions.
II. No treatment may be needed for small, slow-growing lesions in older animals.
III. Full-thickness sclerocorneal resection is indicated for large lesions (Martin, 1981; Wilkie and Wolf, 1991).
   A. Decreases chance of recurrence
   B. May use autologous or heterologous cornea, cartilage of third eyelid, synthetic graft material, or SIS to fill the defect created (Lewin, 1999)
   C. Histopathology required to identify cases with malignant potential (Donaldson et al., 2006)
IV. Photocoagulation by neodymium:yttrium-aluminum-garnet (Nd:YAG) or diode laser may be effective in some cases (Sullivan et al., 1996).
   A. Advantage: noninvasive procedure
   B. Disadvantage: higher recurrence rate

Monitoring of Animal

I. If the mass is not removed surgically because it is small and/or the animal is older, then recheck every 3 to 4 months.
   A. Perform gonioscopy to watch for extension of tumor into the anterior chamber.
   B. Perform tonometry, especially if the filtration angle is involved.
II. After surgical removal, recheck every 1 to 3 weeks until healing is complete, then every 3 to 6 months to check for recurrence.
III. If surgical removal is complete, the long-term prognosis is good.

Squamous Cell Carcinoma

Definition

I. SCC is the neoplastic transformation of corneal or conjunctival epithelial cells, resulting in tumor development.
II. Most commonly, the neoplasm originates from the conjunctiva or limbus and extends onto the cornea secondarily.

Causes and Pathophysiology

I. Ultraviolet damage to epithelium predisposes to development of SCC by inducing squamous metaplasia.
II. Lack of ocular pigment predisposes to development of SCC.

Clinical Signs

I. Tumors are often red, irregularly raised, and may be erosive.

II. Secondary bacterial infection can occur and be associated with areas of necrosis.
III. Ocular discharge and pain may be present, especially if the tumor is necrotic.
IV. The mass may extend to the conjunctiva, eyelid, third eyelid, and orbital tissues.

Diagnosis

I. Clinical appearance is suggestive.
II. Cytological analysis is often misleading because of the concurrent presence of necrosis and bacterial infection.
III. Definitive diagnosis requires biopsy and histopathologic examination.

Differential Diagnosis

I. Feline eosinophilic keratitis or conjunctivitis
II. Corneal granulation tissue
III. Chronic superficial keratitis (pannus)
IV. Viral papilloma (young dogs)
V. Corneal lymphoma

Treatment

I. Local excision by lamellar keratectomy and/or conjunctival resection is undertaken initially.
II. Recurrence after excision is common.
III. Several adjunctive therapies may be attempted to decrease likelihood of recurrence.
   A. Radiation therapy (Rebhun, 1990)
   B. Cryotherapy (Schoster, 1992)
   C. Hyperthermia
   D. Ablation with carbon dioxide lasers (English et al., 1990)
IV. Enucleation is performed if the lesion is too large to excise or if it extends to other ocular tissues.
V. Exenteration is indicated for orbital and/or lid involvement.

Monitoring of Animal

I. Recheck every 3 months in cases of small lesions; recheck every 3 weeks if lesions are large or advanced.
II. Skull radiography, computed tomography scans, or magnetic resonance imaging is indicated to monitor possible orbital recurrence.
III. Prognosis for long-term survival is guarded to poor because of the likelihood of local recurrence.

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CHAPTER 99

Diseases of the Anterior Uveal Tract

A. Michelle Willis

CONGENITAL/DEVELOPMENTAL ABNORMALITIES

Persistent Pupillary Membranes

Definition and Causes

I. Persistent pupillary membranes (PPMs) are remnants of the mesodermal sheet carrying blood vessels that partially fill the anterior chamber during fetal development.
II. PPMs are inherited in the Basenji breed, but the mode of inheritance is unclear (Roberts and Bistner, 1968).
III. Cause is unknown in other breeds of dogs and cats.
  A. Familial occurrence with suspicion of inheritance in other commonly affected breeds
  B. Examples: collie, chow chow, Pembroke Welsh corgi, mastiff breeds
IV. PMMs can also occur as a sporadic, presumably non-inherited event.

Pathophysiology

I. In the developing fetus, the pupillary membrane arises from the collarette region or minor arterial circle of the iris and provides a vascular supply to the developing lens.
II. Atrophy of this membrane begins during fetal life, but may not be complete until the puppy is 4 to 8 weeks of age.
III. Incomplete resorption of this embryonic vasculature and mesenchymal tissue results in retained iris strands.
IV. PPMs may be associated with multiple ocular defects (e.g., microphthalmia, dyscoria, corneal opacification, cataract, retinal dysplasia).
V. Total persistence of the fetal pupillary membrane is rare and associated with other severe ocular anomalies.

Clinical Signs

I. Affected animals are typically asymptomatic, although thick and numerous strands may cause opaque lesions in the cornea and lens, with visual impairment.
II. Several variations of PPMs exist, such as iris-to-iris, iris-to-lens, and iris-to-cornea as well as free-floating strands in the anterior chamber.
  A. Focal pigment deposition on the anterior lens capsule or corneal endothelium may occur with no observable remaining PPM strands.
  B. Iris-to-cornea PPMs can affect the corneal endothelium, with edema or stromal fibrosis occurring at or adjacent to the site of corneal attachment.
  C. Iris-to-lens strands may cause a focal capsular and subcapsular cortical cataract.

Diagnosis

I. Examination of the anterior segment
  A. PPMs originating from collarette zone of the iris
  B. Pigmented strands in anterior chamber
  C. Punctate foci of pigment on anterior lens capsule or corneal endothelium
  D. Other congenital defects, particularly microphthalmia
II. No evidence of trauma or inflammation

Differential Diagnosis

I. Iris synechia
  A. Postinflammatory or posttraumatic
  B. Originate from pupil margin and typically accompanied by other signs of active or prior ocular inflammation (see Anterior Uveitis)
II. Senile iris sphincter muscle atrophy
  A. Strands of iris at the pupillary margin
  B. Possible iris stromal thinning
III. Fibrin strands or vitreous migration
  A. Both are weblike opacities in the anterior chamber and can contact lens or cornea.
  B. Fibrin is associated with anterior uveitis.
  C. Anterior chamber vitreous strands are associated with vitreous degeneration and/or lens instability.
IV. Other congenital abnormalities of the anterior uvea (Table 99-1)

Treatment

I. Usually none required
II. Transection of iris-to-cornea or iris-to-lens PPMs
  A. Intraocular hemorrhage from incised vascularized membranes is the biggest risk.
  B. Electrocautery minimizes bleeding.
  C. Laser surgery may simultaneously rupture and photocoagulate PPM.
III. Penetrating keratoplasty in combination with severing of PPMs

TABLE 99-1

Selected Developmental Abnormalities of the Anterior Uvea

OCULAR DEFECT	DEFINITION	PATHOPHYSIOLOGY	CLINICAL FINDINGS	TREATMENT/COMMENTS
Aniridia	Near or complete absence of iris	Presumed arrested differentiation of optic cup	Widely dilated pupil with rudimentary iris tissue ± photophobia	Use tinted goggles in tolerant dogs for outdoor activity Do not breed animal
Anterior segment dysgenesis	Anomalous development of the cornea, iridocorneal angle, iris, and ciliary body	Primary defect in formation of the neuroectodermal optic cup and abnormal induction of mesenchyme	Congenital blindness with variable microphthalmia, opaque cornea, and absent anterior chamber; occasional congenital glaucoma and buphthalmia	No treatment Inherited in Doberman pinschers, sporadic in other breeds Do not breed animal
Congenital dyscoria	Abnormally shaped pupil	Anomaly of iris stroma and/or musculature	Abnormal pupil shape; minor degree of dyscoria common	No treatment
Coloboma of iris	Incomplete sector of iris *Typical* refers to defect at 6 o'clock position	Incomplete closure of embryonic fissure	Variable-sized notch in iris that may also involve ciliary body and choroid	No treatment Inherited in Australian shepherd dogs
Heterochromia irides	Congenital color difference between two irises or difference in color in same iris	Hypopigmentation of iris; generally correlated with hair-coat color genetics	Blue-colored iris or portion of iris; may be associated with iris stromal hypoplasia and/or deafness (Waardenburg's syndrome)	No treatment Do not breed deaf animals

Modified from Davidson MG: Disorders of the anterior uveal tract. p. 1021. In Morgan RV (ed): Handbook of Small Animal Practice. 3rd Ed. WB Saunders, Philadelphia, 1997.

A. May be indicated if vision is impaired by extensive corneal edema associated with iris-to-cornea PPMs
B. Rarely performed in dogs

IV. Cataract extraction in combination with transection of PPMs
A. It is indicated for PPMs causing complete cataracts and vision loss.
B. Use ultrasonography and electroretinography to confirm that the retina and vitreous are healthy.

Monitoring of Animal

I. Inform the owner of the potential for more serious forms of the condition in the offspring of affected animals.
II. Breeding of affected dogs is discouraged.

Anterior Uveal Cysts

Definition

I. Anterior uveal cysts are epithelial-lined, pigmented structures arising from the posterior, pigmented epithelium of the iris or the ciliary body epithelium.
II. These cysts are either congenital or acquired.

Causes

I. Congenital
A. Failure of two layers of embryonal neuroectoderm to fuse, with fluid accumulation between these contiguous epithelial layers
B. May not be recognized until animal is several years old
C. Commonly affected breeds: Boston terrier, golden retriever (Cocoran and Koch, 1993)
D. Cats: rare

II. Acquired
A. Spontaneous
B. After chronic uveal inflammation or irritation
C. Secondary to uveal degeneration

Clinical Signs

I. Cysts appear as spherical, oval, or elongated, pigmented, intraocular structures.
II. They may be single or multiple.
III. Cysts are variably pigmented, typically pale to dark brown.
IV. They may be attached to the pupillary margin (common in cats) or be free-floating in the anterior chamber, or (occasionally) the vitreous.
V. Cysts attached to the ciliary body are often difficult to visualize without pupillary dilation.
VI. Rupture of uveal cysts may result in pigment deposition on the anterior lens capsule or corneal endothelium.
VII. They may predispose to the development of glaucoma in the golden retriever (Deehr and Dubielzig, 1998; Sapienza et al., 2000) and Great Dane (Spiess et al., 1998).

Diagnosis

I. A spherical, pigmented structure is free-floating in the anterior chamber or attached to the iris margin.
II. Cysts are fluid-filled and typically transilluminate with a bright light source.
III. Large cysts may alter the contour of the iris.
IV. Ultrasonography can differentiate a cyst from a solid mass lesion when the cyst is heavily pigmented.

Differential Diagnosis

I. Anterior uveal melanoma
  A. Solid, variably pigmented, cannot be transilluminated
  B. Alters structure and contour of the anterior uveal tissue
II. Focal pigment deposition on cornea or lens
  A. Postinflammatory or posttraumatic synechia: usually other evidence of prior uveitis or perforating corneal scars
  B. PPMs: congenital

Treatment

I. None required if no interference with vision or impingement on other tissues
II. Removal indicated if cysts interfere with vision or impinge on the corneal endothelium
  A. Neodymium:yttrium-aluminum-garnet (Nd:YAG) or diode laser therapy is used to puncture and ablate cyst wall.
    1. May require general anesthesia
    2. Less invasive than aspiration techniques
    3. Potential for laser damage to lens, iris, or retina
  B. Aspiration of cyst requires general anesthesia.
    1. Make a small limbal incision.
    2. Insert a blunt, 20-gauge needle or automated irrigation-aspiration unit to evacuate cyst contents.

Monitoring of Animal

I. Monitor for enlargement of cysts and associated problems.
  A. Visual deficits
  B. Impingement on corneal epithelium
II. Monitor intraocular pressure (IOP) in golden retrievers and Great Danes.

DEGENERATIVE DISORDERS

Iris Atrophy

Definition and Causes

I. Progressive thinning of the stroma or pupillary portion of the iris
II. Typically associated with aging (senile iris atrophy)
III. May develop after inflammatory conditions of the iris (secondary iris atrophy)
IV. Common in miniature poodles, miniature schnauzers, and Chihuahuas

Clinical Signs

I. Sphincter muscle atrophy
  A. Scalloped or "moth-eaten" pupillary margin
  B. Pigmented strands attached to dyscoric pupillary margin
  C. Typically bilateral but commonly asymmetrical
II. Iris stromal atrophy
  A. Age-associated color change in iris
  B. Fading of natural iris color
  C. Possible foci of hyperpigmentation as stroma lost and pigmented epithelium exposed
    1. Large holes in central iris as pigment epithelium of iris atrophies
    2. Appearance of fundic or tapetal reflex through stromal defects with transillumination
III. Dyscoria, mydriasis
IV. Anisocoria if atrophy is asymmetrical
V. Occasional pseudopolycoria
VI. Incomplete to absent pupillary light responses (PLRs) in advanced cases
VII. Occasional photophobia in bright light
  A. Associated with reduced ability to constrict pupil
  B. Usually subclinical

Diagnosis

I. Clinical appearance and location of iris strands at the pupillary margin allow a presumptive diagnosis.
II. Differentiate from neurological efferent mydriasis with topical miotic drug challenge.
  A. Use a topical, direct-acting, parasympathomimetic agent (2% pilocarpine).
  B. A functional pupillary sphincter muscle responds with significant miosis.
  C. An atrophied iris sphincter does not respond and the pupil remains dilated.

Differential Diagnosis

I. PPMs: congenital, arising from collarette zone of iris
II. Congenital iris coloboma causing dyscoria
III. Postinflammatory synechiae impairing pupil shape and function: usually other indicators of active or prior uveitis
IV. Neurological lesions resulting in mydriasis and an incomplete PLR (see Chapter 105)

Treatment and Monitoring

I. No specific treatment is available or usually warranted.
II. Reduce bright light exposure in animals exhibiting photophobia or consider fitting tolerant dogs with shaded goggles when outdoors.
III. Atrophy is typically progressive, so monitor for bright light sensitivity.

Altered Iris Pigmentation

Definition

I. Benign pigmentary changes in the iris
II. Classification of changes
  A. Ectropion uvea
  B. Iris freckle
  C. Iris nevus
  D. Benign iris melanosis

Causes and Pathophysiology

I. Ectropion uvea
  A. Prominence or proliferation of the pigmented posterior epithelium of the iris with anterior extension through the pupil
  B. Causes
    1. Epithelial hyperplasia with concurrent iris stromal atrophy
    2. Contraction of inflammatory exudates or preiridal fibrovascular membranes on the anterior iris surface, associated with chronic uveal inflammation, creating eversion of the pupillary margin
II. Iris freckle: hyperpigmentation of resident melanocytes, without an increase in cell numbers
III. Iris nevus
  A. More cellular than freckles
  B. Histologically similar to benign iridal melanoma in dogs (Diters et al., 1983)
IV. Benign iris melanosis
  A. Benign, diffuse increase in iridal pigmentation
  B. Possibly associated with chronic uveitis

Clinical Signs and Diagnosis

I. Appearance of lesion
  A. Ectropion uvea
    1. Heavily pigmented, curled edge at pupillary margin
    2. Other signs of uveitis
    3. Commonly seen with hypermature cataract
  B. Iris freckle
    1. Single or multifocal
    2. Absence of a discreet mass or nodule
  C. Iris nevus
    1. More cellular than freckles
    2. May be raised above iris surface, extend into iris stroma, or cause mild iris thickening
  D. Benign iris melanosis
    1. Diffuse pigmentary change in iris
    2. May be associated with chronic uveitis
II. Other ocular examination findings
  A. Normal pupil size and shape
  B. Gonioscopy and IOP
    1. Typically no involvement of iridocorneal angle
    2. Normal IOP
  C. Signs of prior or active uveitis: ectropion uvea

Differential Diagnosis

I. Early or small iridal melanoma
II. Iris atrophy
  A. Natural iris color fades.
  B. Foci of hyperpigmentation may be noted as stroma is lost and pigmented epithelium is exposed.
III. Pigmentary glaucoma (see Chapter 100)

Treatment and Monitoring

I. Reevaluate every 3 to 6 months to assess progression.
II. It is helpful to photograph the affected eye to compare changes at sequential visits.
III. Laser photocoagulation may be tried in progressive lesions of dogs (Cook and Wilkie, 1999) but remains controversial in cats (see Neoplasia).

INFLAMMATORY DISORDERS

Anterior Uveitis

Definition

I. Inflammation of the iris and ciliary body (anterior uveal tract)
II. May occur alone or in conjunction with posterior uveitis

Causes

I. Ocular causes
  A. Lens-induced uveitis
    1. Phacolytic uveitis is a nongranulomatous uveitis caused by resorption of a rapidly progressive or hypermature cataract.
    2. Phacoclastic uveitis is associated with disruption of the lens capsule and release of an excessive amount of lens protein into the anterior chamber that overwhelms the intraocular immune system.
  B. Ocular trauma
    1. Blunt trauma with uveal contusion
    2. Perforating corneal wounds
    3. Septic corneal ulcer or stromal abscess
    4. Surgical manipulation of the anterior segment
  C. Primary ocular neoplasia (see Neoplasia)
II. Systemic infectious diseases
  A. Systemic mycoses
    1. Blastomycosis
    2. Histoplasmosis
    3. Cryptococcosis
    4. Coccidioidomycosis
    5. Candidiasis
  B. Rickettsial infections
    1. Rocky mountain spotted fever (RMSF): *Rickettsia rickettsii*
    2. Ehrlichiosis: *Ehrlichia canis, Ehrlichia platys, Ehrlichia equi*
  C. Protozoal infections
    1. Toxoplasmosis
    2. Neosporosis
    3. Leishmaniasis
  D. Bacterial infections
    1. Septicemia of any cause
    2. Dogs: brucellosis, leptospirosis, Lyme borreliosis
    3. Cats: *Bartonella henselae;* possibly *Yersinia* spp. infection
  E. Viral infections
    1. Canine adenovirus (CAV)
    2. Canine herpesvirus (puppies)
    3. Feline infectious peritonitis (FIP)
    4. Feline immunodeficiency virus (FIV)
    5. Feline leukemia virus (FeLV)
    6. Feline herpesvirus 1 (FHV) (Maggs et al., 1999)
  F. Algal infections in dogs: *Prototheca* spp.

G. Parasitic agents
   1. Aberrant nematode larval migration
      a. Toxocariasis
      b. Dirofilariasis
      c. Ancylostomiasis
      d. Angiostrongylosis
   2. Ophthalmomyiasis interna with dipterous fly larvae (*Cuterebra* spp.)

III. Uveodermatologic or Vogt-Koyanagi-Harada (VKH)–like syndrome
   A. Presumed immune-mediated panuveitis associated with hair and skin lesions
   B. More common in young adult dogs (1 to 4 years old)
   C. Predisposed breeds: Asian or Arctic Circle breeds, such as Akita, chow chow, Samoyed, Siberian husky, Alaskan malamute

IV. Idiopathic anterior uveitis
   A. Diagnosis of exclusion when appropriate diagnostic investigation fails to identify a specific causative agent
   B. Common in older male cats
   C. Syndrome in golden retrievers often associated with iridociliary cysts (Deehr and Dubielzig, 1998; Sapienza et al., 2000)

V. Secondary ocular neoplasia

VI. Miscellaneous causes of disruption of the blood-aqueous barrier
   A. Systemic hypertension
   B. Hyperviscosity syndromes: multiple myeloma, ehrlichiosis
   C. Therapeutic radiation to the head
   D. Reflex uveitis secondary to corneal and scleral diseases

Pathophysiology

I. Lens-induced uveitis
   A. Both humeral and cell-mediated immune responses occur in response to lens antigens.
   B. Phacolytic uveitis develops as follows:
      1. Occurs in response to the release of lens proteins through an intact lens capsule of a cataractous lens
      2. Develops sooner in young dogs and is more difficult to treat than in older dogs (van der Woerdt et al., 1992)
   C. Phacoclastic uveitis has specific characteristics.
      1. Follows massive and sudden release of lens proteins from a ruptured lens capsule
      2. Results in a reversal of T-lymphocytic tolerance

II. Infectious agents
   A. Cause uveitis by direct intraocular replication or intraocular migration of organisms
   B. Stimulate an immune-mediated inflammatory response in uveal tissues
   C. Peculiar response to CAV infection
      1. Acute uveitis is related to intracellular viral replication causing a direct cytopathic effect.
      2. Subacute findings occur from anterior uveal and corneal endothelial immune complex deposition (type III hypersensitivity).
      3. The condition occurs more often with natural infection and the use of modified live CAV-1 vaccine (7 to 21 days after vaccination), although anterior uveitis may occur after the use of the CAV-2 vaccine.
   D. Reflex uveitis from septic corneal disease
      1. Corneal damage stimulates an axonal reflex, resulting in release of substance P, which produces vascular dilatation, altered permeability, and chemotaxis of neutrophils.
      2. Chemical mediators of inflammation are released by the anterior uvea in response to corneal inflammation associated with rapid colonization of the cornea by infectious agents.

III. Uveodermatologic syndrome
   A. Suspected to be an immune-mediated reaction to components of melanocytes in the eyes and skin
   B. Characterized histopathologically by a granulomatous inflammation of ocular tissues and a lichenoid inflammatory cell infiltrate pattern in dermal tissues (see Chapter 92)

IV. Idiopathic uveitis
   A. Presumed to be immunologically mediated
   B. Histopathology of affected tissues: lymphocytic and plasmacytic cellular infiltration
   C. At least partial response to antiinflammatory or immunosuppressive therapy

Clinical Signs

See Table 99-2.

Diagnosis and Differential Diagnosis

I. Complete physical examination

II. Complete ophthalmic examination

III. Complete blood count, biochemistry profile, urinalysis

IV. Thoracic radiography if fungal or neoplastic disease suspected

V. Abdominal radiography and ultrasonography if neoplasia suspected

VI. Serological testing
   A. Evaluation of cats with uveitis
      1. *Toxoplasma gondii* immunoglobulin (Ig)M and G
      2. Viral tests: FIP, FeLV, FIV
      3. *Cryptococcus neoformans* antigen
      4. *Bartonella henselae* IgG
   B. Evaluation of dogs with uveitis
      1. *Blastomyces dermatitidis* and *Histoplasma capsulatum* serology in the southern, midwestern, and mideastern states
      2. *Coccidioides immitis* serology in the southwestern states
      3. *E. canis, E. platys, E. equi, Rickettsia rickettsii*, and *Borrelia burgdorferi* serology in areas endemic for tickborne disease
      4. *Brucella canis* tests particularly in intact animals
      5. Serology for leptospirosis in endemic areas

VII. Aqueocentesis
   A. It may support a diagnosis of ocular toxoplasmosis, intraocular FHV or *Bartonella* spp. infection in cats by comparison of aqueous and serum antibody levels.

TABLE 99-2

Clinical Signs of Anterior Uveitis

CAUSES OR TYPE OF UVEITIS	SIGNS
Nonspecific Signs	
Acute	Conjunctival and scleral injection Photophobia Aqueous flare Miosis Edematous and hyperemic iris Corneal edema: diffuse, perilimbal Decreased intraocular pressure Hypopyon Hyphema
Chronic	Posterior synechia Secondary glaucoma Secondary cataract Keratic precipitates Iris hyperpigmentation Rubeosis iridis Vitreous syneresis Vitreous cellular infiltrate, debris on lens capsule Asteroid hyalosis
Lens-induced uveitis	Presence of hypermature cataract, although may accompany immature but rapidly progressive cataract in young or diabetic dog Hyperpigmentation of iris Pupil resistant to dilation with short-acting mydriatic
Systemic Infectious Diseases	
Canine adenovirus	Typically unilateral Corneal edema obscures anterior chamber Miosis and normal intraocular pressure distinguishes uveitis from glaucoma
Feline immunodeficiency virus	Pars planitis (inflammation of caudal ciliary body) is seen with white infiltrates in anterior vitreous
Fungal	Posterior segment findings predominate with secondary anterior uveitis
Rickettsial, protozoal, and bacterial	Anterior and posterior uveitis are often both present
Uveodermatologic syndrome	Chorioretinitis, retinal detachment, and progressive nontapetal choroidal depigmentation May be preceded or accompanied by depigmentation of fur and skin (see Chapter 92 for description of skin lesions)
Idiopathic Uveitis	
Cats	Cataract formation, lens luxation, and secondary glaucoma are common sequelae
Golden retrievers	Hallmark is pigment on anterior lens capsule, often deposited in a radial pattern Uveal cysts common

   B. Submit cytological testing, culture, or latex agglutination testing for *C. neoformans.*
   C. Culture for *B. henselae*.
   D. Perform polymerase chain reaction assays for *T. gondii, B. henselae* (Powell and Lappin, 2001).

VIII. Vitreocentesis
   A. Submit aspirate for cytological testing, culture, specific antigen testing, or antibody titers.
   B. Risks include hemorrhage from ciliary body or choroid, retinal detachment, lens trauma, and endophthalmitis.
   C. Primarily done in blind eyes when other tests fail to yield a diagnosis.

IX. Cerebrospinal fluid analysis
   A. Recommended in cases with concurrent central nervous system signs

B. Fungal (e.g., *C. neoformans*) or viral (e.g., distemper) titers measured
X. Skin biopsy if uveodermatologic syndrome suspected

Treatment

I. Specific therapy for underlying disease
II. Topical antiinflammatory therapy
  A. Corticosteroid agents
    1. Highly soluble prednisolone acetate 1% ophthalmic solution is the optimal choice.
    2. Prednisolone sodium phosphate and dexamethasone are additional options.
    3. Frequency (three to six times daily) depends on severity of clinical signs, with cautious tapering after resolution and control of signs.
  B. Nonsteroidal antiinflammatory medications
    1. Flurbiprofen 0.03%, suprofen 1%, diclofenac 0.1%
    2. Dose: BID to QID
    3. Synergistic with topical corticosteroid agents, so may help reduce frequency of topical corticosteroid medications
    4. May increase IOP
III. Topical mydriatic and cycloplegic therapy
  A. Reduces risk of posterior synechiae formation and decreases painful iridociliary muscle spasm
  B. Parasympatholytic agents
    1. Atropine 1% to affect pupillary dilation
      a. Frequency is SID to QID.
      b. It may exacerbate preexisting glaucoma or keratoconjunctivitis sicca (KCS).
    2. Tropicamide 1%
      a. Has a short-acting duration (1 to 4 hours)
      b. Useful if secondary glaucoma or KCS is a concern
  C. Sympathomimetic agents
    1. Phenylephrine 2.5% to 10% in conjunction with atropine two to six times daily
    2. May induce tachycardia or arrhythmias, especially in small animals
IV. Subconjunctival corticosteroid
  A. Does not replace use of topical steroidal medications but may have adjunctive effect in severe cases
  B. Long-acting choices are as follows:
    1. Triamcinolone 4 to 8 mg
    2. Methylprednisolone acetate 4 to 8 mg
  C. Not used in cases of corneal infection, ulceration, or suspected fungal uveitis
V. Systemic antiinflammatory therapy
  A. Warranted if posterior segment inflammation is present or if anterior uveitis is not controlled by high-frequency topical steroid administration
  B. Prednisone
    1. Antiinflammatory dose: 0.25 to 0.5 mg/kg PO BID, tapered once clinical signs are controlled
    2. Immunosuppressive dose: 1 to 2 mg/kg PO BID for certain forms of immune-mediated uveitis (e.g., VKH syndrome) or golden retriever uveitis (Sapienza et al., 2000)
    3. Used *only* after complete diagnostic evaluation has ruled out infectious disease
  C. Systemic nonsteroidal antiinflammatory drugs
    1. Helpful when systemic steroidal agents are contraindicated (e.g., diabetes mellitus, certain infectious diseases)
    2. Aspirin
      a. Dogs: 10 to 25 mg/kg PO BID for 1 to 3 weeks
      b. Cats: 6 mg/kg PO every 72 hours
    3. Carprofen: 2 mg/kg PO BID in dogs
    4. Meloxicam (Giuliano, 2004)
      a. Dogs: 0.2 mg/kg PO once, followed by 0.1 mg/kg PO SID
      b. Cats: 0.2 mg/kg PO once, followed by 0.1 mg/kg PO every 2 to 3 days
  D. Azathioprine
    1. It helps to reduce or eliminate the dose of corticosteroid medications required long-term to control immune-mediated uveitis.
    2. Dose is 2 mg/kg PO SID initially, then tapered to QOD.
    3. Dose is tapered based on response to therapy and blood parameters (can cause myelosuppression and hepatotoxicity).
VI. Surgical therapy
  A. Lensectomy for phacolytic or phacoclastic uveitis
  B. Enucleation
    1. Recommended in blind, painful eyes with chronic uveitis or secondary glaucoma that are unresponsive to medical therapy.
    2. Indicated to remove nidus of chronic mycotic infection in blind eyes unresponsive to therapy.

Monitoring of Animal

I. Reevaluate frequently (every 3 to 5 days) until control of inflammation is achieved.
II. Monitor for sequelae of chronic uveitis (secondary glaucoma, cataract formation).
III. Monitor for onset or resolution of posterior segment lesions.
IV. Prognosis varies depending on the underlying cause of the uveitis.
  A. Lens-induced uveitis
    1. Phacolytic uveitis is typically responsive to topical steroid therapy if instituted early.
    2. Phacoclastic uveitis is poorly responsive to medical therapy; surgical removal of all lens material shortly after lens capsule rupture carries a more favorable prognosis (Davidson et al., 1991).
  B. Infectious uveitis
    1. Fungal infection
      a. Fair to good prognosis: focal granulomatous chorioretinal lesions and mild anterior uveitis present
      b. Poor prognosis: advanced disease present
    2. Rickettsial uveitis
      a. Excellent prognosis: RMSF
      b. Fair prognosis: *E. canis*

3. Bacterial infections: good prognosis if primary disease resolves
4. Protozoal uveitis
   a. Toxoplasmosis: generally favorable prognosis
   b. Leishmaniasis: response of uveitis highly correlated with systemic response to therapy (Pena et al., 2000)
5. CAV-induced uveitis
   a. Prognosis is variable but often favorable.
   b. Vision may be compromised by persistent corneal edema or glaucoma.
6. Uveodermatologic syndrome
   a. Maintaining remission is challenging; recurrences are common.
   b. Side effects of high-dose corticosteroid therapy can be problematic.
   c. Long-term prognosis for vision is guarded to poor.
7. Idiopathic uveitis
   a. Recurrences are common, as are secondary sequelae.
   b. Prognosis is variable and dependent on response to antiinflammatory therapy.

HYPHEMA

Definition

I. Hyphema is blood in the anterior chamber.
II. It may be clotted or unclotted.

Causes

I. Developmental abnormalities
   A. Persistent hyperplastic tunica vasculosa lentis
   B. Persistent hyaloid artery
   C. Collie eye anomaly
   D. Vitreoretinal dysplasia
II. Blunt or penetrating ocular trauma
III. Coagulopathies
   A. Thrombocytopenias and thrombocytopathies
   B. Clotting factor deficiencies
   C. Disseminated intravascular coagulation
IV. Hyperviscosity syndromes
   A. Polycythemia vera
   B. Multiple myeloma, ehrlichiosis
V. Systemic hypertension
VI. Primary or metastatic neoplasia
VII. Uveal or retinal neovascularization
   A. Chronic uveitis
   B. Chronic glaucoma
VIII. Iatrogenic
   A. Diagnostic paracentesis
   B. Intravitreal injection
   C. Intraocular surgery
   D. Transscleral laser cyclophotocoagulation

Clinical Signs

I. Red blood cells circulating in or settled ventrally in the anterior chamber
II. Blood clot in anterior chamber
   A. Blood from trauma or uveitis usually clots.
   B. Blood from immune-mediated thrombocytopenia or warfarin toxicity rarely clots.
III. Possible rebleeding episode with contraction of clot

Diagnosis

I. If other signs of bleeding are seen, then rule out coagulopathy (see Chapters 67 and 68).
II. Systolic blood pressure is measured to rule out hypertension.
   A. Systolic pressure >170 mm Hg in both cats and dogs is compatible with hypertension.
   B. Investigate causes of hypertension (see Chapter 48).
III. Serology for infectious diseases associated with vasculitis is also indicated.
   A. *Ehrlichia* spp.
   B. *Rickettsia rickettsii*
   C. *Borrelia burgdorferi*
IV. Ocular ultrasonography helps identify the following:
   A. Intraocular tumor
   B. Retinal detachment
   C. Lens dislocation
V. Skull radiographs may reveal orbital fractures or metallic projectiles.

Treatment and Monitoring

I. Treat underlying disease if possible.
II. Limit activity to reduce risk of rebleeding.
III. Administer topical corticosteroid agent three to six times daily until resolution.
   A. Prednisolone acetate 1%
   B. Dexamethasone 0.1%
   C. Prednisolone sodium phosphate 1%
IV. Consider topical phenylephrine 2.5% to 10% to promote vasoconstriction and mydriasis.
V. Consider topical atropine.
VI. Consider intracameral tissue plasminogen activator for fibrinous clots.
   A. Inject 25 μg (0.1 mL of a 250 μg/mL solution) (Martin et al., 1993).
   B. It is most effective within the first 48 hours.
   C. Main risk is rebleeding.
VII. Monitor for secondary glaucoma from the following:
   A. Fibrin deposition in iridocorneal angle
   B. Posterior synechia and iris bombe
VIII. Prognosis for vision is variable and depends on the amount of bleeding and the underlying cause.

NEOPLASIA

See Table 99-3.

TABLE 99-3

Neoplasia

TYPE OF TUMOR	PATHOPHYSIOLOGY	CLINICAL SIGNS	DIAGNOSIS	TREATMENT	PROGNOSIS
Primary					
Anterior uveal melanoma	Arises from melanocytes in uveal tract Most common primary ocular tumor in dog and cat Forms: 1. Nodular in dog 2. Diffuse or nodular in cats	Pigmented mass in iris or, less commonly, ciliary body: 1. Amelanotic variants possible 2. Alteration in iris contour 3. Dyscoria with diffuse stromal involvement 4. Possible pigmentation of sclera adjacent to involved region of iris	Finding a mass on examination Systemic work-up: 1. Physical exam 2. CBC 3. Chemistry profile 4. Urinalysis 5. Thoracic and abdominal radiographs 6. Ultrasound: ocular and abdominal 7. Aspiration of cells 8. Histopathology	Laser ablation: small pigmented masses in dogs not involving iridocorneal angle or impinging on corneal endothelium 1. For localized iris or ciliary mass 2. High risk for hemorrhage Enucleation	Low metastatic potential in dogs High metastatic potential in cats: 1. Prognosis poorer with invasion of ciliary body or secondary glaucoma 2. Quarterly examination in cats: lymph node palpation, hepatic enzyme evaluation, thoracic radiography and abdominal US
Adenoma/ adenocarcinoma	Arise from iridociliary epithelium	More common in dog than cat Pink mass in iris or ciliary body protruding through pupil Adenocarcinoma more likely to invade sclera	As above	Enucleation is recommended in most cases because progressive expansion of tumor results in uveitis, glaucoma, and blindness	Both have low metastatic potential
Medulloepithelioma	Arises from embryonal neuroepithelial tissue	Typically present in younger dogs, but may go undiagnosed for years	As above	Enucleation is recommended in most cases because progressive expansion of tumor results in uveitis, glaucoma, and blindness	Low metastatic potential
Feline intraocular sarcoma	Occurs in eyes with previous penetrating trauma	Usually associated with lens capsule rupture Time from trauma to recognition of tumor variable (1-10 yr)	As above	Enucleation is treatment of choice.	Aggressive intraocular destruction and scleral/ extrascleral extension are common
Osteosarcoma	Osteoid-producing mesenchynal tumor	Associated corneal changes; inflammation and glaucoma may prelude specific evaluation of uveal tract	As above	Enucleation	Guarded

CBC, complete blood count; *US,* ultrasound.

TABLE 99-3

Neoplasia—*cont'd*

TYPE OF TUMOR	PATHOPHYSIOLOGY	CLINICAL SIGNS	DIAGNOSIS	TREATMENT	PROGNOSIS
Secondary					
LSA	Usually a component of multicentric disease	± Pink mass in uvea ± Lymphadenopathy or signs of systemic disease	As above	Specific chemotherapy Topical steroid therapy to control inflammation Palliative enucleation for painful eye nonresponsive to therapy	Variable depending upon systemic involvement
Metastatic	Hematogenous spread from distant primary	Often similar clinical appearance regardless of type Bilateral involvement more common than with primary tumor.	As above	As above	Guarded
TVT	Venereal transmission; hematogenous or lymphatic metastasis	Pale white-pink mass in iris or ciliary body Involvement of other mucosal surfaces	As above	Specific chemotherapy	Guarded to poor, especially with secondary ocular disease
All Tumors					
		Nonspecific: 1. Secondary glaucoma: a. Tumor invasion of iridocorneal angle b. PIFM development over irido corneal angle 2. Lens displacement 3. Anterior uveitis 4. Hyphema			

LSA, Lymphosarcoma; *TVT,* transmissible venereal tumor; PIFM, preiridal fibrovascular membrane.

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CHAPTER 100

Glaucoma

Ian P. Herring

Definition

I. Glaucoma is a multifactorial disease characterized by an elevation of intraocular pressure (IOP) beyond that which is compatible with the health of the eye.
II. Glaucoma results in permanent vision loss through death of retinal photoreceptors, retinal ganglion cells, and their axons (i.e., optic nerve).

Causes

I. Primary and breed-related glaucoma (Bedford, 1975)
   A. Primary glaucoma is a heritable condition with certain breed predispositions (Table 100-1).
   B. Overall prevalence of primary breed-related glaucoma in purebred dogs has recently been estimated at approximately 0.89%, with the prevalence in certain breeds exceeding 5% (Gelatt and Mackay, 2004).
   C. IOP elevation occurs from a spontaneous increase in aqueous outflow resistance at the level of the iridocorneal angle and ciliary cleft.
   D. Glaucoma is often categorized based on gonioscopic appearance of the filtration angle.
      1. Open angle
         a. Angle appears normal before and in the early stages of glaucoma.
         b. Angle collapse and closure occurs late in the disease.
      2. Narrow to closed angle (most common form of canine primary glaucoma)
         a. Pectinate ligaments appear shortened or nonexistent.
         b. Base of iris is in apposition (or nearly so) to the peripheral cornea.
      3. Pectinate ligament dysplasia and mesodermal goniodysgenesis
         a. Individual pectinate ligaments, if visualized, are short and wide.
         b. In some cases a solid sheet of tissue with occasional "flow holes" spans the filtration angle.
         c. Concurrent narrowing or closure of the angle may be noted.
   E. Bilateral disease potential exists.
      1. Both eyes usually do not become affected at the same time.

TABLE 100-1

Dog Breeds Predisposed to Primary Glaucoma

BREED	GONIOSCOPIC FILTRATION ANGLE APPEARANCE
Alaskan malamute	Not defined
Akita	Narrow to closed
American cocker spaniel	Narrow to closed
Basset hound	Narrow to closed/mesodermal goniodysgenesis
Beagle	Open
Boston terrier	Not defined
Bouvier des Flandres	Narrow/pectinate ligament dysplasia
Bullmastiff	Not defined
Chow chow	Narrow to closed
Dalmatian	Not defined
English cocker spaniel	Narrow to closed
English springer spaniel	Narrow to closed
Fat-coated retriever	Narrow to closed
Giant schnauzer	Not defined
Great Dane	Not defined
Greyhound	Not defined
Italian greyhound	Not defined
Miniature pinscher	Not defined
Miniature schnauzer	Not defined
Norwegian elkhound	Open
Poodle	Open/narrow to closed
Samoyed	Narrow to closed
Shar-pei	Narrow to closed
Shih tzu	Not defined
Shiba Inu	Narrow to closed/pectinate ligament dysplasia
Siberian husky	Narrow to closed/pectinate ligament dysplasia
Smooth-haired fox terrier	Not defined
Welsh springer spaniel	Narrow to closed
Wirehaired fox terrier	Not defined

2. The exception to this is open-angle glaucoma, in which bilateral onset is common.

F. Although filtration angle malformations are congenital, most animals are clinically afflicted at 3 to 10 years of age.

G. Primary glaucoma occurs in cats, but is rare.

II. Secondary glaucoma

A. It often affects only one eye.

B. It may be bilateral if the inciting condition affects both eyes.

C. Common causes are as follows:

1. Uveitis
   a. Acute uveitis, if severe enough, may cause IOP elevations related to blockage of aqueous drainage by iridal swelling, fibrin, hyphema, or hypopyon.
   b. With chronicity, uveitis of any cause has the potential to cause glaucoma.
   c. Chronic uveitis is the most common cause of glaucoma in cats (Wilcock et al., 1990).
2. Hyphema
   a. Hyphema may be associated with trauma, coagulopathies, uveitis, intraocular neoplasia, hypertension, and retinal detachment.
   b. Glaucoma is likely in dogs with hyphema secondary to retinal disease (Nelms et al., 1993).
3. Lens luxation (Curtis, 1990)
   a. Distinct breed predisposition exists for spontaneous lens luxation in dogs.
   b. Luxation may also occur in association with hypermature cataracts, chronic uveitis, or senile degeneration of lens zonules.
   c. Severe secondary glaucoma can occur rapidly after anterior lens luxation and is the major reason to recommend early surgical removal of displaced lenses.
   d. Animals with lens subluxation and posterior lens luxation are also at risk for development of glaucoma, but less so than animals with anterior lens luxation (Glover et al., 1995).
4. Intraocular neoplasia
   a. It may cause glaucoma through mechanical compression of the filtration angle, obstruction of the angle with tumor cells, preiridal fibrovascular membrane formation, or hyphema.
   b. Diffuse iris melanoma is a common cause of glaucoma in cats (Wilcock et al., 1990).
5. Melanocytic glaucoma (Peterson-Jones, 1991)
   a. It occurs in middle-aged to older Cairn and Scottish terriers.
   b. Pigmented cells accumulate in the filtration angle and within the scleral venous plexus.
6. Aqueous humor misdirection (Czederpiltz et al., 2005)
   a. Anterior displacement of the lens resulting in a shallow anterior chamber is a prominent feature of the condition.
   b. It occurs in older cats and is often unilateral at initial presentation.
7. Trauma
   a. Blunt ocular trauma can occasionally result in acute, severe elevations in IOP.
   b. Hyphema after blunt trauma may predispose to glaucoma.
8. Aphakia
   a. Glaucoma may occur after lens removal surgery (Paulsen et al., 1986; Biros et al., 2000; Lannek and Miller, 2001).
   b. It may develop early in the postoperative period or months to years after surgery.

D. Breed-related conditions resulting in secondary glaucoma in the dog are as follows:

1. Lens luxations in terrier breeds
2. Ocular melanosis in Cairn and Scottish terriers
3. Iridociliary cysts and uveitis in golden retrievers
4. Vogt-Koyanagi-Harada (VKH)–like syndrome in Arctic Circle and other breeds

III. Congenital glaucoma

A. It is rare in dogs and cats.

B. It is related to extensive maldevelopment of the anterior segment of the eye, including the filtration angle.

C. IOP elevation occurs within the first few months of life.

Pathophysiology

I. Normal IOP and aqueous humor dynamics

A. The range of normal IOP in dogs and cats is approximately 10 to 25 mm Hg.

B. IOP is primarily determined by (1) the balance between aqueous humor production by the nonpigmented epithelium of the ciliary body and (2) aqueous humor outflow through the conventional (trabecular) and unconventional (uveoscleral) routes.

II. Aqueous outflow obstruction

A. Outflow obstruction in primary glaucoma is related to poorly understood biochemical and ultrastructural changes at the level of the filtration angle and ciliary cleft that may include the following:

1. Altered or increased glycosaminoglycan deposition within the aqueous outflow pathway in open-angle glaucoma
2. Reverse pupillary block (Miller et al., 2003)
3. Anterior segment inflammation and pigment dispersion (Reilly et al., 2005)
4. Physical closure of the filtration angle (Gum et al., 1993)

B. Outflow obstruction in secondary glaucoma may be related to a number of mechanisms (Peiffer et al., 1990; Smith et al., 1993).

1. Preiridal fibrovascular membrane formation associated with uveitis, chronic retinal detachment, or intraocular neoplasia may occlude the filtration angle.
2. Cellular deposition may occlude the filtration angle in glaucoma secondary to inflammation, hyphema, melanosis, and intraocular neoplasia.

3. Peripheral anterior synechiae may form and close the filtration angle in glaucoma secondary to uveitis, anterior lens luxation, or intraocular neoplasia.
4. Pupillary block may occur from annular posterior synechia, anterior vitreous herniation, and subluxated lenses.
   a. Aqueous humor is unable to flow through the blocked pupillary aperture.
   b. Pressure builds behind the iris, causing it to balloon forward and close the filtration angle.

III. Mechanisms of ocular pathology in glaucoma
   A. Direct pressure effects
      1. Corneal endothelial cell decompensation and death resulting in corneal stromal edema
      2. Stretching of globe (buphthalmos)
      3. Iris sphincter paralysis resulting in mydriasis
      4. Optic nerve compression and shearing at the lamina cribrosa resulting in axonal death
   B. Effect of abnormal aqueous humor composition and flow
      1. Cataract formation
      2. Corneal endothelial decompensation and death resulting in corneal stromal edema
   C. Excitotoxic amino acids (e.g., glutamate)
      1. Glutamate is neurotoxic to retinal ganglion cells and axons of the optic nerve.
      2. Elevated intravitreal glutamate levels have been demonstrated in affected dogs (Brooks et al., 1997).
      3. Histologic evidence of retinal glutamate toxicosis has been documented in dogs with primary glaucoma (McIlnay et al., 2004).
   D. Microcirculatory disturbance
      1. Optic nerve head microcirculatory autoregulation mechanisms may be defective in primary glaucoma.
      2. IOP-induced ischemia results in retinal ganglion cell death or increases the cells' susceptibility to excitotoxic amino acids.
   E. Permanent vision loss
      1. It is related primarily to damage to the ganglion cell layer of the retina and the optic nerve.
      2. Rapidity of onset is related to the severity and duration of IOP elevations.

Clinical Signs

I. Acute
   A. Ocular pain manifested by blepharospasm and/or rubbing eye
   B. Ocular redness from conjunctival hyperemia and/or episcleral injection
   C. Ocular discharge
   D. Corneal edema
   E. Dilated pupil
   F. Vision loss
   G. Optic nerve and peripapillary retinal edema and hemorrhage
   H. Behavioral changes related to vision loss and ocular discomfort

II. Chronic
   A. Possibly any acute sign
   B. Buphthalmos: enlargement of globe
   C. Haab's striae: gray to white linear corneal opacities caused by breaks in Descemet's membrane related to corneal stretching
   D. Lens subluxation and aphakic crescent: secondary to lens zonule rupture as the globe enlarges
   E. Cataract
   F. Peripapillary tapetal hyperreflectivity or hyperpigmentation
   G. Optic nerve cupping and atrophy

Diagnosis

I. Suggestive clinical signs
II. High likelihood in predisposed breeds of dogs (see Table 100-1)
III. IOP measurement (tonometry)
   A. IOP is measured by applanation, indentation, or rebound tonometry.
      1. Indentation tonometers (e.g., Schiotz) are very affordable and provide a reasonably accurate estimation of IOP, but they can be difficult to use in uncooperative animals.
      2. Applanation tonometers are more expensive but are convenient to use and are more accurate than indentation tonometers.
      3. Rebound tonometers are also expensive, but are convenient to use and correlate well with applanation tonometers (Gorig et al., 2006).
      4. Topical ophthalmic anesthetic is required for indentation and applanation tonometry, but is not used for rebound tonometry.
      5. Digital (palpation) estimation of IOP is unreliable.
   B. IOP is measured in both eyes for comparison.
   C. Animals with clinical disease usually have an obvious IOP elevation on presentation, although an elevation in pressure of >5 mm Hg in the affected eye compared with the normal eye is also suggestive of glaucoma.
   D. A single reading may not reflect the true status of IOP, because IOP in glaucoma may vary widely during the day, as well as from day to day.
   E. Several factors may lead to artifactual elevation in tonometric readings.
      1. Animal excitement or fear
      2. Excessive restraint, particularly with pressure around the neck
      3. Blepharospasm
      4. Inadvertent digital pressure on the eye when opening the eyelids
IV. Gonioscopy
   A. Gonioscopy is visualization of the filtration drainage angle using a goniolens.
   B. It is useful in distinguishing primary from secondary glaucoma.
   C. It may be difficult to perform in affected eyes because of corneal edema.

D. Filtration angle abnormalities are common in the unaffected eye of animals with primary glaucoma.

Differential Diagnosis

I. Uveitis
II. Corneal edema from other causes
III. Scleritis
IV. Exophthalmos
V. Lagophthalmos

Treatment

I. General concepts
  A. Control of IOP is the only known means by which the vision loss can be delayed.
  B. No known cure exists for glaucoma.
  C. At best, the disease can be controlled for a period.
  D. Glaucoma must be treated aggressively with a combination of medical and surgical therapy.
II. Goals of therapy
  A. Preservation of vision in affected eyes
  B. Prophylactic therapy for unaffected, at-risk eyes
  C. Resolution of pain
III. Treatment strategies
  A. In visual or recently visual eyes with significantly elevated IOPs (>35 to 40 mm Hg), emergency treatment with hyperosmotic medications or topical ophthalmic prostaglandin analogues is indicated.
    1. Maintenance medications are administered concurrently.
    2. Early surgical treatment is also considered.
  B. With signs consistent with glaucoma but IOPs <35 mm Hg, hyperosmotic treatment is unnecessary.
    1. Other medical antiglaucoma treatments are instituted immediately.
    2. Early surgical treatment may also be considered.
  C. In eyes that are blind and buphthalmic from chronic, end-stage glaucoma, a salvage procedure is recommended, because such eyes do not regain vision after control of IOP and benefit minimally from prolonged medical therapy.
  D. In primary glaucoma cases, prophylactic medication of the unaffected eye is recommended (Miller et al., 2000).
  E. Cases of secondary glaucoma must be treated for both the glaucoma and the underlying condition.
IV. Medical antiglaucoma therapy
  A. Emergency treatment
    1. Topical ophthalmic prostaglandin analogue (e.g. latanoprost), one drop to the affected eye
      a. Repeated in 5 to 10 minutes
      b. Often results in a dramatic IOP reduction within 20 to 40 minutes
      c. Contraindicated if glaucoma is secondary to anterior lens luxation
      d. Can combine with hyperosmotic therapy, but this is generally unnecessary
    2. Mannitol 1 to 2 g/kg IV over 20 to 40 minutes
      a. This medication is hyperosmotic.
      b. Water is withheld for 1 to 2 hours to possibly increase its effect.
      c. It is contraindicated in animals with congestive heart failure.
      d. Avoid use in dehydrated animals and those with renal failure.
      e. Dose may be repeated in 2 to 4 hours if needed.
    3. Glycerin 1 to 2 g/kg PO
      a. This medication is hyperosmotic.
      b. It is less effective than IV mannitol.
      c. It is contraindicated in diabetics and animals with congestive heart failure.
      d. Common gastrointestinal side effects are seen.
    4. Anterior chamber centesis
      a. Centesis is generally not recommended as a therapeutic procedure.
      b. The IOP reduction achieved via centesis is short-lived.
      c. Potential complications include laceration of iris or lens, hyphema, and introduction of infection.
  B. Maintenance medications
    1. In most animals, a combination of medications is required to achieve and maintain satisfactory control of IOP.
    2. Carbonic anhydrase inhibitors are generally considered the most effective medications for IOP reduction in the dog, and topical agents have largely replaced the oral forms.
      a. Dorzolamide *(Trusopt),* one drop to affected eye BID to TID
      b. Brinzolamide *(Azopt),* one drop to affected eye BID to TID
      c. Dorzolamide combined with timolol *(Cosopt),* one drop to affected eye TID
      d. Methazolamide 2 to 4 mg/kg PO BID to TID
      e. Acetazolamide 5 to 10 mg/kg PO BID to TID; CAUTION: Often avoided because side effects common
    3. Miotic drugs are moderately to highly effective, but they are contraindicated in the presence of anterior lens luxation and will exacerbate uveitis.
      a. Pilocarpine 2%, one drop to affected eye TID to QID
      b. Demecarium bromide 0.125%, one drop to affected eye BID
        (1) No longer commercially available
        (2) Can be obtained from compounding pharmacies
        (3) Should not be used in cats
    4. Prostaglandin analogues are moderately to highly effective but are contraindicated in the presence of anterior lens luxation and may exacerbate uveitis.
      a. Latanoprost *(Xalatan),* one drop to affected eye SID to BID
      b. Bimatoprost *(Lumigan),* one drop to affected eye SID to BID
      c. Travoprost *(Travatan),* one drop to affected eye SID to BID

d. Also effective emergency antiglaucoma medications
e. Ineffective in cats

5. Beta-adrenergic blocking agents are mildly to moderately effective, but cannot often be relied on as the sole medical therapy.
   a. Timolol maleate 0.5%, one drop to affected eye BID
   b. Betaxolol 0.5%, one drop to affected eye BID
6. Sympathomimetics are only mildly effective and cannot be relied on as the sole medical therapy.
   a. Epinephrine 1% or 2%, one drop to affected eye BID to QID
   b. Dipivalyl epinephrine (dipivefrin), one drop to affected eye BID to QID

C. Prophylactic medication (Slater et al., 1986; Miller et al., 2000)
1. Medicating the clinically unaffected eyes of dogs with primary glaucoma delays the onset of clinical disease.
2. Topical β-adrenergic blocking agents and topical miotic agents (demecarium bromide) appear equally effective at delaying disease onset (Miller et al., 2000).
3. Other treatments (topical carbonic anhydrase inhibitors, topical prostaglandin analogues) may also be useful.

D. Potential future medical treatment modalities
1. Excitatory amino acid antagonists
2. Calcium channel blockers

E. Contraindicated medication
1. Use of topical mydriatic agents, particularly atropine, is contraindicated in glaucomatous animals.
2. When treating other ophthalmic conditions (e.g., uveitis) in dogs predisposed to primary glaucoma, topical atropine must be used with caution.

F. Topical corticosteroid medications
1. For underlying uveitis and inflammation
2. When the cornea is not ulcerated

V. Surgical therapy

A. In visual or potentially visual eyes, surgery is recommended early in the disease process when the animal has the most to gain.

B. Prophylactic surgery in normotensive, at-risk eyes is controversial and generally not recommended.

C. Surgery is rarely, if ever, curative, and most animals continue to require some level of medical therapy for optimal IOP control.

D. Surgical procedures are designed to increase aqueous humor outflow or decrease aqueous production.

E. Procedures that increase aqueous humor outflow include the following aqueous humor shunting procedures (Peiffer et al., 1977; Gelatt et al., 1987; Bedford, 1989; Bentley et al., 1996, 1999; Cullen, 2004):
1. Gonioimplants
   a. Aqueous humor is diverted from the anterior chamber via synthetic tubing to an explant in the subconjunctival space.
   b. Aqueous humor diversion to the frontal sinus has also been reported recently.
   c. Synthetic implants may be nonvalved or may use a valve that opens only above a specific pressure to prevent postoperative ocular hypotony.
   d. Several subconjunctival explant configurations have been devised to increase the absorptive surface area for diverted aqueous humor.
   e. Gonioimplants are the most common and successful aqueous shunting procedure in use today.
2. Iridencleisis
   a. In this procedure, a radial section of iris is positioned under the bulbar conjunctiva through a limbal incision, allowing drainage of aqueous humor to the subconjunctival space.
   b. Because of low success rates, this procedure is uncommonly performed.
3. Cyclodialysis
   a. Sclerotomy is performed posterior to the limbus beneath the bulbar conjunctiva.
   b. By inserting a spatula through the sclerotomy site between the iris and ciliary body and the overlying sclera, a fistula is then created between the anterior chamber and the sclerotomy site, allowing an alternate route for aqueous egress.
   c. Cyclodialysis may be combined with an iridencleisis procedure.
   d. Because of low success rates, this procedure is uncommonly performed.
4. Acute complications
   a. Severe iridocyclitis and hyphema are the most common complications.
   b. Complication rates and severity of complications are lowest with gonioimplants.
5. Long-term complications
   a. They include shunt failure from occlusion by fibrin, cellular debris, or bleb fibrosis.
   b. Tissue plasminogen activator may be used to dissolve fibrin in a blockage.
   c. Intraoperative use of antifibrotic medications (e.g., mitomycin C) may delay fibrosis at the surgical site, but improved long-term bleb function associated with this treatment remains unsubstantiated.
   d. Surgical resection of fibrotic tissue may also prolong success.

F. Procedures that reduce aqueous humor production include the following:
1. Cyclophotocoagulation involves partial laser ablation of ciliary body epithelium.
   a. Neodymium:yttrium-aluminum-garnet (Nd:YAG) and diode lasers are both effective.
   b. Laser energy is applied transsclerally with the probe placed over the region of the pars plicata of the ciliary body.
   c. Potential complications include corneal ulceration, hyphema, cataract formation, iridocyclitis, and postoperative IOP elevations.

2. Cyclocryotherapy involves application of extreme cold to the surface of the globe over the region of the ciliary body to cause partial destruction of the ciliary body.
   a. Liquid nitrogen and nitrous oxide are both effective cryogens.
   b. Complications include uveitis and postoperative IOP spikes that may be prolonged and severe, limiting the usefulness of this technique in visual eyes.

G. Combination surgical procedures using laser cyclophotocoagulation and anterior chamber shunts are commonly performed (Bentley et al., 1999; Sapienza and van der Woerdt, 2005).

VI. Salvage procedures for end-stage glaucomatous eyes
   A. Goals
      1. After vision is lost, the primary goal of therapy is animal comfort.
      2. Surgical procedures to maintain control of IOP are rarely curative, and many animals become refractory to medical therapy.
      3. Medical therapy is also expensive and has potential side effects.
      4. Salvage procedures are considered for most blind eyes.
   B. Enucleation
      1. Surgical removal of the globe relieves discomfort associated with glaucoma and has few complications.
      2. Ancillary procedures to prevent inward sagging of eyelids into an empty orbit may be performed to improve postoperative cosmesis.
         a. Orbital implant of silicone or methylmethacrylate (Nasisse et al., 1988b)
         b. Nonabsorbable suture mesh implant (Hamor et al., 1993)
         c. Reconstruction using autogenous tissues (Mughannam and Reinke, 1994)
   C. Evisceration with intrascleral prosthesis (Brightman et al., 1977)
      1. Intraocular contents are removed and replaced with a silicone prosthetic sphere.
      2. Significant corneal scarring usually results, but animals are eventually comfortable and owner satisfaction with cosmesis is high.
      3. Intrascleral prosthesis is contraindicated in glaucoma secondary to intraocular neoplasia and has a high complication rate in cases with preexisting corneal ulceration or keratoconjunctivitis sicca.
   D. Intravitreal gentamicin injection in dogs (Moller et al., 1986)
      1. Gentamicin (15 to 25 mg) injected into the vitreous destroys the ciliary epithelium.
      2. Agent is toxic to lens and retina; therefore the procedure is only performed on blind eyes.
      3. Concurrent intravitreal injection of dexamethasone (0.25 to 0.5 mg) and/or topical treatment with ophthalmic corticosteroid medications is required to control postoperative intraocular inflammation.
      4. Volume of aqueous humor or vitreous equal to the gentamicin and dexamethasone injection volume is removed from the eye by centesis before injection.
      5. Inadvertent lens laceration during injection results in severe lens-induced uveitis.
      6. Outcome is difficult to predict and may include a normotensive and cosmetic eye, recurrence of glaucoma, or phthisis bulbi.
      7. Procedure is *not* performed in cats, because of their potential for forming posttraumatic ocular sarcomas.

VII. Treatment of the underlying disease process in secondary glaucomas
   A. Intracapsular lens extraction is indicated in cases of anterior lens luxation.
   B. Appropriate treatment for uveitis with elucidation and treatment of underlying diseases is required in cases of glaucoma secondary to uveitis.
   C. Enucleation is recommended for eyes with glaucoma secondary to intraocular neoplasia.

VIII. Prognosis
   A. Long-term prognosis for maintenance of vision in eyes affected with primary glaucoma is guarded to poor.
   B. Visual prognosis in eyes with secondary glaucoma is guarded and depends partly on the success of managing the underlying condition.

Monitoring of Animal

I. Once the disease is under control, IOP is monitored regularly (every 3 to 4 weeks) by tonometry.

II. It is unclear what level of IOP is safe in glaucomatous eyes.
   A. In an affected but visual eye, a high-normal IOP (20 to 25 mm Hg) may lead to continued vision loss and indicates a need for more aggressive medical and/or surgical measures.
   B. Ideal IOP in visual eyes is ≤15 to 20 mm Hg to prevent continued optic nerve damage.

III. Permanent vision loss, especially with concurrent loss of IOP control, is an indication for a salvage procedure.

IV. Educating the owner about the clinical signs of glaucoma may improve early detection of rising IOP or pressure spikes, especially in the normal eye.

V. Monitoring IOP of the unaffected eye in primary glaucoma cases is performed regularly (every 6 to 12 weeks) to allow early detection of IOP elevation.

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CHAPTER 101

Diseases of the Lens and Vitreous

Carmen M.H. Colitz

CONGENITAL/DEVELOPMENTAL DISORDERS

See Table 101-1.

ACQUIRED DISORDERS

Cataracts

Definition

I. Any opacity of the lens regardless of the cause
II. Classification of cataracts (Davidson et al., 1990; Davidson and Nelms, 1999)
  A. By degree of opacification of lens and stage of maturity
    1. Incipient: <10% of tapetal reflection obstructed
    2. Early immature: 10% to 50% of tapetal reflection obstructed
    3. Late immature: 51% to 99% of tapetal reflection obstructed
    4. Mature: 100% of tapetal reflection obstructed
    5. Hypermature
      a. Cortical lens material may undergo liquefaction, and part of the tapetal reflex may be seen.
      b. Lens capsule may be wrinkled, with multifocal, dense, white plaques.
      c. Anterior chamber depth may be increased.
      d. Signs of lens-induced uveitis may be noted.
      e. Resorption of lens material with restoration of functional vision is uncommon except in dogs <1 year of age.
    6. Morgagnian: type of hypermature cataract wherein the nucleus falls into the ventral portion of the lens capsule
  B. By location
    1. General locations for opacities are as follows:
      a. Anterior or posterior capsule
      b. Anterior or posterior cortex
      c. Nucleus
      d. Equator
    2. Progression of cortical and equatorial cataracts more likely than capsular and nuclear cataracts
  C. By age of onset (does not imply cause)
    1. Congenital: present at birth
    2. Juvenile: few months to 6 years
    3. Senile: dog >6 years in large breeds and >10 years in small breeds

Causes

I. Congenital
  A. Opacification of lens present at birth
    1. From abnormal formation of primary or secondary lens fibers
    2. From exposure of the dam to toxic or infectious agents (Carmichael et al., 1965; Koch and Rubin, 1967)
  B. Inherited in some breeds (Table 101-2)
II. Inherited
  A. See Table 101-2 for affected breeds.
  B. Specific mutations have not been identified in most breeds of dog.
  C. Recently, mutations in the HSF4 gene have been identified in cataracts occurring in three breeds of dogs (Mellersh et al., 2006).
    1. Australian shepherd: inherited as an autosomal dominant trait
    2. Staffordshire bull terrier and Boston terrier: inherited as an autosomal recessive trait
III. Nutritional
  A. Arginine deficiency
    1. Puppies and kittens fed milk replacer
    2. Begins during third week after birth
  B. Other amino acid deficiencies: rare in dogs and cats
IV. Metabolic
  A. Hyperglycemia
    1. Elevated glucose levels saturate hexokinase and activate sorbitol pathway, allowing glucose to accumulate in the lens, leading to rupture of the lens fibers and opacification.
    2. Diabetes mellitus is a common cause of cataracts in dogs.
  B. Hypocalcemia
    1. Associated with renal failure, primary hypoparathyroidism, or secondary hypoparathyroidism
    2. Bilaterally symmetrical, multifocal, punctate opacities in outer cortex that progress to coalescing lamellar cortical opacities (Paterson and Delamere, 1992)

TABLE 101-1

Congenital and Developmental Disorders of the Lens

LESION	DEFINITION	CAUSE	CLINICAL FINDINGS	DIAGNOSTICS	TREATMENT
Aphakia	Absence of lens	Developmental anomaly	Absence of lens or lens capsule	Dilated ophthalmologic examination	None
Microphakia	Small lens	Developmental anomaly	Reduced lens diameter, elongated ciliary processes and zonules, whole lens visible in pupil aperture	Dilated ophthalmologic examination	No treatment is indicated, but monitor for changes in lens position and opacification; if either occurs, then extract lens
Lens coloboma of equatorial lens	Notchlike defect of equatorial lens	Developmental anomaly	Typically see notch at ventral aspect of lens	Dilated ophthalmologic examination	No treatment is indicated unless lens luxates or cataract occurs, then extract lens
Lenticonus/ lentiglobus	Cone-like deformity of lens/cone-like deformation of globe	Developmental anomaly	Usually see posterior protrusion of lens into vitreous; cataract may be present; may be associated with microphthalmia	Ophthalmic examination with dilated pupil; ultrasonography	Lensectomy if cataract present with vision impairments
Persistent hyperplastic tunica vasculosa lentis (PHTVL)	Embryonic vasculature around lens fails to regress	Developmental anomaly; may be inherited in the Doberman pinscher	Leucocoria, cataract, ± abnormal pupil function; inability to visualize fundus	Slit-lamp examination; ultrasonography	Indicated if vision impaired: lens extraction and anterior vitrectomy
Persistent hyperplastic primary vitreous (PHPV)	Embryonic vasculature extending from the optic nerve to the posterior lens capsule	Developmental anomaly; may be inherited in the Doberman pinscher	Leucocoria; cataract, inability to visualize fundus	Dilated ophthalmologic examination; ultrasonography	Indicated if vision is impaired: lens extraction and anterior vitrectomy
Persistent hyaloid artery	Failure of regression of a portion or all of the hyaloid artery	Developmental anomaly	A tubular vessel-like structure located between the lens and optic nerve that may or may not contain blood; usually seen as a tubular vessel-like structure adhered to the posterior lens capsule	Ophthalmic examination with dilated pupil and slit-lamp biomicroscopy	No treatment is indicated

TABLE 101-2

Characteristics of Selected Hereditary Cataracts in Dogs

BREED*	AGE OF ONSET	MODE OF INHERITANCE	LOCATION	PROGRESSION	ASSOCIATED FINDINGS†
Afghan	Juvenile	Not defined	Equatorial	Progressive	None
Akita	Congenital	Not defined	Nuclear and cortical	Variable progression	Microphthalmia, retinal dysplasia
Alaskan malamute	Juvenile	Not defined	Posterior subcapsular	Variable progression	None
American cocker spaniel	Juvenile or adult	Autosomal recessive	Cortical	Progressive	None
Australian shepherd dog	Congenital or juvenile	Autosomal dominant	Nuclear and cortical	Nonprogressive	Microphthalmia, retinal dysplasia, colobomas
Basenji	Congenital	Not defined	Anterior capsular	Nonprogressive	Persistent pupillary membranes (PPM)
Beagle	Congenital	Not defined	Anterior capsular	Nonprogressive	PPM
Boston terrier	Congenital or juvenile	Autosomal recessive	Nuclear and cortical	Progressive	None
	Adult	Not defined	Equatorial, subcapsular	Slow progressive	None
Cavalier King Charles spaniel	Congenital	Not defined	Nuclear and cortical	Progressive	Microphthalamia, lenticonus
Chesapeake Bay retriever	Juvenile or adult	Not defined	Posterior subcapsular	Variable progression	None
Chow chow	Congenital	Not defined	Nuclear and cortical	Variable progression	Microphthalmia, PPM, retinal dysplasia, nystagmus
Collie	Congenital	Not defined	Nuclear and cortical	Unknown	Microphthalmia, retinal dysplasia, colobomas
Doberman pinscher	Congenital	Dominant with incomplete penetrance	Posterior subcapsular	Variable progression	Persistent hyperplastic primary vitreous or tunica vasculosa lentis
English cocker spaniel	Congenital	Not defined	Anterior capsular	Nonprogressive	PPM, microphthalmia, retinal dysplasia
Flat-coated retriever	Juvenile or adult	Not defined	Posterior subcapsular	Nonprogressive	None
German shepherd dog	Congenital	Autosomal dominant	Nuclear	Nonprogressive	None
	Juvenile	Autosomal recessive	Posterior Y suture	Variable progression	None
Golden retriever	Juvenile or adult	Not defined	Perinuclear	Progressive	None
	Juvenile or adult	Not defined	Posterior subcapsular	Nonprogressive	None
Labrador retriever	Congenital	Incomplete dominance	Nuclear and cortical	Variable progression	Vitreoretinal dysplasia, skeletal chondrodysplasia
	Juvenile or adult	Not defined	Perinuclear	Progressive	None
	Juvenile or adult	Not defined	Posterior subcapsular	Nonprogressive	None
Miniature schnauzer	Congenital	Autosomal recessive	Nuclear and cortical	Variable progression	Posterior lenticonus, microphthalmia
Old English sheepdog	Congenital	Not defined	Nuclear and cortical	Progressive	PPM, microphthalmia, retinal dysplasia
Poodle					
Toy and miniature	Juvenile or adult	Not defined	Cortical	Progressive	None
Standard	Juvenile	Not defined	Equatorial	Progressive	None

Modified from English RV: Diseases of the lens and vitreous. p. 1036. In Morgan RW (ed): Handbook of Small Animal Practice. 3rd Ed. WB Saunders, Philadelphia, 1997 with permission.

*All dogs with cataracts should be evaluated for retinal degeneration.

†These findings may or may not be present.

TABLE 101-2

Characteristics of Selected Hereditary Cataracts in Dogs—*cont'd*

BREED*	AGE OF ONSET	MODE OF INHERITANCE	LOCATION	PROGRESSION	ASSOCIATED FINDINGS†
Rottweiler	Juvenile or adult	Not defined	Posterior subcapsular and cortical	Nonprogressive	None
Samoyed	Congenital	Autosomal recessive	Nuclear and cortical	Variable progression	Retinal detachment, skeletal chondrodysplasia
Siberian husky	Juvenile	Not defined	Posterior subcapsular, equatorial	Variable progression	None
Staffordshire terrier	Congenital Congenital	Not defined Not defined	Nuclear and cortical Posterior subcapsular	Progressive Nonprogressive	None Persistent hyperplastic primary vitreous or tunica vasculosa lentis
Welsh springer spaniel	Juvenile	Autosomal recessive	Cortical	Progressive	None
West Highland white terrier	Congenital Juvenile	Autosomal recessive Not defined	Nuclear and cortical Posterior Y suture	Progressive Nonprogressive	Microphthalmia None

C. Hypercalcemia: abnormalities in lens metabolism that cause lens epithelial cell death (Paterson and Delamere, 1992)

V. Exposure to toxins
  A. Most toxic cataracts begin in the cortical region near the equator or in the Y-suture regions.
  B. Drugs administered at much higher doses than normal can cause such cataracts.
    1. Diazoxide (Schiavo, 1976)
    2. Phenylpiperazine (Susick et al., 1991)
    3. Dinitrophenol (Martin, 1975)
    4. Long-term ketoconazole administration at 6.0 to 13.9 mg/kg/day (da Costa et al., 1996)
    5. Chronic oral administration of dimethyl sulfoxide at 2.5 to 40 g/kg
    6. Other examples: naphthalene, ouabain, digitalis, heavy metals, chlorpromazine, diquat, and hygromycin B (Sanford et al., 1981; Davidson and Nelms, 1999)

VI. Environmental or physical injury
  A. Blunt trauma (Davidson et al., 1991)
    1. Blunt injury causes contrecoup or compressive forces that damage lens epithelium and lens fiber cells.
    2. It may also cause lens capsule rupture and phacoclastic uveitis (see Chapter 99).
  B. Sharp trauma (Davidson et al., 1991)
    1. Penetrating ocular trauma that disrupts the anterior lens capsule
    2. Causes cataractous changes and phacoclastic uveitis
  C. Irradiation
    1. Orthovoltage irradiation (Jamieson et al., 1991; Paterson and Delamere, 1992)
    2. Megavoltage irradiation (Roberts et al., 1987; Paterson and Delamere, 1992)
    3. Ultraviolet irradiation
  D. Electric cord shock (Reddy, 1999)
  E. Microwave exposure (Michaelson et al., 1971)

VII. Secondary to inflammation (Engle and Spencer, 1995)
  A. Moderate to severe uveitis, regardless of cause, can result in anterior subcapsular or equatorial cataracts.
  B. Inflammatory mediators may diffuse across the lens capsule and disrupt normal metabolism of the lens epithelial cells.
  C. Resorbing, typically hypermature, cataracts cause lens-induced (phacolytic) uveitis, although any stage of cataract can cause uveitis.

VIII. Secondary to retinal degeneration (Zigler and Hess, 1985)
  A. Cataractous changes from release of water-soluble dialdehydes from peroxidation of photoreceptor lipid membranes are toxic to lens cellular membranes.
  B. These cataracts begin at the posterior subcortical region and progress anteriorly.

IX. Secondary to other ocular defects
  A. Persistent pupillary membranes (Barnett and Knight, 1969)
  B. Persistent tunica vasculosa lentis (Boeve et al., 1992)
  C. Persistent hyperplastic primary vitreous (Boeve et al., 1992)
  D. Anterior segment dysgenesis (Cook, 1995)
  E. Lens instability (subluxation or luxation)

X. Senility (Davidson and Nelms, 1999)
  A. Secondary to age-related changes in lens metabolism
  B. Equatorial cortical opacities common

Pathophysiology

I. Normal lens metabolism is directed toward maintaining transparency.

II. Any abnormality in the metabolism of the lens may result in a cataract through the following mechanisms:
  A. Changes in the ratio of lens protein types
  B. Alterations in metabolic pumps on the cell membranes
  C. Alterations in antioxidant activity
  D. Degradation of lens proteins

Clinical Signs

I. Age and breed of dog may indicate an inherited predisposition.

II. Visual impairment may be difficult for the owner to assess.
  A. Dogs often compensate for vision loss from slowly progressive cataracts.
  B. Dogs also compensate well with unilateral cataracts.

III. Leukocoria (change in color of the lens to white or blue) may be the first sign noticed.

IV. History may include the following:
  A. Previous uveitis
  B. Previous trauma
  C. Milk replacer fed when very young
  D. Variable visual impairment based on stage and location of cataracts
    1. Incipient: no change in vision
    2. Early immature: no change in vision
    3. Late immature: may see impairment on affected sides
    4. Mature: impairment on the affected sides
    5. Hypermature: impairment on affected sides unless resorption allows return of vision

V. Clinical signs of lens-induced uveitis may be present.
  A. Corneal edema, conjunctival hyperemia
  B. Aqueous flare
  C. Possibly miosis
  D. Blepharospasm and photophobia
  E. Associated with most stages of cataract
  F. Not always clinically evident

VI. Signs of secondary glaucoma may also occur.
  A. Clinical signs similar to those of lens-induced uveitis
  B. Scleral injection
  C. Possibly buphthalmia
  D. Elevated ocular pressure

VII. Lens luxation is uncommon except in hypermature cataracts, but subluxation may be evident with buphthalmia.

Diagnosis

I. Complete ophthalmic examination
  A. Slit lamp biomicroscopy with a dilated pupil to locate and stage the cataract, and to assess the cornea and anterior chamber
    1. Incipient cataracts are very small and difficult to locate without dilation and slit lamp biomicroscopy.
    2. Immature cataracts are more evident but still require magnification to characterize.
    3. Fundic examination is still possible with all early-immature and some advanced, late-immature cataracts.
    4. Mature cataracts involve the entire lens and do not allow the fundus to be visualized.
    5. Hypermature cataracts have an irregular anterior lens capsule, often with wrinkles or dense white plaques; with resorption, small areas of fundic reflex are seen (Colitz et al., 1999).
    6. Morgagnian cataracts allow some fundic reflex to be seen, and the nucleus of the lens is in the ventral portion of the lens capsule.
  B. Fundic examination (if possible) to rule out retinal diseases
  C. Measurement of intraocular pressure via tonometry
    1. Low pressures with uveitis
    2. High pressures with glaucoma
  D. Electroretinography to rule out retinal degeneration
  E. Ultrasonography to assess vitreous for degeneration and retina for detachments
II. Complete laboratory workup
  A. Rule out diabetes mellitus and other systemic illnesses.
  B. Diagnosis of inherited cataracts is based on signalment, location of cataracts, and exclusion of other causes, so laboratory tests are usually normal.

Differential Diagnosis

I. Nuclear sclerosis
  A. It begins in dogs at approximately 6 to 7 years of age and progresses slowly; does not cause visual impairment in the early stages.
  B. Homogeneous bluish appearance to the nucleus of the lens with clear cortex is seen.
  C. Fundus is still visible.
II. Other causes of leukocoria
  A. Persistent tunica vasculosa lentis
  B. Persistent hyperplastic primary vitreous
  C. Vitreal inflammation, pars planitis
III. Other causes of opacification within the eye
  A. Corneal edema or other corneal opacities (see Chapter 98)
  B. Aqueous flare, ± hypopyon
  C. Lipid flare with high serum triglyceride levels
  D. Intraocular neoplasia

Treatment

I. Medical therapy to stabilize underlying causes or associated conditions
  A. Dietary correction in young puppies and kittens
  B. Medical management of lens-induced uveitis (see Chapter 99)
    1. Topical corticosteroids, such as 1% prednisolone acetate or 0.1% dexamethasone
    2. Topical nonsteroidal antiinflammatory drugs in diabetic dogs
    3. Topical atropine or tropicamide for ciliary spasm and miosis, as well as to prevent posterior synechia
II. Criteria for surgical removal of lens
  A. Animal is in good health.
  B. Diabetes mellitus and associated hyperlipidemia are moderately to well controlled.
  C. Lens-induced uveitis is under control (although lensectomy and antiinflammatory agents are best approach).
  D. No evidence of secondary glaucoma is found, although concomitant endolaser ciliary ablation can be performed if vision is still present.
  E. No retinal degeneration or detachment discovered with electroretinography and ultrasonography, respectively.
  F. Preferably an immature cataract is present, although any stage of cataract may be operable.
III. Surgical options
  A. Phacoemulsification
    1. Ultrasonic energy breaks up the cataract so that it can be aspirated through a phacoemulsification needle (Gilger, 1997).
    2. Preferred technique for removal of all cataracts, except subluxated lenses.
    3. Insertion of an intraocular lens prosthesis into the capsular bag returns the eye to normal vision.
  B. Extracapsular lens extraction
    1. Rarely undertaken
    2. Requires a larger incision, with potential for more postoperative inflammation
  C. Discission and aspiration
    1. Feasible only in highly liquefied lenses
    2. Replaced by phacoemulsification
IV. Postoperative care
  A. Postsurgical therapy is vital to a successful outcome.
  B. Administer topical corticosteroids four or more times daily for 2 weeks, then taper per ophthalmologist's recommendations.
  C. Use topical antibiotics QID to prevent infection.
  D. Topical, short-acting, mydriatic agents (tropicamide) may be used to encourage pupil movement and prevent posterior synechia.
  E. Oral antibiotic therapy is often used in diabetic animals or if the posterior capsule has been breached.
  F. Oral nonsteroidal antiinflammatory agents may be used if uveitis is moderate to severe.
V. Postoperative complications
  A. Wound dehiscence and self-inflicted trauma are decreased with use of an Elizabethan collar.
  B. Uveitis is expected postoperatively and is worse with hypermature cataracts and in cases of presurgical lens-induced uveitis (van der Woerdt et al., 1992).
  C. Hyphema and vitreal hemorrhage are uncommon.

D. Ocular hypertension may occur 3 to 12 hours postoperatively and can often be managed with antiglaucoma medications (Smith et al., 1996).
E. Endophthalmitis is a rare complication (Taylor et al., 1995).
F. Retinal detachment and secondary glaucoma are potential long-term sequelae (Nassise and Davidson, 1999; Sigle and Nassise, 2005).
G. Posterior capsular opacification (secondary cataract) is the most common long-term complication of canine cataract surgery (Glover and Constantinescu 1997; Wilkie and Colitz, 2006).

Monitoring of Animal

I. Likelihood of progression of cataracts
   A. Nuclear cataracts and capsular cataracts are unlikely to progress.
   B. Cortical and equatorial cataracts will likely progress.
II. Success rate of surgeries
   A. Short-term success rate for animals undergoing phacoemulsification approaches 95% (Nasisse and Davidson, 1999).
   B. Short-term success rates are lower for animals with hypermature cataracts.
   C. Success rates diminish with time from opacification of the remaining lens capsule, detachment of the retina, and delayed onset of glaucoma.
III. Animals that are not candidates for surgery are examined two to three times yearly to monitor for lens-induced uveitis, secondary glaucoma, and lens subluxation or luxation.

Lens Subluxation and Luxation

Definition

I. Luxation is a total dislocation of the lens from its normal location within the patellar fossa, either anteriorly (into anterior chamber) or posteriorly (into vitreous chamber).
II. Subluxation is partial dislocation of the lens in any direction.

Causes

I. Congenital luxations: rare
II. Primary inherited luxations
   A. Usually bilateral but asymmetrical in presentation
   B. Dogs between 3 and 7 years of age (Curtis, 1990)
   C. Occurs in many terrier breeds: Sealyham, Jack Russell, wirehaired fox terrier, others (Curtis 1990; Davidson and Nelms, 1999; Morris and Dubielzig, 2005)
   D. Other predisposed breeds: border collie, German shepherd dog, certain spaniels, Chinese shar-pei (Curtis and Barnett, 1980; Foster et al., 1986)
III. Luxations secondary to other ocular conditions
   A. Glaucoma
   B. Chronic uveitis
   C. Hypermature, resorbing cataracts
   D. Trauma (rare)
   E. Intraocular neoplasia
IV. Idiopathic: older dogs or cats with no obvious predisposing causes

Pathophysiology

I. Pathophysiology of primary lens luxations is not completely understood; however, an inherited defect affects the zonules of the lens, resulting in zonular fiber dysplasia (Morris and Dubielzig, 2005).
II. With secondary luxations, the pathophysiology depends on the cause.
   A. Buphthalmia associated with glaucoma results in stretching and rupture of the zonules.
   B. Chronic uveitis may cause zonulolysis and is common in cats with chronic uveitis (Nasisse and Glover, 1997).
   C. Hypermature cataracts that are resorbing become smaller, thereby stretching the zonules.
   D. Zonulolysis from lens-induced uveitis may also cause zonule rupture in cases of hypermature cataracts.
   E. Traumatic causes can produce severe sight-threatening injuries, although breeds predisposed to lens luxation do not require extensive trauma to cause luxation (Nasisse and Davidson, 1999).

Clinical Signs

I. Signs with anterior luxations
   A. Acute changes
      1. Blepharospasm, epiphora
      2. Corneal edema, episcleral injection
      3. Blindness from either glaucoma or retinal detachment
   B. Chronic changes: corneal edema from endothelial damage, cataract, anterior uveitis, glaucoma
II. Signs with posterior luxations
   A. Variable blepharospasm
   B. Conjunctival hyperemia
   C. Possibly corneal edema, blindness
   D. Chronic changes: anterior uveitis, cataract, glaucoma, retinal detachment
III. Signs with subluxations
   A. Possibly no clinical signs
   B. Cataract
   C. Corneal edema, signs of uveitis or glaucoma

Diagnosis

I. Anterior luxation
   A. Painful, often cloudy eye
   B. Evidence of lens movement into anterior chamber
      1. Shallow anterior chamber
      2. Lens trapped in pupil
      3. Lens sitting anterior to iris
      4. Vitreous herniation into anterior chamber
   C. Increased intraocular pressure (often 30 to 90 mm Hg)
   D. Blindness
      1. Acute cases: secondary to acute glaucoma
      2. Chronic cases: secondary to chronic glaucoma, retinal detachment, and/or cataract formation
II. Posterior luxation

A. Deep anterior chamber with posterior movement of the iris
B. Iridodonesis (quivering of the iris)
C. Visualization of lens in the vitreal cavity
D. Possible vitreous herniation into anterior chamber

III. Subluxation
A. Aphakic crescent: a portion of the pupil is devoid of the lens, allowing visualization of the fundus or fundic reflex
B. Iridodonesis and phacodonesis (quivering of the lens with eye movement)
C. Vitreous herniation into anterior chamber around portions of the lens

IV. Ancillary tests
A. Fundic examination (if possible) to evaluate health of retina and optic nerve
B. Electroretinogram and ultrasonography to assess health of retina if cannot be visualized

Treatment

I. Anterior lens luxations require immediate medical and surgical intervention, on an emergency basis.
II. Posterior lens luxations are not considered an emergency.
III. Animals with glaucoma are treated with parenteral and topical drugs to lower their intraocular pressures as quickly as possible (see Chapter 100).
IV. Surgery for anterior and posterior lens luxations involves an intracapsular lens extraction, with or without introduction of a sulcus intraocular lens prosthesis (Glover et al., 1995; Nasisse and Glover, 1997).
V. Some surgeons perform phacoemulsification, carefully using a two-handed technique to avoid the large incision necessary for intracapsular lens extraction, with insertion of a foldable sulcus intraocular lens implant.
A. Prognosis is better if glaucoma is not present before surgery.
B. The most common causes of failure to save vision are secondary glaucoma and retinal detachment.
C. Greater success is achieved if surgery is performed before damage occurs to aqueous outflow pathways and the retina.

VI. Surgical intervention for subluxated lenses depends on degree of subluxation.
A. If a significant number of zonules are present, then lens extraction via phacoemulsification may be attempted.
B. If the lens is significantly subluxated, then intracapsular lens extraction is indicated after breakdown of the rest of the zonules (Nasisse and Davidson, 1999); alternatively, a two-handed phacoemulsification approach may be attempted.
C. A posteriorly subluxated lens may require no therapy, particularly in blind animals with quiet eyes; evaluate the animal periodically for secondary glaucoma; however, topical prostaglandin analogs are often used to cause miosis and trap the lens in the vitreous cavity, which will control intraocular pressure.
D. If unremitting glaucoma and blindness are present, then enucleation or evisceration with an intrascleral prosthesis is indicated.

Monitoring of Animal

I. Nonsurgical cases (blind, nonglaucomatous, posterior luxation, quiet eye) are monitored periodically for the following:
A. Elevations in intraocular pressure and institution of appropriate therapy
B. Signs of uveitis and administration of appropriate medical therapy
C. Consideration of enucleation, evisceration with intrascleral prosthesis, or chemical ciliary ablation with gentamicin (dogs only) if intraocular pressure elevation or uveitis develop or become intractable

II. Postoperatively, these cases require frequent monitoring for a successful outcome.
A. Weeks to months of administration of topical corticosteroid medications
B. Frequent monitoring of intraocular pressure for late-onset glaucoma and treatment of ocular hypertension as needed
C. Periodic monitoring for retinal detachments

DEGENERATIVE DISORDERS

See Table 101-3.

INFLAMMATORY DISORDERS

Vitritis and Hyalitis

Definition

I. Secondary infiltration of inflammatory cells into the vitreous from adjacent affected structures
II. May be associated with hemorrhage into the vitreous

Causes

I. Any cause of anterior or posterior uveitis (see Chapters 99 and 102)
II. Neoplasia
III. Blunt or perforating trauma
IV. Parasites

Pathophysiology

I. The vitreous has no direct vascular or nerve supply; therefore inflammatory or neoplastic cellular infiltrates develop secondary to neighboring inflammatory reactions (Boeve and Stades, 1999).
II. Traumatic incidents and inflammation can cause hemorrhage into the vitreous from the uvea or retina.
III. Hemorrhage in the vitreous is destructive to the gel structure, resulting in liquefaction, and may lead to vitreal fibrinous membranes that can cause retinal detachments (Miller et al., 1986; Boeve and Stades, 1999).
IV. Parasitic larva of *Dirofilaria immitis, Toxocara canis, Echinococcus* spp., and certain flies may migrate into the vitreous,

TABLE 101-3

Degenerative Disorders of the Vitreous

DISORDER	DEFINITION	CAUSES	CLINICAL SIGNS	DIAGNOSIS	TREATMENT
Synchysis scintillans	Cholesterol particles in liquefied vitreous that are mobile but do not return to their initial positions after movement	Associated with posterior uveitis and retinal degeneration	No visual impairment associated with this disorder	Ophthalmic examination with dilated pupil	No treatment necessary
Syneresis	Degeneration of the vitreous resulting in separation of the liquid and solid components	Aging, inflammation, or unknown causes	No visual impairment associated with this disorder, but predisposed to retinal detachment	Ophthalmic examination with dilated pupil	No treatment necessary
Asteroid hyalosis	Multiple, small particles of calcium or phospholipids in the vitreous that are mobile but return to their initial position after movement	Associated with retinal degeneration or posterior uveal changes; often no apparent cause	No visual impairment associated with this disorder	Ophthalmic examination with dilated pupil	No treatment necessary

causing a local inflammatory reaction, uveitis, or cysts (Boeve and Stades, 1999).

Clinical Signs

I. Variable visual impairment
II. Hemorrhage and/or cloudy (exudate) vitreous
III. Signs of anterior uveitis
  A. Corneal edema
  B. Aqueous flare
  C. Miosis, blepharospasm
IV. Signs of posterior uveitis
  A. Hyporeflective lesions in tapetal fundus
  B. Retinal hemorrhages
  C. Subretinal transudate or exudate
V. Signs of secondary glaucoma (see Chapter 100)

Diagnosis

I. Ocular examination under pupil dilation using slit lamp biomicroscopy and indirect ophthalmoscopy
II. Ultrasonography if anterior ocular media are opaque
III. Complete blood count and serum biochemistry profile to rule out systemic disease
IV. Serology for infectious agents capable of causing uveitis (see Chapter 99)
V. Radiography of chest and abdomen for signs of infectious or metastatic disease
VI. Careful vitreous aspirate if other tests are nondiagnostic and the eye is blind

Treatment and Monitoring

I. Treat the underlying cause.
II. Noninfectious diseases may benefit from systemic corticosteroid medications or other antiinflammatory agents.
III. Treat infectious diseases with appropriate antimicrobial and antiinflammatory agents.
IV. Cellular turnover rates are extremely slow in the vitreous compartment, so resolution and clearing may take weeks or months.

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CHAPTER 102

Disorders of the Posterior Segment

Robert D. Larocca

CONGENITAL/DEVELOPMENTAL DISORDERS

Retinal Dysplasia

Definition

I. Retinal dysplasia is an abnormal development and differentiation of the retina that results in folds of the sensory retina.
II. Severity of the retinal dysplasia varies from simple folds to geographic lesions and retinal detachment.
III. The disease is nonprogressive and unilateral or bilateral.
IV. It may affect vision, depending on the severity.

Causes

I. Inherited forms
  A. Variable inheritance patterns from autosomal recessive to dominant
  B. Component of multiple ocular anomalies: microphthalmos, colobomas, persistent hyperplastic primary vitreous
II. Acquired forms
  A. Infectious causes
    1. Canine adenovirus
    2. Canine herpesvirus
    3. Canine parvovirus
    4. Feline panleukopenia
    5. Feline leukemia virus
  B. Nutritional causes: vitamin A deficiency
  C. Toxins
  D. Radiation (x-ray) damage in newborns (Shively et al., 1972)
  E. Intrauterine trauma

Pathophysiology

I. Five theories have been suggested for spontaneous retinal dysplasia (Silverstein et al., 1971; Appleyard et al., 2006).
  A. Hyperplastic extension of neural retina into abnormal sites away from the pigmented epithelium
  B. Secondary to detachment of the neural retina from the retinal pigment epithelium (RPE) during development
  C. Occurs in areas without pigment epithelium
  D. Dysplastic processes without evidence of separation from the RPE
  E. Reduced levels of nuclear and mitochondrial transcripts in the retina and RPE of affected miniature schnauzers, suggesting lower energy supply to the retina and RPE (Appleyard et al., 2006)
II. Retinal dysplasia from exposure to physical, chemical, or infectious agents may result from efforts of the retina to regenerate, thereby producing gliosis, pigment cell migration, disorganization of retinal layers, and rosette formation.

Clinical Signs

I. Mild forms have no effect on vision.
  A. Folds and geographic lesions: usually no significant visual loss
  B. Retinal detachment: blind, dilated unresponsive pupils
II. Skeletal chondrodysplasia with a stunted appearance may be seen in certain breeds.
  A. Labrador retriever
  B. Samoyed
III. Retinal dysplasia is an autosomal recessive condition associated with persistent hyperplastic primary vitreous in the miniature schnauzer (Grahn et al., 2004).

Diagnosis

I. Because the condition is a congenital defect, dysplasia can be seen as early as the eyes can be examined via a fundic examination.
II. Geographic retinal dysplasia may not be visible until after 10 weeks of age (Holle et al., 1999).
III. Extent of the funduscopic changes varies.
  A. Retinal folds
    1. Tapetal region: small, linear or round, dark-gray hyporeflective lesions
    2. Nontapetal region: small, white-gray, round or linear vermiform streaks
  B. Geographic dysplasia
    1. Hyperreflective to hyperpigmented lesions
    2. Usually located in the dorsal tapetum at the region of the bifurcation of the major dorsal retinal vein
  C. Retinal detachment
    1. Retina free-floating
    2. Partial detachments possible
    3. Possible hemorrhage with the detachment

Differential Diagnosis

I. A condition similar to retinal folds can be detected at an early age in many breeds.
   A. These folds are believed to arise from a disparity in growth of the inner and outer retinal layers and, therefore, are not a true dysplasia.
   B. They typically appear as white vermiform streaks in the nontapetal retina, often near the optic disc.
   C. These folds resolve as the eye grows in size.
   D. True retinal dysplasia does not resolve with time.
II. Multifocal folds and geographic dysplasia can resemble postinflammatory chorioretinal scarring.

Treatment and Monitoring

I. Retinal dysplasia is usually a nonprogressive condition for which no treatment exists.
II. If retinal folds of uncertain etiology are diagnosed at an early age (<16 weeks), the dogs are rechecked again at 1 year of age to determine if the folds are true dysplasia or physiologic folds.
III. Affected animals with any form of retinal dysplasia are not to be used for breeding.

Collie Eye Anomaly

Definition and Cause

I. Collie eye anomaly (CEA) is an abnormal development of the posterior vascular and fibrous tunics of the eye.
II. CEA is a bilateral disease of rough- and smooth-coated collies, the Shetland sheepdog, Australian shepherd, and border collie.
III. The extent of the lesions can vary between the two eyes, but both eyes usually have choroidal hypoplasia.
IV. Defects of the sclera, vasculature, choroid, retina, and optic nerve can be seen.
V. Inheritance pattern is autosomal recessive (Yakeley et al., 1968; Bedford, 1982; Lowe et al., 2003).

Pathophysiology

I. Abnormal mesodermal differentiation results in colobomas of the sclera, choroid, and optic disc.
II. Colobomas may originate from embryologic deformities in the primitive epithelial papilla or from an abnormality in the closure of the fetal fissure.
III. Hemorrhage is thought to be caused by fragility of retinal neovascularization that extends into the vitreous (Barrie et al., 1981).
IV. Retinal detachments may be secondary to colobomatous defects from accumulation of fluid between the RPE and neural retina.

Clinical Signs

I. Only the major forms of CEA (i.e., large optic disc colobomas, retinal detachment, severe hemorrhage) affect vision.
II. Severely affected, blind puppies may exhibit pendular nystagmus or strabismus.

Diagnosis

I. Diagnosis is made via a fundic examination.
   A. Choroidal hypoplasia
      1. Area temporal to the optic disc in which a lack of pigment in the RPE and absence of tapetal tissue exist
      2. Maldevelopment of the choroidal vasculature
      3. Region temporal to the disc with increased exposure of the sclera (white appearance) and a scarcity of choroidal vessels
   B. Posterior polar coloboma
      1. Usually seen as a pit in the temporal or nasal side of the optic disc
      2. Gray to pink indentations or "blurry areas"
      3. Disappearance of adjacent retinal vessels into the defect
   C. Retinal vessel tortuosity
   D. Retinal detachment
      1. Partial or total
      2. Dilated, unresponsive pupils with complete detachments
   E. Hemorrhages
      1. Retinal or vitreal hemorrhage
      2. Hyphema: rare
II. Dogs are evaluated at an early age (6 to 7 weeks).
   A. Mild choroidal hypoplasia defects may disappear later (3 to 7 months of age) from a proliferation of pigment in the RPE.
   B. These dogs are termed *go normals*.
III. Merle-colored dogs can be difficult to evaluate.
   A. They lack pigment in the RPE and choroid.
   B. Evaluate these dogs carefully in the region temporal to the disc for a decrease in the choroidal vasculature.
IV. A DNA-based test is now available to detect CEA in the Australian shepherd, border collie, Lancashire heeler, collie, Shetland sheepdog, and Nova Scotia duck tolling retriever.
   A. Test can identify normal, carrier, and affected dogs.
   B. All affected dogs, regardless of severity, are homozygous for the same mutant gene.

Differential Diagnosis

I. Other primary colobomas from failure of the optic fissure to close may appear similar but are not accompanied by choroidal hypoplasia.
II. Central optic disc coloboma can be difficult to differentiate from a normal, deep physiologic cup.
III. Retinal detachment associated with retinal dysplasia can be difficult to differentiate from that of CEA.

Treatment and Monitoring

I. CEA is not a progressive disease, although severe defects such as large colobomas or vitreal changes may result in inflammation, hemorrhage, or detachment at a later date.
II. Most retinal detachments occur before 1 year of age.
III. Laser photocoagulation is rarely used to treat retinal detachments associated with CEA (Roberts, 1966; Kottow, 1982).
IV. Dogs with colobomas, retinal detachment, or hemorrhages are not to be bred.

V. Because of the high prevalence of CEA in the collie breed, owners find it difficult to stop breeding mildly affected animals (although this is ideal).

Optic Nerve Hypoplasia and Micropapilla

Definition and Cause

I. Optic nerve hypoplasia (ONH) is a congenital defect of the optic nerve that results in blindness.
II. Micropapilla is a small-appearing optic nerve that does not result in blindness.
III. ONH is an inherited condition in miniature and toy poodles and can be seen in many breeds (Kern and Riis, 1981; Rubin, 1989).
IV. ONH can be unilateral or bilateral.

Pathophysiology

I. The origin of ONH may be abnormal differentiation of the retinal ganglion cell layer or premature ganglion cell death (Collins, 1996).
II. Some of the nerve fibers fail to reach the disc, resulting in a small optic disc.
III. Micropapilla may be a milder form of hypoplasia not severe enough to significantly affect vision.

Clinical Signs

I. A unilateral condition may go unnoticed unless mydriasis is present.
II. Bilateral ONH results in blindness from birth.
  A. Affected puppies may circle or wander aimlessly.
  B. Mydriasis and absent menace reflexes are present in the affected eye(s).
III. Dogs with micropapilla have apparent normal vision.

Diagnosis

I. Micropapilla
  A. Fundic examination reveals a small optic disc in the affected eye, but vasculature and other structures are normal.
  B. The eye is visual, with normal pupillary light responses.
  C. Electroretinogram (ERG) and visual evoked potentials (VEPs) are normal.
II. Optic nerve hypoplasia
  A. Optic disc is small and dark, and the vasculature and other retinal structures appear normal.
  B. Eye is blind, often with a dilated, slow to unresponsive pupil.
  C. ERG shows normal *a* waves, slightly decreased amplitude and duration of *b* waves, and the VEPs are abnormal.

Differential Diagnosis

I. Optic nerve aplasia
  A. No optic disc is visible, and the retinal vasculature is often abnormal on fundic examination.
  B. ERG and VEPs are absent.
II. Optic nerve atrophy secondary to inflammatory events
  A. Animal previously visual and became blind in affected eyes
  B. May have circumpapillary inflammatory changes on funduscopy
III. Optic nerve atrophy secondary to glaucoma
  A. Optic nerve has cupped appearance.
  B. Other signs or findings are suggestive of glaucoma.
IV. Optic nerve atrophy secondary to progressive retinal atrophy (PRA)
  A. Significant evidence of retinal atrophy and optic nerve atrophy (see Generalized Progressive Retinal Atrophy)
  B. Animal previously visual

Treatment and Monitoring

I. These are congenital defects and are nonprogressive.
II. No corrective therapy is possible.
III. Do not breed affected dogs.

DEGENERATIVE DISORDERS

Generalized Progressive Retinal Atrophy

Definition and Causes

I. PRA encompasses an inherited group of retinal degenerations that leads to vision loss.
II. Most forms of PRA are inherited in an autosomal recessive manner, except for the following:
  A. X-linked PRA in the Siberian husky and Samoyed
  B. Autosomal dominant forms in the Abyssinian cat
  C. Dominant PRA in the English mastiff and bull mastiff
III. Two general types of PRA exist: early onset and late onset.
  A. Early-onset disorders are characterized by photoreceptor dysplasias in which certain photoreceptors fail to develop normally.
  B. Late-onset disorders are characterized by premature degeneration of the photoreceptors after they have developed normally.

Pathophysiology

I. Many forms of PRA exist, based on the enzymatic cause.
  A. Rod-cone dysplasia 1 (rcd1): early-onset disorder of Irish setters (Aguirre et al., 1978; Ray et al., 1995)
  B. Rod-cone dysplasia 2 (rcd2): early-onset disorder of collies (Chader et al., 1981)
  C. Rod-cone early-onset retinal degeneration: Persian cats (Rah et al., 2005)
  D. Photoreceptor dysplasia (pd): miniature schnauzers (Parshall et al., 1991)
  E. X-linked PRA: Siberian huskies (Acland et al., 1994)
  F. Early retinal degeneration (erd): Norwegian elkhounds (Acland and Aguirre, 1987)
  G. Progressive rod-cone degeneration 1 (prcd1)
    1. It is a late-onset PRA that affects many breeds.
    2. Affected breeds include toy, miniature, and standard poodles; American and English cocker spaniels; Labrador retrievers; and Portuguese water dogs (Aguirre et al., 1982; Aguirre and Acland, 1988, 1989).

H. Progressive rod-cone degeneration 2 (prcd2): an early-onset PRA of Tibetan terriers (Millichamp et al., 1988; Gould et al., 1995)
I. Dominant PRA of mastiffs
   1. It is the only dominant form of canine PRA.
   2. A single copy of the mutant gene causes the disease (no carrier state).
J. Cone degeneration: early-onset disorder of German shorthaired pointers

II. Photoreceptor metabolism and function are affected by abnormal cyclic guanosine 3′,5′-monophosphate metabolism or failure of photoreceptor outer segment renewal.
III. Pathophysiology of PRA in many breeds remains unknown.

Clinical Signs

I. All forms of PRA that affect the rod photoreceptors first have the same initial development of nyctalopia (night blindness).
II. Most cases lead to complete blindness because the cones are also eventually affected.
III. PRA is a bilateral disease and affects both eyes equally.
IV. Age of onset and rate of progression vary among breeds (Table 102-1).

Diagnosis

I. Diagnosis is based on clinical signs of nyctalopia along with fundic examination findings.
   A. Signs of night blindness can be evaluated by maze testing in both photopic and scotopic conditions.
   B. Navigational deficiency is noted in dim light.
   C. Pupillary light responses are generally slow.
II. Fundic findings are diagnostic at various stages of PRA (see Table 102-1).
   A. Tapetal hyperreflectivity
   B. Retinal vascular attenuation
   C. Optic nerve atrophy (dark appearance)
III. PRA can be detected via ERG.
   A. ERG detects retinal photoreceptor abnormalities before visible fundic changes (see Table 102-1).
   B. ERG findings depend on the specific type of PRA.
   C. Most forms of PRA result in a faster progression of rod degeneration.
   D. ERG changes consist of reduced amplitudes and prolonged implicit times of the waveforms, especially the *b* wave.
IV. DNA testing via a blood sample detects PRA in many breeds (Optigen LLC, Ithaca, N.Y. [607-257-0301], www.optigen.com).
   A. DNA tests for all forms of PRA are mutation-based tests; no marker-based tests are available at this time.
   B. The rcd1 PRA test is used to identify normals versus carriers and confirms the affected status of Irish setters.
   C. Dominant PRA test detects the actual mutation affected mastiffs.
   D. The prcd PRA test identifies the specific DNA mutation causing prcd-PRA.
      1. It detects normal dogs (homozygous normal).
      2. It detects carriers (heterozygous).
      3. It detects affected dogs (homozygous mutant).

TABLE 102-1

Summary of Fundic and Electroretinographic Findings in Generalized Progressive Retinal Atrophy and Hereditary Distrophy

BREED	DISORDER	EARLIEST FUNDIC LESION	EARLIEST ERG ABNORMALITY
Akita	Degeneration	6 mo-3 yr	1.5-2.0 yr
American cocker spaniel	prcd Degeneration	2-5 yr	9 mo
Briard	Retinal dystrophy	4-6 yr	5 wk
Collie	rcd2 Dysplasia	16 wk	6 wk
English cocker spaniel	prcd Degeneration	3-8 yr	1.5-3.0 yr
Irish setter	rcd1 Dysplasia	16 wk	6 wk
Labrador retriever	prcd Degeneration	3-6 yr	1.0-1.5 yr
Miniature longhaired dachshund	Degeneration	6 mo	4 mo
Miniature schnauzer	Degeneration	1.5-5.0 yr	6 wk
Norwegian elkhound	erd Degeneration	6 mo-1 yr	5-6 wk
	Rod dysplasia (rd)	5 mo-1 yr	6 wk
Papillon	Degeneration	1-5 yr	9 mo-1.5 yr
Toy, miniature, standard poodles	prcd Degeneration	3-5 yr	9 mo
Portugese water dog	prcd Degeneration	3-6 yr	1.5 yr
Samoyed	Degeneration	2-5 yr	1.5-2.0 yr
Siberian husky	X-linked degeneration	6 mo-2 yr	1.0-1.5 yr
Tibetan terrier	Degeneration	1.0-1.5 yr	10 mo

ERG, Electroradiogram; *prcd*, progressive rod-cone degeneration; *rcd2*, rod-cone dysplasia type 2; *rcd1*, rod-cone dysplasia type 1; *erd*, early retinal degeneration.

4. Dogs that test as homozygous normal can be bred to any other dog.
5. If a dog is suspected of having PRA based on fundic examination, then it must test as a homozygous mutant to truly be PRA.
6. Dogs that can be tested with the prcd PRA test include the Chesapeake Bay retriever, American cocker spaniel, American Eskimo dog, Australian cattle dog, Australian stumpy tail cattle dog, Chinese crested, Entlebucher Mountain dog, Finnish Lapphund, Kuvasz, Lapponian herder, miniature poodle, Nova Scotia duck tolling retriever, Swedish Lapphund, toy poodle, English cocker spaniel, Labrador retriever, and Portuguese water dog.

E. X-linked PRA test is a mutation-based test that identifies normals, carriers, and affected Siberian huskies and Samoyeds.
F. Type A PRA test is a specific mutation-based test for the miniature schnauzer.
   1. Type A PRA appears to have partial dominance expression, because some carriers appear affected via clinical or ERG findings.
   2. Because carriers may have signs of disease, researchers recommend that only homozygous normal schnauzers are used for breeding.
G. The rcd3 PRA test is a mutation-based test involving the PDE6A gene of Cardigan Welsh corgis.

Differential Diagnosis

I. RPE dystrophy or central PRA (Table 102-2)
II. Hereditary retinal dystrophy in briards (see following section)
III. Neuronal ceroid lipofuscinosis (see Table 102-2)
IV. Mucopolysaccharide storage diseases (see Chapters 65 and 81)
V. Retinal degeneration secondary to chorioretinitis
VI. Retinal degeneration secondary to optic neuritis
VII. Retinal degeneration secondary to chronic glaucoma
VIII. Sudden acquired retinal degeneration (SARD) (see later in this chapter)

Treatment and Monitoring

I. No treatment is available for PRA.
II. Because affected animals develop a progressive loss of vision, instruct owners on how to protect and care for blind pets.
III. Secondary cataracts are a frequent finding and may require medical treatment for lens-induced uveitis (see Chapters 99 and 101).
IV. Do not breed animals diagnosed with PRA.

Hereditary Retinal Dystrophy

Definition and Cause

I. Hereditary retinal dystrophy is a congenital disorder previously known as *congenital stationary night blindness* (CSNB).
II. Dogs are night-blind from birth and have a variable progression to complete blindness (Wrigstad et al., 1994).
III. An autosomal recessive inheritance pattern is suspected in the briard (Narfstrom et al., 1994).

Pathophysiology

I. Disorientation of the rod outer segments is seen histologically at 5 weeks of age.
II. The RPE develops inclusions, mainly located in the central and midperipheral tapetal regions, at 3.5 months of age.
III. Inclusions increase in number and spread peripherally with age.
IV. Rod photoreceptor degeneration is apparent in the peripheral tapetal retina histologically at 7 months of age.
V. At 7 years of age, the photoreceptor degeneration progresses from the central and midperipheral tapetal retina to the peripheral fundus (Wrigstad et al., 1994).
VI. A defect in retinal polyunsaturated fatty acid metabolism is suspected (Anderson et al., 1997).

Clinical Signs

I. Dogs are night-blind from birth.
II. Rapid horizontal nystagmus is seen frequently in puppies.
III. Pupils are generally mydriatic.
IV. Fundic examinations are normal early in the disease.

Diagnosis

I. Diagnosis is based on suspicious clinical signs in the briard breed.
II. DNA-based testing is currently available.
   A. A mutation in the RPE65 gene results in retinal dysfunction and RPE accumulation of lipid vacuoles (Aguirre et al., 1998).
   B. This mutation was found in both dogs with CSNB and dogs with retinal dystrophy, suggesting the two disorders are molecularly identical.
   C. A mutation-based gene test can identify normal, carriers, and affected dogs via a simple blood test.
III. ERG helps characterize the disorder.
   A. Absent *a* and *b* waves are detected in the dark-adapted state at 7 to 12 months of age.
   B. Reduction of 50% to 70% is present in the 30-Hz flicker fusion in the light-adapted state (Nilsson et al., 1992).

Differential Diagnosis

I. PRA (see previous section)
II. RPE dystrophy (see Table 102-2)

Treatment and Monitoring

I. Dogs that are only night-blind at birth frequently retain some sight until 6 to 7 years of age.
II. DNA-based test allows for selection of breeding dogs that will not produce affected puppies.
III. Recent studies using gene therapy offer hope for restoring vision to animals with this disease (Acland et al., 2001).

TABLE 102-2

Miscellaneous Retinal Degenerations

DISORDER	DEFINITION	BREEDS AFFECTED	CLINICAL SIGNS	DIAGNOSIS	PROGNOSIS
Hemeralopia	Day blindness from a selective cone degeneration	Alaskan malamute, German shorthaired pointer	Loss of vision in bright light	Clinical signs and ERG revealing absent cone function	Most animals retain dim-light vision
Central PRA (retinal pigment epithelial dystrophy, RPED)	A primary disease of the RPE with secondary retinal degeneration Occurs predominantly in the United Kingdom Very rare in the United States	Briard, Labrador retriever, golden retriever, English cocker spaniel, English springer spaniel, border collie, rough- and smooth-coated collie, Shetland sheepdog, Chesapeake Bay retriever	Vision loss is not noticed until late in the disease process Peripheral vision is usually spared until late	Ophthalmoscopic findings of multifocal pigment spots within the tapetal retina	Vision loss is not apparent until late in the disease
Neuronal ceroid lipofuscinosis	Inherited and progressive lipid storage disease that results in retinal degeneration and encephalopathy	English setter, Dalmatian, border collie, Tibetan terrier, Polish owczarek nizinny, miniature schnauzer	Progressive blindness usually occurring at 1 yr of age Neurological signs of ataxia, muscle weakness, and dementia usually develop	Diagnosis usually based on clinical signs and signalment Definitive diagnosis requires histopathology	Poor prognosis because the neurological disease is progressive and usually fatal
Vitamin E deficiency retinal degeneration	A slowly progressive visual loss resembling RPED; secondary to vitamin E deficiency	Any breed is susceptible	Progressive blindness beginning at 3-5 yr of age Neurologic, muscular, and reproductive defects may also be seen	Ophthalmoscopic findings reveal a mottled tapetal fundus with multiple discrete yellow-brown pigment spots and bars A deficiency in serum vitamin E also detected	Poor prognosis because progressive retinal degeneration leads to complete blindness if the deficiency is not corrected very early
Fluoroquinolone-induced retinal degeneration	A degeneration to the retina of cats attributed to a toxic affect from enrofloxacin	All cats	Dilated pupils and blindness	Ophthalmoscopic findings of retinal degeneration along with recent use of enrofloxacin	Poor prognosis; blindness usually irreversible
Borzoi chorioretinopathy	An acquired condition that initially manifests as focal retinal edema and loss of choriocapillaris and tapetum With time the retina degenerates and becomes hyperreflective, with RPE hyperpigmentation and clumping	Borzoi	No significant visual impairment for up to 7 years	Ophthalmoscopic findings of focal, peripheral, tapetal, hyperreflective and pigmented areas	Poor owing to progressive retinal changes that may result in visual impairment

ERG, Electroretinogram; *PRA*, progressive retinal atrophy; *RPED*, retinal pigment epithelial dystrophy; *RPE*, retinal pigment epithelium.

INFLAMMATORY AND INFECTIOUS DISORDERS

Chorioretinitis

Definition and Causes

I. Chorioretinitis is an inflammation of the posterior uvea (choroid) that also spreads to include the retina.
II. Chorioretinitis can be unilateral or bilateral.
III. It is usually a manifestation of a systemic disease process.
IV. Causes are numerous (Box 102-1; see Tables 104-5 and 104-7).

Pathophysiology

I. Inflammation of the retina and choroid often starts as an infiltrate of inflammatory cells surrounding blood vessels.
II. As the inflammation and vascular response increases, the retina becomes edematous (translucent appearance).
III. Accumulation of exudates between the photoreceptors and the RPE results in a detachment of the neural retina.
IV. Inflammation of the RPE causes a release of pigment, and the RPE can become hyperplastic, forming fibrouslike membranes.
V. Inflammation may lead to hemorrhage from retinal or choroidal vessels.

Clinical Signs

I. Ocular clinical signs vary depending on the severity of the inflammation and whether bilateral disease is present.
   A. Loss of vision is apparent if severe inflammation results in detachment or involves most of the retina.
   B. Such animals have dilated and minimally responsive pupils.
   C. Many animals also have signs of anterior uveitis (e.g., aqueous flare, scleral injection, squinting).
II. Many animals with chorioretinitis have clinical signs of a systemic illness.

Diagnosis

I. Funduscopic findings help differentiate active from inactive chorioretinitis.
   A. Active lesions have raised, fluffy, and irregular edges.
      1. Tapetal retina: dark gray-brown lesions
      2. Nontapetal retina: white-gray raised lesions
      3. Tortuosity or dilatation of blood vessels, hemorrhages, perivascular edema
      4. Subretinal granuloma formation or retinal detachment
   B. Inactive lesions have flat, sharp borders.
      1. Tapetal retina: hyperreflective scars, with or without areas of hyperpigmentation
      2. Nontapetal retina: flat, white-gray depigmented scars
      3. Possible vascular attenuation
      4. Possible optic nerve atrophy
II. Systemic causes are evaluated by a thorough physical examination, complete blood count, serum biochemistries, urinalysis, serology, radiography, ultrasonography, cytology, and histopathology of lesions, as indicated.

Box 102-1

Causes of Chorioretinitis

Infections

Viral: canine distemper virus, canine herpesvirus, feline infectious peritonitis, feline leukemia virus
Rickettsial: canine ehrlichiosis, Rocky Mountain spotted fever
Fungal: aspergillosis, blastomycosis, cryptococcosis, histoplasmosis, coccidioidomycosis, geotrichosis, pseudallescheriasis, acremoniasis
Bacterial: brucellosis, bartenellosis, leptospirosis, tuberculosis, any agent capable of inducing septicemia
Algal: protothecosis (dogs)
Protozoal: toxoplasmosis, neosporosis, leishmaniasis
Parasitic: *Toxocara canis, Angiostrongylus vasorum*, ophthalmomyiasis

Immune-Mediated

Thrombocytopenia
Autoimmune hemolytic anemia
Systemic lupus erythematosus
Uveodermatologic syndrome or Vogt-Koyanagi-Harada-like syndrome
Granulomatous meningoencephalitis

Metabolic Conditions

Diabetes mellitus
Hyperviscosity syndromes
Systemic hypertension
Anemia
Uremia

Immunological or Neoplastic Conditions

Lymphosarcoma
Choroidal melanoma
Retinoblastoma
Metastatic tumors
Malignant histiocytosis
Monoclonal gammopathies

Toxins

Enrofloxacin in cats

Trauma

Blunt
Surgical
Penetrating foreign bodies

Differential Diagnosis

I. Retinal dysplasia can appear similar to postinflammatory retinal scars, especially geographic dysplasia, in which an area of hyperreflectivity occurs with hyperpigmentation.
II. Multifocal hyperpigmented lesions associated with RPE dystrophy can appear similar to chorioretinitis.

III. End-stage PRA can appear similar to end-stage chorioretinal scarring.

Treatment

I. Treatment of chorioretinitis involves treating the underlying cause.
II. If anterior uveitis accompanies the chorioretinitis, then this condition is also treated (see Chapter 99).
III. If no infectious agents are identified, then systemic anti-inflammatory therapy is used.
  A. Prednisone 2.2 mg/kg PO SID, then tapered as a positive response is noted
  B. Azathioprine 2.2 mg/kg PO SID for immune-mediated disorders in dogs
IV. Systemic antibiotic therapy is indicated if an infectious cause is determined.
  A. Broad-spectrum antibiotics
    1. Dogs: chloramphenicol 25 to 50 mg/kg PO TID
    2. Cephalexin 22 to 30 mg/kg BID to TID
    3. Amoxicillin/clavulanic acid 20 mg/kg PO BID
    4. Dogs: enrofloxacin 2.5 to 5.0 mg/kg PO BID
  B. Rickettsial infections
    1. Tetracycline 22 mg/kg PO TID in dogs and 15 mg/kg PO TID in cats
    2. Doxycycline 5 to 10 mg/kg PO SID
  C. Fungal infections
    1. Itraconazole 5 to 10 mg/kg PO SID to BID for 6 to 12 months
    2. Amphotericin 0.5 mg/kg IV three times weekly until maximum dose of 6 mg/kg
    3. Dogs: fluconazole 2.5 to 5.0 mg/kg PO SID for 8 to 12 weeks
    4. Ketoconazole 10 to 15 mg/kg PO BID for 3 to 6 months
  D. Toxoplasmosis
    1. Clindamycin 10 to 20 mg/kg PO BID
    2. Trimethoprim-sulfadiazine 15 to 30 mg/kg PO BID and pyrimethamine 0.25 to 0.5 mg/kg PO SID for 7 to 10 days
V. Pars plana vitrectomy can be used for the treatment of ophthalmomyiasis interna posterior (Ollivier et al., 2006).

Monitoring of Animal

I. Repeated fundic examinations are used to assess response to therapy.
II. Resolution of chorioretinal inflammation, granulomas, or retinal detachments suggest successful therapy.
III. Chorioretinal inflammation frequently leads to retinal scarring.
IV. Prolonged therapy (6 to 12 months) is usually needed for fungal infections.

Optic Neuritis

Definition

I. Optic neuritis is an inflammation of the optic nerve.
II. Optic neuritis may be either unilateral or bilateral.
III. The optic papilla and/or the retrobulbar optic nerve may be affected.

Causes

I. Infectious diseases
  A. Canine distemper virus
  B. Blastomycosis
  C. Histoplasmosis
  D. Cryptococcosis
  E. Toxoplasmosis
  F. Neosporosis
  G. Tickborne infections: ehrlichiosis, Rocky Mountain spotted fever, Lyme borreliosis, tickborne encephalitis virus
II. Idiopathic forms
III. Immune-mediated diseases (see Box 102-1)
IV. Trauma
  A. Proptosis
  B. Surgical trauma of contralateral optic nerve via traction during enucleation
  C. Probing or biopsy of retrobulbar tissues
V. Granulomatous meningoencephalitis
VI. Vitamin A deficiency (rare)

Clinical Signs

I. Clinical signs are dependent on whether the disease is unilateral or bilateral.
II. Bilateral optic neuritis results in acute blindness with dilated and unresponsive pupils.
III. Other neurological signs may be noted.

Diagnosis

I. Funduscopy is often helpful if the papilla is affected.
  A. Swollen optic disc with blurring of margins and evidence of raised vessels over the surface of the disc
  B. Hyperemia or hemorrhage of disc
  C. Loss of physiologic cup within the disc
  D. Possible peripapillary retinal edema and detachment
II. Retrobulbar optic neuritis may not affect the optic disc, so the retina appears normal on funduscopy.
III. The cause of the optic neuritis must be evaluated.
  A. Complete laboratory data base, serological tests
  B. Thoracic radiography to evaluate for systemic fungal infection
  C. Cerebrospinal fluid analysis (see Chapter 23)
  D. Serum vitamin A levels
IV. ERG and VEPs are performed in cases of suspected retrobulbar optic neuritis to differentiate it from SARD.

Differential Diagnosis

I. Passive papilledema associated with increased intracranial pressure
II. Pseudopapilledema
  A. It is a normal variant in which there is an abundance of myelination of optic nerve axons beyond the anterior lamina cribrosa, resulting in a raised appearance of the optic disc.

B. The physiologic cup is still visible with pseudopapilledema.
III. Optic nerve neoplasia or neuropathy
IV. SARD
V. Blindness from central nervous system diseases

Treatment

I. Treatment is aimed at the underlying cause if one can be found.
II. Treat immune-mediated or idiopathic causes with prednisone 2.2 mg/kg PO SID, then taper as a positive response is noted.
III. See other therapies as outlined for chorioretinitis (see previous section).
IV. Vitamin A supplementation is used if deficient.

Monitoring of Animal

I. Repeated fundic examinations are used to assess response to therapy.
II. Optic neuritis frequently leads to permanent blindness from secondary atrophy of the optic nerve.

Retinal Detachments

Definition

I. Retinal detachment is a separation between the neurosensory retina and the RPE.
II. Subretinal fluid accumulates in the potential space that is a remnant of the embryonic optic vesicle.
III. Retinal detachments can be partial or complete and unilateral or bilateral.

Causes

I. Three types of retinal detachments exist, and each has different causes.
II. Rhegmatogenous detachments are associated with tears or breaks in the retina that allow liquefied vitreous to enter the subretinal space.
   A. Retinal tears can be caused by vitreal traction (e.g., vitreal degeneration, vitreal prolapse, lens luxation, posterior capsule tears).
   B. Hypermature cataracts and secondary vitreal degeneration can result in secondary tears.
   C. Blunt trauma to the eye infrequently results in retinal detachment.
   D. Spontaneous detachment occurs in Shih Tzus (Vainisi et al., 1990).
III. In nonrhegmatogenous detachments, subretinal fluid or blood usually accumulates from inflammation or hemodynamic causes.
   A. Systemic diseases: hypertension, infections, hyperviscosity, immune-mediated diseases, neoplasia
   B. Vitreal hemorrhage, degeneration, or movement
IV. Congenital or developmental detachments are conditions in which the neurosensory retina never attached to the underlying RPE or failed to remain attached.
   A. Retinal dysplasia
   B. CEA
   C. Persistent hyperplastic primary vitreous (see Chapter 101)

Pathophysiology

I. The pathogenesis of rhegmatogenous retinal detachments requires a break in the retina and an abnormal vitreous.
   A. Most retinal detachments occur in the peripheral retina where the vitreous has the strongest attachment to the retina.
   B. Traction frequently leads to a break in the retina and liquefied vitreous moves into the subretinal space, resulting in the detachment.
II. Nonrhegmatogenous retinal detachments arise from effusion of an exudate, hemorrhage, or transudate into the subretinal space, resulting in separation of the neurosensory retina from the RPE; a tear is not present.

Clinical Signs

I. Partial retinal detachments frequently go unnoticed.
II. Complete retinal detachments result in loss of vision.
   A. Pupils are dilated and minimally responsive or fixed.
   B. A "floating veil" of vessels may be visualized within the pupil with a simple penlight.

Diagnosis

I. Fundic examination is frequently diagnostic.
   A. Veil or funnel-like film attached to the optic disc
   B. Focal or generalized area of raised tissue or vessels
   C. Possible retinal hemorrhages
   D. Possible opaque inflammatory lesions or granulomas
II. Peripheral retinal tears frequently require the aid of scleral depression to be visualized.
III. Ocular ultrasonography is used to evaluate the posterior segment when the anterior segment is opaque.
IV. When any acquired retinal detachment is diagnosed, a systemic cause must be ruled out.
   A. Serous detachments in older cats are most commonly associated with systemic hypertension.
      1. Measure systemic blood pressure.
      2. Evaluate blood tests and urinalysis for causes of hypertension (see Chapter 48).
   B. Test for the following if exudative and granulomatous detachments are found:
      1. Cats: feline infectious peritonitis virus
      2. Cats, dogs: systemic fungal infections, neoplasia
      3. Dogs: protothecosis
      4. See Chorioretinitis, earlier in this chapter
   C. A subretinal aspirate can be performed in severe cases, if other diagnostic tests are inconclusive.

Treatment and Monitoring

I. Treatment is based on the cause and type of detachment.
II. Nonrhegmatogenous retinal detachments are treated medically.
   A. Treat the underlying systemic disease (see Chapters 48, 111, 112, 115, and 116).

B. Effective treatment of systemic hypertension often results in reattachment of the retina, with variable return of vision.
C. Fungal-induced detachments frequently lead to blindness from retinal damage and scarring, despite systemic therapy.
D. Immune-mediated or inflammatory detachments treated with prednisone at 2.2 mg/kg PO SID may reattach and regain function.

III. Rhegmatogenous retinal detachments require surgical treatment to correct the detachment.
A. The goal of surgical correction is to reappose the retina and the RPE and seal the breaks by creating a chorioretinal adhesion.
B. Retinal breaks are treated via laser photocoagulation, transscleral cryopexy, or scleral buckling.
C. Retinal breaks with small areas of subretinal fluid surrounding them can be treated with laser photocoagulation or transscleral cryopexy.
D. If vitreous pathology or traction accompanies the detachment, then a vitrectomy is needed in addition to the previous procedures.
E. Detachments from large bullous lesions and large tears frequently require a vitrectomy and infusion of either silicone oil or pneumatic gas to tamponade the retina against the RPE before a pexy procedure (Vainisi and Packo, 1995).

IDIOPATHIC DISORDERS

Sudden Acquired Retinal Degeneration

Definition

I. SARD is degeneration of the entire retina that results in complete blindness.
II. SARD occurs in adult dogs of any breed, with large-breed dogs, dachshunds and miniature schnauzers predisposed.

Causes

I. The cause of SARD is unknown.
II. Several theories have been suggested.
A. Autoimmune mechanism, though unlikely (Bellhorn et al., 1988; Gilmour et al., 2006; Keller et al., 2006)
B. Faulty fat metabolism (Moore, 1984)
C. Elevated vitreal glutamate levels suggesting excitotoxicity (Abrams et al., 1995)
III. Retinal degeneration associated with SARD involves an apoptic event involving the outer nuclear layer (Miller et al., 1998).

Pathophysiology

I. Acute dysfunction of the photoreceptor outer segments (both rods and cones) occurs and is followed by degeneration of the other layers of the retina.
II. All areas of the retina appear to be affected equally, and the changes are irreversible.

Clinical Signs

I. Major clinical sign is acute vision loss without signs of ocular inflammation.
II. Pupils are usually dilated and slow or unresponsive.
III. Many dogs also exhibit signs of polyuria and polydipsia, polyphagia, and recent weight gain.

Diagnosis

I. History of acute onset of blindness with no other apparent ocular changes is suggestive of SARD.
II. Fundic examination is often normal in acute disease.
III. Fundic examination in chronic cases resembles that of PRA (retinal degeneration).
IV. Definitive diagnosis is based on complete extinguishing of the ERG.
V. Other findings may include the following:
A. Elevated serum levels of alkaline phosphatase, aminotransferases, cholesterol, and bilirubin
B. Cortisol response test results suggestive of hyperadrenocorticism

Differential Diagnosis

I. Optic neuritis
A. Dogs with retrobulbar optic neuritis can have a normal fundic examination.
B. ERG findings are usually normal; VEPs are abnormal.
II. Cortical blindness
A. ERG is normal; VEPs are abnormal.
B. Fundic examination and pupillary light responses are usually normal.
III. End-stage PRA
A. PRA has a prolonged, progressive course of visual loss.
B. Late-stage SARD is indistinguishable funduscopically or on ERG from PRA.

Treatment and Monitoring

I. No treatment for SARD exists; it results in permanent blindness.
II. If polyuria, polydipsia, and weight gain are present, then testing for hyperadrenocorticism is performed and monitoring continues for several months.
III. Most of these signs subside without treatment in several weeks to months.

METABOLIC DISORDERS

Hypertensive Retinopathy

Definition

I. Retinal pathology associated with systemic hypertension is known as *hypertensive retinopathy*.
II. *Systemic hypertension* is defined as a systolic arterial blood pressure >170 mm Hg (Stiles et al., 1994).
III. Most ocular lesions are seen when the systolic pressures are >200 mm Hg.
IV. Ocular changes may include retinal edema, retinal hemorrhages and vessel alterations, retinal detachment, and hyphema.

Causes

I. Cat
  A. Chronic renal failure
  B. Hyperthyroidism
  C. High-salt diets (Turner et al., 1990)
  D. Hyperglycemia induced by megestrol acetate (Glaze and Gelatt, 1999)
  E. Primary, essential hypertension (rare)
II. Dog
  A. Chronic renal failure
  B. Hyperadrenocorticism
  C. Pheochromocytoma
  D. Renin-secreting renal tumors
  E. Polycythemia
  F. Diabetes mellitus
  G. Hypothyroidism and associated hypercholesterolemia
  H. Primary, essential hypertension (rare)

Pathophysiology

I. Precapillary vasoconstriction of the retinal arterioles occurs with systemic hypertension via autoregulation and results in ischemia and retinal degeneration with chronicity (Stiles et al., 1994).
II. As the endothelial cells and vascular smooth muscles deteriorate, serum and blood cells leak into the surrounding retinal tissue.
III. Ocular lesions that arise (e.g., retinal edema, serous exudates, retinal vessel tortuosity, hemorrhage, complete detachment) are dependent on the extent of vascular injury and the degree of hypertension.
IV. Retinal detachment may develop from choroidal vascular damage and leakage of fluid into the subretinal space (Spencer, 1985).
V. Retinal hemorrhages, edema, and intraretinal edema most likely occur secondary to retinal vascular damage.
VI. Retinal vessels can develop a "boxcar" appearance following vascular smooth muscle necrosis and focal dilatations.

Clinical Signs

I. Retinal detachment and severe retinal hemorrhage can lead to acute blindness.
II. Many small hemorrhages, retinal vessel tortuosity, and mild retinal edema go unnoticed.
III. Many animals exhibit signs of systemic illness associated with the cause of the hypertension.

Diagnosis

I. Funduscopic findings of one or more lesion compatible with hypertension along with repeated measurements of systemic blood pressure >170 mm Hg systolic are diagnostic for hypertensive retinopathy.
II. Once the diagnosis is confirmed, a search is undertaken for the underlying cause (see Chapter 48).

Differential Diagnosis

I. Clotting disorders
  A. Immune-mediated thrombocytopenia
  B. Myelophthisic neoplasia
  C. Estrogen-induced bone marrow suppression
  D. Infections: ehrlichiosis
  E. Toxins: warfarin type compounds
II. Hyperviscosity syndrome
III. Neoplasia of the posterior segment causing hemorrhage or detachment
IV. Polycythemia
V. Systemic lupus erythematosus

Treatment and Monitoring

I. Control of systemic blood pressure is the primary goal (see Chapter 48).
II. Treatment of the underlying disease (e.g., renal, hyperthyroid diseases) is also pursued.
III. If anterior segment inflammation or hemorrhage is also present, then topical prednisolone acetate 1% is instituted.
IV. Prognosis for return of vision with successful control of hypertension is fair in the dog and guarded in the cat.

NUTRITIONAL DISORDERS

Vitamin E Deficiency (Retinal Degeneration)

See Table 102-2.

Taurine Deficiency Retinopathy

Definition and Cause

I. Taurine retinopathy—or feline central retinal degeneration (FCRD)—is a specific retinal degeneration of cats induced by low levels of taurine.
II. The degeneration is bilaterally symmetrical and involves the central sensory retina.
III. Dietary content of 500 to 750 ppm of taurine is needed to prevent retinal pathology (Glaze and Gelatt, 1999).
IV. Cats fed dog food can develop FCRD from inadequate taurine levels in dog foods (Aguirre, 1978).
V. Taurine deficiency has been found in a group of Newfoundlands, although none of these animals showed signs of retinal degeneration (Backus et al., 2003).

Pathophysiology

I. Taurine is an essential dietary amino acid in cats because they have limited ability to synthesize it.
II. Dietary deficiency or malabsorption of taurine results in low plasma and retinal taurine levels within 5 weeks (Glaze and Gelatt, 1999).
III. Taurine acts as a neurotransmitter and functions to maintain cell membranes (Glaze and Gelatt, 1999).
IV. Taurine acts as an antioxidant, and taurine supplementation is known to alleviate oxidative stress in the retina (Militante and Lombardini, 2004).
V. Retinal cone dysfunction occurs within 10 weeks of onset of taurine deficiency, with cell death occurring in another 10 weeks (Schmidt et al., 1976).
VI. Cone photoreceptors are affected first and most severely.
VII. Taurine deficiency also causes dilated cardiomyopathy (see Chapter 10).

Box 102-2

Posterior Segment Neoplasia

Classification	Clinical Signs	Diagnostic Tests	Treatment	Prognosis
Primary tumors				
Adenomas/ adenocarcinomas Medullepithelioma Retinoblastoma/ glioma Astrocytoma Choroidal melanoma	Obvious mass within the eye, hyphema, uveitis, glaucoma, enlargement of the eye, dilated and non-responsive pupil, blindness	Ocular ultrasound is helpful with an opaque media. Evaluate for signs of other primary sources and with various imaging techniques. Consider aspirate of intraocular mass, or blind vitreal aspirate. Enucleated globes must be evaluated microscopically.	Smaller focal posterior segment tumors may be treated with laser or cryosurgery (rare). Large primary tumors are treated with enucleation. Enucleation is also considered when secondary glaucoma, uveitis/hyphema, blindness, or chronic pain are present or to reach a diagnosis. Intraocular lymphoma can be treated with systemic chemotherapy. Other secondary tumors are treated as appropriate for the primary tumor.	Most primary intraocular tumors are considered to be benign but locally destructive. Secondary tumors are considered metastatic lesions and therefore have a much more guarded prognosis for general health.
Secondary tumors Lymphoma Mammary gland adenocarcinoma Thyroid adenocarcinoma Pancreatic adenocarcinoma Renal carcinoma Neurogenic sarcoma Hemangiosarcoma				

Clinical Signs

I. No apparent clinical signs are noted early in the disease.
II. If the deficiency continues, then a complete degeneration can occur with blindness.

Diagnosis

I. Funduscopic findings are often diagnostic for FCRD.
   A. Earliest lesion, Stage 1: granularity in the area centralis in the tapetal retina
   B. Stage 2: an elliptical hyperreflective lesion in the tapetal retina temporal to the optic disc
   C. Stage 3: a second hyperreflective lesion appears nasal to the optic disc
   D. Stage 4: coalescence of the two elliptical lesions to form a band of hyperreflectivity
   E. Stage 5: generalized hyperreflectivity, vascular attenuation, optic nerve atrophy
II. Many cats develop a static lesion that does not progress, indicating a focal incident of taurine deficiency that has resolved.
III. Measurement of plasma or blood taurine levels confirms the disease.
IV. Also rule out a concurrent dilated cardiomyopathy.

Differential Diagnosis

I. Stage 5 taurine retinopathy is similar in appearance to end-stage PRA.
   A. ERG is attenuated in both conditions.
   B. Plasma taurine values are normal with PRA.
II. Blindness associated with enrofloxacin administration in cats has a more rapid onset and produces more generalized retinal degeneration at the onset (Gelatt et al., 2001).

Treatment and Monitoring

I. An appropriate taurine-supplemented diet is given.
II. Also supplement taurine at 250 to 500 mg PO SID to BID.
III. If treated early enough, retinal dysfunction and progression of the disease can be stopped.
IV. If retinal degeneration (photoreceptor cell death) has already occurred, it cannot be reversed.

NEOPLASIA

See Box 102-2.

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CHAPTER 103

Diseases of the Orbit

Albert J. Mughannam

CONGENITAL DISORDERS

Microphthalmos

Definition

I. The globe is congenitally smaller than normal.
II. Potential concurrent abnormalities include cataract, anterior segment abnormalities, and retinal dysplasia.

Causes and Pathophysiology

I. Exposure to teratogen or abnormality during development of the eye in utero
II. Often idiopathic
III. Inherited in the miniature schnauzer, Australian shepherd, collie, Shetland sheepdog, Doberman pinscher, Cavalier King Charles spaniel
IV. Associated with excessive white coat color in some breeds

Clinical Signs

I. The globe is abnormally small in size.
II. Depending on its size, the microphthalmic globe may not fill the orbit completely, resulting in protrusion of the third eyelid, enophthalmos, and drooping of the lower lid.
III. Excessive accumulation of mucus and debris can occur and lead to chronic conjunctivitis.
IV. Associated conditions include cataract, anterior segment abnormalities, and retinal dysplasia.
V. Microphthalmia can be unilateral or bilateral.
VI. Vision is variable, depending on the degree of deformity.

Diagnosis

I. Diagnosis is based on the abnormally small size of the eye.
II. Measure the diameter of the cornea and compare it with the fellow eye.
III. Diagnosis is difficult in a young animal with bilaterally small eyes.

Differential Diagnosis

I. Phthisis bulbi
II. Enophthalmos
    A. Secondary to ocular pain
    B. Loss of retrobulbar fat
    C. Horner's syndrome

Treatment and Monitoring

I. Microphthalmia alone does not require treatment.
II. If entropion is severe, consider entropion surgery.
III. If clinical signs are noted and the eye is blind, consider enucleation.
IV. Cataract extraction is indicated in selected cases.
    A. Cornea must be clear enough to allow complete visualization of the lens.
    B. Adequate retinal function must be present.
        1. Evaluate light reflexes (pupillary light and dazzle reflexes).
        2. Electroretinography quantifies function of the retina.

DEGENERATIVE DISORDERS

Phthisis Bulbi

Definition

I. Globe atrophied (smaller than normal) secondary to chronic inflammation
II. Acquired, not congenital

Causes

I. Trauma
II. Inflammation
    A. Chronic uveitis, prior hyphema
    B. Previous intraocular surgery with complications

Pathophysiology

I. Chronic uveal inflammation has several deleterious effects.
    A. Fibrotic membrane formation occurs, as well as atrophy of uvea.
    B. Uvea ceases to produce aqueous humor.
    C. Intraocular pressure decreases and the globe shrinks.
II. Tissue contraction leads to disorganized, atrophied globe.

Clinical Signs

I. Abnormally small globe
    A. Subsequent enophthalmos
    B. Chronic conjunctivitis caused by accumulated mucus
II. Corneal scarring, edema, vascularization, or persistent uveitis
III. Evidence of discomfort while inflammation is active
    A. Blepharospasm

B. Pawing at the eye
IV. Uveitis: aqueous flare, conjunctival hyperemia, iridal hyperemia
V. Blindness

Diagnosis

I. Abnormally small globe
II. History of trauma, chronic uveitis, prior hyphema
III. Supportive evidence of skull trauma, penetrating foreign body
IV. Low intraocular pressure on tonometry

Differential Diagnosis

I. Microphthalmos
II. Enophthalmos

Treatment

I. Topical antiinflammatory medication for persistent uveitis
   A. Prednisolone acetate 1% or sodium phosphate BID to QID
   B. Neomycin-polymyxin-dexamethasone BID to QID
II. Enucleation if discomfort persists
   A. Chronic uveitis
   B. Chronic conjunctivitis
   C. Secondary entropion

Monitoring of Animal

I. Regular recheck examinations (every 2 to 3 months) to evaluate for discomfort while on medication
II. None required if no inflammation or discomfort present

Orbital Fat Prolapse

Definition

I. Normal retrobulbar fat is located caudal and ventral to the globe.
II. Orbital fat may prolapse rostrally into the subconjunctival space, thereby causing the conjunctiva to balloon outward.

Causes and Pathophysiology

I. The cause is usually unknown.
II. Orbital fat is normally separated from the subconjunctival space by orbital fascia.
   A. Senile degeneration of this fascia may allow fat herniation.
   B. Chronic inflammation may also weaken the orbital fascia.

Clinical Signs

I. Soft, noninflamed swelling of the conjunctiva is seen.
II. Pain is uncommon.
III. Prolapse may be intermittent.
IV. Exophthalmos, enophthalmos, and protrusion of the third eyelid are variable depending on the position of the prolapsed fat.
V. Globe position can be normal.
VI. This condition is only reported to be unilateral.

Diagnosis and Differential Diagnosis

I. Fine-needle aspirate reveals adipocytes.
II. Histological examination of excised tissue is conclusive.
III. Retropulsion of the globe is minimally inhibited.
IV. Cellulitis and abscessation, orbital hemorrhage, and masticatory myositis are painful.
V. A vascular lesion, although nonpainful, is likely to be pulsatile; color flow Doppler ultrasonography will identify abnormal blood flow.
VI. Orbital neoplasia, although typically nonpainful, is usually slowly progressive and occurs in older animals.
VII. Mucocele or cyst reveals saliva on fine-needle aspirate.

Treatment and Monitoring

I. Because this condition is not painful and is unlikely to predispose to more serious consequences, treatment is usually not necessary.
II. Surgical excision can be curative but may also predispose to further fat prolapse unless the orbital fascia is closed securely.

INFLAMMATORY DISORDERS

Mucoceles and Cysts

Definition

I. A salivary mucocele is a cavity filled with accumulated mucous secretion from leakage of saliva from the zygomatic salivary gland or its duct.
II. A retention cyst results from persistent glandular secretion.
III. The zygomatic salivary gland lies within the ventrolateral aspect of the orbit.

Causes and Pathophysiology

I. Inflammation, obstruction, or rupture of the salivary duct obstructs salivary flow.
II. Inflammation of the oral mucosa obstructs salivary outflow.
III. The cause of a retention cyst is unknown.

Clinical Signs

I. Fluctuant swelling of the conjunctiva
   A. If diseased tissue is caudal to globe: exophthalmos and third eyelid protrusion
   B. If diseased tissue is rostral to globe: enophthalmos
   C. Location of swelling variable: dorsal or medial to globe, within lower lid stroma, associated with third eyelid
II. Possible change in position of globe (Table 103-1)
III. Minimal pain on opening the mouth or palpation of the globe
IV. Unilateral
V. Possible swelling of the soft palate adjacent to the ipsilateral upper left molar teeth
VI. Conjunctival or oral swelling usually slowly progressive and nonpainful
VII. Retropulsion of globe almost normal

TABLE 103-1

Clinical Signs Associated with Orbital Disease

CLINICAL FINDING	POSSIBLE CAUSES
Exophthalmos	Rostral protrusion of the globe from a space-occupying lesion caudal to the equator May be confused with buphthalmos (defined as enlargement of the globe)
Protrusion of the third eyelid	From a space-occupying lesion caudal to the globe Could also be caused by enophthalmos, Horner's syndrome, tetanus, or idiopathic protrusion of the third eyelid
Enophthalmos	From a space-occupying lesion rostral to the equator May result from microphthalmos, phthisis bulbi, loss of orbital fat, Horner's syndrome, or retraction of the globe from pain
Conjunctival hyperemia	From vascular congestion or inflammation Nonspecific sign seen with many ocular diseases
Swelling of the soft palate caudal to the last molar tooth	The ventral floor of the orbit is composed of soft tissue. The medial aspect of the orbital floor lies immediately above the soft palate caudal to the last molar tooth.
Strabismus	From fibrosis or inflammation of the extraocular muscles
Vision loss or decreased pupillary light reflex	From optic nerve damage
Changes in retinal morphology	Indentation of the globe by the orbital process

Diagnosis

I. Ultrasonography reveals a fluid-filled mass (Table 103-2).
II. Fine-needle aspiration reveals saliva, which may be blood stained.
III. Retrograde sialography with radiographic contrast material shows filling of the lesion.
IV. Computed tomography (CT) or magnetic resonance imaging (MRI) provides more detail.

Differential Diagnosis

I. Cellulitis and abscessation, orbital hemorrhage, and masticatory myositis are painful.
II. Orbital neoplasia usually occurs in older animals.
III. Ultrasonographic findings of fluid-filled mass tend to rule out orbital fat prolapse and vascular lesions.

Treatment and Monitoring

I. Surgical excision of the affected gland and mucocele is curative.
II. Orbitotomy may be necessary.
III. Lid paresis from inadvertent incision of the palpebral nerves can occur postoperatively.
IV. Diminished aqueous tear production (keratoconjunctivitis sicca) can arise from interruption of innervation to the lacrimal gland if the palpebral nerves are damaged.

Cellulitis and Abscessation

Definition

I. Cellulitis is diffuse inflammation of the orbital tissues from infection or primary inflammation.
II. Abscessation is a localized collection of purulent material.

Causes and Pathophysiology

I. Usually idiopathic
II. Extension of infection from nearby structures: sinuses, zygomatic salivary gland, molar and premolar tooth roots
III. Infection: hematogenous, usually bacterial; fungal or parasitic causes rare (*Toxocara canis* in dogs)
IV. Foreign material: plant matter migrating from mouth
V. Steroid-responsive conditions
   A. Sialadenitis in dogs (Simison, 1993)
   B. Eosinophilic infiltrate in cats (Dziezyc et al., 1992)

Clinical Signs

I. Exophthalmos with protrusion of third eyelid; enophthalmos rarely
II. Pain and inability to retropulse globe
III. Pain on opening mouth from pressure of the ramus of the mandible on the orbital tissues
IV. Systemic signs: lethargy, inappetence, fever
V. Possibly an inflammatory leukogram
VI. Possible swelling and erythema of the soft palate adjacent to the ipsilateral molar teeth
VII. Possible conjunctivitis and increased intraocular pressure from tamponade
VIII. Usually unilateral
IX. Onset usually acute
X. Corneal ulceration or keratitis from exposure

Diagnosis and Differential Diagnosis

I. Diagnosis is primarily based on clinical signs.
   A. Acute onset
   B. Pain
   C. Unilateral condition

TABLE 103-2

Modalities for Diagnosis of Orbital Disease

DIAGNOSTIC MODALITY	ADVANTAGE	POTENTIAL DISADVANTAGE
General physical examination, including oral and dental examination	Aids in diagnosis of those conditions that affect other parts of the body, such as neoplasia and bleeding disorders	None
Systemic evaluation: chest and abdominal radiographs, laboratory testing	Aids in diagnosis of those conditions that affect other parts of the body, such as neoplasia and bleeding disorders	None
Digital retropulsion of globes	Aids in localization of the lesion, characterization of orbital disease (e.g., soft cyst vs. firm), and detection of pain	Results possibly inconclusive
Skull radiography	Allows evaluation of bony portions of orbit, nasal cavity, and teeth Detects radiodense foreign bodies	General anesthesia usually required
Ultrasonography	Allows imaging of the orbital soft tissues Particularly good for abscesses Doppler capabilities may help distinguish vascular lesions	Expense or availability of equipment
Computed tomography	Allows superior imaging of orbital tissues, particularly bone	Expense and availability of equipment General anesthesia required
Magnetic resonance imaging	Allows superior imaging of orbital tissues, particularly soft tissues	Expense and availability of equipment General anesthesia required
Fine-needle aspiration	Can offer cellular diagnosis Three potential locations for aspiration: 1. Into the ventral aspect of the orbit via the soft palate caudal to the last molar tooth 2. Medially along the bony orbital wall via the medial canthus 3. Laterally at the junction of the orbital ligament and zygomatic arch	Requires at least heavy sedation and often general anesthesia There is risk of piercing the globe, vessels or nerves. Introduction of infection possible
Trucut biopsy	Can offer precise tissue diagnosis	Requires at least heavy sedation and often general anesthesia Risk of piercing the globe, vessels, or nerves Introduction of infection possible

II. See Table 103-2 for diagnostic options.
   A. Ultrasonography is ideal.
   B. Inflammatory conditions are usually located laterally, whereas neoplasms are usually located medially (Mason et al., 2001).
III. Orbital hemorrhage is also usually painful, unilateral, and associated with an acute onset.
   A. Periocular tissues may be bruised, and frank bleeding may be noted.
   B. See Chapters 68 and 124 for discussion of bleeding disorders, particularly from rodenticide toxicity.
IV. Masticatory myositis is painful; however, the condition is usually bilateral.
V. Orbital neoplasia is usually not painful, is of relatively slow onset, and tends to occur in older animals.

Treatment

I. Focal orbitotomy via an oral approach is performed (Table 103-3).
   A. If abscessation is suspected, then drainage must be attempted.
   B. Cellulitis may respond solely to medical therapy.
   C. On attempted drainage, if frank pus is encountered, then bacterial culture and gentle lavage are considered.
   D. Vigorous lavage forces purulent material deeper into the orbit and must be avoided.
   E. Lack of purulent discharge does not necessarily rule out infection.
II. Following antibiotics may be used:
   A. Ampicillin 22 mg/kg PO TID

TABLE 103-3

Surgical Treatment of Orbital Disease

PROCEDURE	TECHNIQUE/RATIONALE
Enucleation of globe	Allows direct exploration of the orbit Performed if the eye is blind, irreversibly painful, or severely proptosed such that repositioning is not possible
Exenteration	Removal of all orbital contents May be the procedure of choice for an orbital neoplasm
Orbitotomy	
1. Oral approach	Incision is made into the mucosa of the soft palate caudal to the last molar tooth; a hemostat is then bluntly advanced through the medial pterygoid muscle into the ventral aspect of the orbital; drainage of fluid (usually pus) or biopsy is then possible
2. Zygomatic arch resection	Zygomatic arch is approached surgically and then removed via osteotomy Allows access to the lateral, dorsal, or ventral aspects of the orbit (Slatter and Abdelbaki, 1979; Gilger et al., 1994)
3. Dorsal approach	Skin incision is made lateral to the sagittal crest to allow undermining and reflection of the frontalis muscle Allows access to the dorsomedial and caudomedial aspects of the orbit (Ramsey and Fox, 1997)
4. Conjunctival approach	Incision is made directly into the conjunctiva Allows access to lesions rostral to the equator of the globe

B. Amoxicillin 22 mg/kg PO BID
C. Amoxicillin 22 mg/kg with clavulanic acid 13.75 mg/kg PO BID
D. Cephalexin 22 mg/kg PO BID

III. A single antiinflammatory dose of dexamethasone 0.5 to 1.0 mg/kg SC may be given to help reduce swelling and control pain.
IV. If the globe is inflamed or excessively exposed as a result of the exophthalmos, then an antibiotic ointment is applied to prevent infection and provide lubrication.

Monitoring of Animal

I. Improvement in clinical signs is usually noted within 2 to 3 days.
II. Complete resolution can take 2 to 4 weeks.
III. Lack of improvement indicates the need for further diagnostic tests (see Table 103-2).
A. Ultrasonography
B. Radiography
C. MRI or CT

Myositis

Definition

I. Masticatory myositis is inflammation of the masticatory muscles (i.e., temporalis, masseter, and pterygoideus muscles).
II. Extraocular myositis is inflammation of the extraocular muscles.

Causes

I. Immune-mediated cause is suspected.
A. Most skeletal muscles in the dog are types 1 and 2A.
B. Masticatory muscles in the dog are composed of type 2C muscle fibers, and this unique characteristic may explain the susceptibility of these muscles to immune-mediated inflammation.
II. Some breeds are predisposed to these disorders.
A. Masticatory myositis: German shepherd dog, Weimaraner, Labrador retriever, golden retriever (Gilmour et al., 1992)
B. Extraocular myositis: golden retriever most common, also Doberman pinscher, German shepherd dog, and other large-breed dogs (Ramsey et al., 1995)

Pathophysiology

I. Muscle tissues become infiltrated with inflammatory cells.
II. Swollen masticatory muscles fill the orbit and impinge on the globe, resulting in exophthalmos.
III. Swollen extraocular muscles impinge directly on the globe, resulting in exophthalmos.

Clinical Signs

I. Masticatory myositis (see Chapter 82)
A. Bilateral exophthalmos, protrusion of the third eyelid, conjunctivitis during the early stages
B. Pain on opening the mouth
C. Trismus (difficulty opening the mouth)
D. Pain on palpation of the temporal muscles and on globe retropulsion
E. Acute onset
F. Fever and anorexia common
G. Muscle fibrosis, atrophy, and subsequent enophthalmia with chronicity
H. Sudden vision loss possible (Glauberg and Beaumont, 1979)

I. Age of onset 3.1 years in one study (Gilmour et al., 1992)

II. Extraocular myositis
   A. Exophthalmos usually bilateral; excessive sclera showing circumferentially; protrusion of the third eyelid rare
   B. Not painful
   C. Often normal retropulsion of globes
   D. No systemic manifestations
   E. Vision loss uncommon
   F. Muscle fibrosis, atrophy, and subsequent enophthalmia with chronicity (Ramsey et al., 1995)
   G. Mean age of onset 13.5 months in one study (Ramsey et al., 1995)

Diagnosis

I. Bilateral exophthalmos is a characteristic feature.
II. Complete blood count may reveal eosinophilia with masticatory myositis, although this finding is nonspecific.
III. In masticatory myositis, electromyography often shows waveforms consistent with active inflammation, or atrophy in later stages of the disease.
IV. Muscle biopsy reveals predominantly lymphocytes and plasma cells in either condition, with histiocytes, eosinophils, and neutrophils noted less frequently.
V. Orbital imaging may reveal muscle swelling.
   A. Ultrasonography
   B. CT or MRI

Differential Diagnosis

I. Cellulitis and abscessation: painful but usually unilateral
II. Orbital hemorrhage: painful but usually unilateral, with periocular hemorrhage
III. Neoplasia: usually nonpainful and unilateral

Treatment

I. Institute systemic corticosteroid drugs at immunesuppressive doses (prednisone 2.2 mg/kg PO BID) for both types of myositis.
   A. Initially treat for 3 to 4 weeks, followed by a slow, tapering schedule.
   B. Lower dose and/or shorter duration are unlikely to be effective.
II. Azathioprine may be considered.
   A. As an adjunct to lower the dose of prednisone over the long term
   B. Dosage: 2.2 mg/kg PO SID; reduced to 1 to 2 mg/kg QOD for maintenance
   C. Found to be of limited benefit for extraocular myositis in one study (Ramsey et al., 1995).
III. Forcing open the jaws under anesthesia may be necessary for fibrotic masticatory myositis; however, a potential exists for fracturing the jaw.

Monitoring of Animal

I. Long-term medication is necessary for both conditions to maintain remission of clinical signs.
II. Side effects from medications must be monitored.
   A. Liver damage from long-term steroidal agents
   B. Bone marrow suppression from azathioprine
III. Fibrosis and atrophy of affected muscles may cause enophthalmos and strabismus.

VASCULAR DISORDERS

Definition

I. Two types of orbital vascular lesions are reported in small animals.
II. A varix is an enlarged and tortuous vein or artery.
III. An arteriovenous fistula is an abnormal communication between an artery and vein.

Causes and Pathophysiology

I. Congenital
II. Posttrauma
III. Precise cause difficult to establish in most cases

Clinical Signs

I. Intermittent and pulsating nonpainful exophthalmos, protrusion of the third eyelid, and/or conjunctival mass
II. More pronounced exophthalmos when the head is ventral to the heart because of positional hypertension
III. Systolic murmur or "bruit" with a fistula; none with a varix
IV. History of trauma
V. Lesion only unilateral

Diagnosis

I. The intermittent and pulsatile nature of the exophthalmos, third eyelid protrusion, and/or conjunctival swelling are highly suggestive.
II. Ultrasonography, particularly with color flow Doppler, helps identify the lesion.
III. MRI and CT can provide further detail.
IV. Contrast arteriography and venography are rarely performed.

Differential Diagnosis

I. Orbital fat prolapse may be intermittent but is not pulsatile.
   A. It is less likely to be associated with third eyelid protrusion or exophthalmos.
   B. Cytological findings include of adipocytes on aspirate.
II. Other orbital conditions rarely produce intermittent exophthalmos.

Treatment and Monitoring

I. Surgical excision is risky because hemostasis is difficult.
II. Orbital exenteration with meticulous hemostasis is curative for a fistula (Rubin and Patterson, 1965).
III. Coil embolization may be undertaken (Adkins et al., 2005).

NEOPLASIA

Definition and Causes

I. Neoplasms can arise from any orbital tissue (Table 103-4).
II. Local extension from neighboring structures and metastasis are common.

TABLE 103-4

Orbital Neoplasms

TUMOR ORIGIN	REFERENCES
Primary	
Adenoma	Headrick et al., 2004
Osteosarcoma: most frequent in dog	Kern, 1985; Cottrill et al., 1987; Hendrix and Gelatt, 2000
Mast cell tumor	Kern, 1985
Reticulum cell sarcoma	Kern, 1985
Fibrosarcoma	Kern, 1985; Hendrix and Gelatt, 2000
Chondrosarcoma	Magrane, 1965
Chondroma rodens (parosteal osteoma)	Jones et al., 1997
Hemangiopericytoma	Beltran et al., 2001
Meningioma of optic nerve	Mauldin et al., 2000
Neurofibrosarcoma	Kern, 1985; Andrew, 1999
Rhabdosarcoma (skeletal extraocular muscles)	Siebold, 1974
Lymphoma	Aquino et al., 1999
Liposarcoma	Hamor et al., 1999
Astrocytoma	Martin et al., 2000
Hemangiosarcoma	Gwin et al., 1982; LeCouteur et al., 1982
Secondary by Extension	
Regional adenocarcinoma	
Nasal	Kern, 1985; Hendrix and Gelatt, 2000
Salivary gland (usually zygomatic)	Ratto, 1991
Lacrimal	Rebhun and Edwards, 1977
Zygomatic gland adenoma	Giudice et al., 2005
Squamous cell carcinoma (from sinuses, eyelids, mouth; more common in cats)	Kern, 1985; Gilger et al., 1992
Melanoma (extension from globe, lids)	Gwin et al., 1982; Roels, 1998
Myxoma/myxosarcoma	
Metastatic	
Multicentric lymphoma	Kern, 1985; Gilger et al., 1992
Adenocarcinoma	
Uterus	Bellhorn, 1972
Mammary gland	Bellhorn, 1972
Kidney	Bellhorn, 1972
Thyroid	Barron et al., 1963
Sweat gland	Moise et al., 1982
Hemangiosarcoma	Gilger et al., 1992
Squamous cell carcinoma	Hamilton et al., 1984
Melanoma	Barron et al., 1963; Hyman et al., 2002
Transitional cell carcinoma	Szymanski et al., 1984
Meningioma	Perez et al., 2005
Fibrosarcoma	Gilger et al., 1992

Modified from Cook CS: Diseases of the orbit. p. 1076. In Morgan RV (ed): Handbook of Small Animal Practice, 3rd Ed. WB Saunders, Philadelphia, 1997; with permission.

Clinical Signs

I. Signs and signalment are often suggestive of orbital neoplasms.
   A. Usually occurs older animals (Hendrix and Gelatt, 2000; Attali-Soussay et al., 2001)
      1. Average age in dogs is 8.2 to 8.7 years.
      2. Average age in cats is 12.5 years.
   B. Usually slowly progressive and nonpainful
   C. Likely to occur medially and/or ventrally from tumor extension from neighboring tissues

II. If the mass is located caudal to the globe, then exophthalmos and protrusion of the third eyelid are seen.

III. If the mass is located rostral to the globe, then enophthalmos is seen.

IV. Vision loss with mydriasis occurs if the optic nerve is affected.
V. Corneal ulceration or keratitis from exposure is possible.

Diagnosis

I. Radiography is sometimes helpful.
   A. To assess involvement of bony orbit
   B. Thoracic radiographs to assess for metastasis
II. Ultrasonography may reveal a soft-tissue mass.
III. MRI and CT provide the greatest detail.
IV. Biopsy is required to obtain a definitive diagnosis.

Differential Diagnosis

I. Orbital cellulitis and abscessation: acute, painful, ± fever
II. Orbital cyst, mucocele: fluid-filled mass on ultrasonography
III. Orbital hemorrhage: acute, painful, tissues appear hemorrhagic, associated with systemic bleeding disorder
IV. Myositis: bilateral
   A. Masticatory myositis: painful
   B. Extraocular myositis: young dogs, globes retropulse easily
V. Idiopathic sclerosing pseudotumor in cats (Billson et al., 2006)
   A. Pseudotumor: an idiopathic mass lesion with accompanying inflammation
   B. Initial unilateral orbital involvement that progresses to bilateral
   C. Onset and progression over weeks to months
   D. Progressive immobility of normal orbital structures
   E. Clinical signs: exophthalmos, reduced ocular and eyelid motility, conjunctivitis, exposure keratitis
   F. No known cause or successful treatment

Treatment

I. General principles
   A. Most orbital neoplasms are malignant.
   B. Most orbital neoplasms are primary in dogs and secondary in cats.
      1. The most common tumor types in dogs are osteosarcoma, fibrosarcoma, and nasal adenocarcinoma.
      2. The most common tumor type in cats is the squamous cell carcinoma.
   C. Prognosis is usually poor.
II. Surgery
   A. Enucleation (removal of globe) with removal of neoplasm
      1. Procedure of choice if the globe is invaded by neoplasm
      2. Appropriate if the eye is blind or irreversibly painful
      3. May be necessary if the eye is visual, to allow access to the neoplasm
   B. Exenteration (removal of orbital contents)
      1. Procedure of choice if the neoplasm invades the globe and orbital structures
      2. More invasive than enucleation
         a More likely to induce hemorrhage
         b. Comprehensive knowledge of orbital anatomy required
   C. Orbitotomy
      1. Includes various surgical approaches that are based on the location of lesion (see Table 103-3).
      2. Ideal procedure if the lesion can be removed completely while preserving the globe; however, the surgeon may need to convert to exenteration during surgery if the neoplasm is extensive.
      3. Preoperative CT or MRI is recommended to help select a surgical approach.
III. Adjunctive therapy
   A. Chemotherapy may be used alone for lymphoma and mast cell tumors.
   B. Doxorubicin has been used for orbital sarcoma (Schoster and Wyman, 1978).
   C. Radiation therapy may be beneficial for nasal tumors (Adams et al., 1987; Roberts et al., 1987; Evans et al., 1989).

Monitoring of Animal

I. Surgical excision offers palliation, but recurrence is usually expected within several months.
II. Adjunctive therapy may delay recurrence.
III. Indications for euthanasia include the following:
   A. Neoplasm too extensive for surgical excision
   B. Systemic disease evident from metastasis

TRAUMA

Traumatic Proptosis

Definition

Proptosis is movement of the globe beyond the bony orbital rim occuring secondary to trauma.

Causes and Pathophysiology

I. Proptosis is caused by some type of trauma, such as blunt trauma or a dog fight.
II. Proptosis occurs very easily in brachycephalic breeds, because the orbit is shallow.
III. In cats and nonbrachycephalic dogs, severe trauma is required to cause proptosis.

Clinical Signs

I. Acute extreme exposure of globe
II. Corneal ulceration or keratitis from exposure
III. Mydriasis if the optic or oculomotor nerves are damaged
IV. Miosis from severe uveitis or sympathetic nerve damage
V. Conjunctivitis, chemosis, and/or conjunctival hemorrhage
VI. Lateral strabismus from rupture of medial rectus, ventral oblique, and ventral rectus muscles

Diagnosis and Differential Diagnosis

I. Diagnosis is based on history of trauma and acute onset, with classic clinical findings.
II. Perform a general physical examination to rule out other injuries.
III. Orbital hemorrhage may appear very similar clinically (acute onset, painful); therefore rule out possible rodenticide

exposure or other bleeding abnormalities (e.g., von Willebrand disease).

IV. Orbital abscessation and cellulitis, although painful and often acute in onset, rarely cause proptosis.

V. Orbital neoplasia rarely results in acute proptosis.

Treatment

I. Replace the globe into the orbit promptly to possibly restore vision.

II. Under general anesthesia, lubricate the globe with sterile ophthalmic ointment.

III. Using digital pressure or the flat surface of a scalpel handle and concurrent traction on the eyelid margins via forceps or sutures (preplacement of horizontal mattress sutures for temporary tarsorrhaphy), gently reposition the globe into the orbit.

IV. Horizontal mattress sutures are used to perform partial temporary tarsorrhaphy (closure of palpebral fissure).
   A. Sutures must be placed accurately.
      1. Sutures placed too deeply will rub the cornea.
      2. Shallow placement causes the eyelid margins to invert and rub the cornea.
   B. Place the suture directly into the orifices of the meibomian glands.
   C. A small portion of the palpebral fissure is left open medially for observation and medication administration.
   D. Two or three sutures are ideal.

V. A single antiinflammatory dose of dexamethasone 0.5 to 1.0 mg/kg SC may be given to help reduce swelling and control pain.

VI. Topical antibiotics are used BID to TID to prevent infection.

VII. Systemic antibiotics are used if infection is likely (dog bite or other penetrating injury).
   A. Ampicillin 22 mg/kg PO TID
   B. Amoxicillin 22 mg/kg PO BID
   C. Amoxicillin 22 mg/kg with clavulanic acid 13.75 mg/kg PO BID
   D. Cephalexin 22 mg/kg PO BID

VIII. Analgesics and antiinflammatory medications are given as needed.
   A. Aspirin at 5 to 10 mg/kg PO BID for dogs, and at 6 mg/kg PO QOD for cats
   B. Carprofen for dogs 2.2 mg/kg PO BID
   C. Butorphanol 1 mg/4.54 kg PO BID (dog or cat)

Monitoring of Animal

I. In the immediate postoperative period, monitor for the following:
   A. Excessive swelling at tarsorrhaphy site
      1. Possible need to revise tarsorrhaphy sutures
      2. Cold compresses to reduce swelling
   B. Protective collar to prevent self-inflicted trauma

II. Sutures are removed within 1 to 2 weeks pending resolution of orbital swelling.

III. Prognosis for vision is usually poor.
   A. Good prognostic indicators include proptosis in a brachycephalic dog, positive pupillary light reflex (direct or indirect), normal posterior segment examination findings, and presence of vision at the time of initial examination.
   B. Poor prognostic indicators include proptosis in nonbrachycephalic breeds or cats, hyphema, no visible pupil, facial fractures, optic nerve damage, and avulsion of three or more extraocular muscles.
   C. Enucleation at presentation is considered if clinical signs are catastrophic.
      1. Rupture of most or all extraocular muscles
      2. Globe rupture

IV. After removal of tarsorrhaphy sutures, monitor for the following:
   A. Recurrent proptosis
      1. Indicates irreversible damage to multiple extraocular muscles
      2. Either enucleation or permanent partial tarsorrhaphy indicated
   B. Permanent globe deviation from extraocular muscle avulsion
   C. Keratoconjunctivitis sicca secondary to lacrimal gland or duct damage
   D. Corneal anesthesia from nerve damage that predisposes to corneal ulceration

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CHAPTER 104

Ocular Manifestations of Systemic Disease

Charles M. Stuhr | Emilia F. Wood

INTRODUCTION

I. The vascular nature of the eye combined with its clear media allows visualization of signs that may otherwise be masked in other tissues.
   A. These signs are commonly, but not always, bilateral.
   B. They alert the clinician to a list of differential diagnoses and a series of tests that may lead to a definitive diagnosis.

II. The goal of this chapter is to list common or prominent systemic diseases by the most obvious clinical sign noted on an ophthalmic examination.
   A. Clinical signs are grouped into the following categories:
      1. Eyelid and periocular symptoms (Table 104-1)
      2. Corneal opacities (Table 104-2)
      3. Red eye
         a. Inflammation with a prominent mucoid or mucopurulent discharge consistent with conjunctivitis or keratitis (Table 104-3)
         b. Inflammation with a mild serous or mucoid discharge consistent with uveitis (Table 104-4)
      4. Ocular hemorrhage (Table 104-5)
      5. Cataract formation (Table 104-6)
      6. Fundic lesions with or without visual deficits (Table 104-7)
   B. No one clinical sign is pathognomonic for any one disease.
   C. If primary ocular disease is ruled out or systemic signs accompany the ocular abnormalities listed, then consider the diagnostic tests described.
   D. These lists are not all-inclusive and specifically exclude the rare storage diseases and experimental toxicities.

TABLE 104-1

Systemic Diseases Associated with Eyelid and Periocular Symptoms

SPECIES	CLINICAL SIGNS	DISORDER	DIAGNOSTIC TESTS	COMMENTS
Dog, cat	Periocular alopecia ± pruritus; crusting	Demodicosis, scabies	Skin scrape	Demodicosis is easier to diagnose than scabies with skin scraping
Dog, cat	Periocular alopecia ± pruritus; crusting	Dermatophytosis	Wood's lamp, culture	Transmissable to and from people
Dog	Periocular alopecia ± pruritus; crusting	Leishmaniasis	Skin scrape, biopsy	See Table 104-4
Dog > cat	Narrow palpebral fissure	*Clostridium tetani*	Anaerobic culture	Nictitans protrusion, "sardonic grin" History of penetrating wound
Dog > cat	Muscle spasms	Strychnine toxicity	Color of vomitus can be green or pink from dye marker in bait	Inducible tetanic convulsions Vomiting and diarrhea
Dog	Depigmentation	Vogt-Koyanagi-Harada disease	Biopsy	Also seen on face, feet, and scrotum, with rare ulceration Intraocular symptoms (see Table 104-4)
Cat	Depigmentation	Chédiak-Higashi syndrome	Blood smears Hair analysis	Inborn error of metabolism Photophobia Intraocular depigmentation
Dog > cat	Crusting, ulceration	Pemphigoid complex	Skin biopsy	Associated atopy common
Dog	Crusting, ulceration	Systemic lupus erythematosus	Skin biopsy	Keratoconjunctivitis sicca and anterior uveitis reported
Dog, cat	Crusting, ulceration	Drug eruption	Skin biopsy History of recent drug administration	Topical or parenteral use
Dog > cat	Edema, urticaria pruritus	Atopy/allergy	Intradermal skin test Enzyme-linked immunosorbent assay	Seasonal history important
Dog	Purulent discharge; crusting, alopecia, and erythema	Juvenile cellulitis	Cytology	Primarily in puppies less than 3 months old Bilateral

>, More commonly affected than.

TABLE 104-2

Systemic Diseases Associated with Corneal Opacities

SPECIES	CLINICAL SIGNS	DISORDER	DIAGNOSTIC TESTS	COMMENTS
Dog, cat	Multifocal granular haze	Inborn errors of metabolism	See discussion of primary disease (Chapters 23 and 81)	Mucopolysaccharidosis with associated facial dysmorphism Lysosomal storage diseases Multifocal retinal spots can be observed

TABLE 104-2

Systemic Diseases Associated with Corneal Opacities—*cont'd*

SPECIES	CLINICAL SIGNS	DISORDER	DIAGNOSTIC TESTS	COMMENTS
Dog > cat	Arcus lipoides, multifocal punctate anterior stromal deposits	Hyperlipidemia	Fasting serum triglycerides and cholesterol, free thyroxine, thyroid-stimulating hormone levels	Lipemia retinalis and lactescent aqueous humor are also possible Rule out hypothyroidism Primary disease in schnauzers
Dog	Arcus lipoides, lipid keratopathy	Hypothyroidism	Same for hyperlipidemia	Peripheral neuropathies, keratoconjunctivitis sicca, and blepharitis possible
Dog	Central corneal calcium deposits	Hyperadrenocorticism	Low-dose dexamethasone suppression test Adrenocorticotropic hormone (ACTH) stimulation test	Corneal erosions possible over deposits
Dog	Generalized edema	Infectious canine hepatitis	Enzyme-linked immunosorbent assay	Immune-mediated effects on uvea and corneal endothelium See Table 104-4
Dog	Multifocal punctate deposits	Corticosteroid associated	History of use ACTH stimulation test preferred	More often associated with topical than parenteral administration May develop rapidly

>, More commonly affected than.

TABLE 104-3

Systemic Diseases Associated with a Red Eye: Inflammation with a Prominent Mucoid or Mucopurulent Discharge Consistent with Conjunctivitis or Keratitis

SPECIES	CLINICAL SIGNS	DISORDER	DIAGNOSTIC TESTS	COMMENTS
Dog	Conjunctivitis, KCS	Distemper	Conjunctival cytology and IFA test Serology of CSF or serum	Retinochoroiditis (active and inactive) Optic neuritis
Dog	KCS	Sulfonamide toxicity	Schirmer tear test	Increased risk with smaller dogs (Berger et al., 1995)
Cat	Conjunctivitis, keratitis, KCS, corneal erosions, sequestrum, plaques	Herpesvirus-1	Conjunctival or corneal PCR test IFA Conjunctival cytology with intranuclear inclusions	Current or prior upper respiratory infection Signs recur with stress Unilateral lesions more common in adults
Cat	Conjunctivitis	*Chlamydophila felis*	PCR IFA Conjunctival cytology with intracytoplasmic inclusions	Organisms are difficult to culture or observe Typically unassociated with corneal disease Cytological abnormalities noted in first 2 weeks of active disease
Cat	Conjunctivitis	*Mycoplasma felis* and *Mycoplasma gatae*	PCR IFA Conjunctival cytology with cell membrane inclusions	Organisms are difficult to culture or observe Typically unassociated with corneal disease

KCS, Keratoconjunctivitis; *IFA,* immunofluorescent antibody; *CSF,* cerebrospinal fluid; *PCR,* polymerase chain reaction.

TABLE 104-4

Systemic Diseases Associated with a Red Eye: Inflammation with a Mild Serous or Mucoid Discharge Consistent with Uveitis

SPECIES	CLINICAL SIGNS	DISORDER	DIAGNOSTIC TESTS	COMMENTS
Dog, cat	Uveitis, glaucoma, retinal detachment	Metastatic neoplasia	Dependent on clinical signs	Lymphoma is most common, but many neoplasms spread to the eye and orbit
Dog > cat	Uveitis, keratitis, corneal edema, conjunctivitis, chorioretinitis, orbital cellulitis, glaucoma, retinal granulomas, optic neuritis, retinal detachment	Blastomycosis, histoplasmosis, coccidioidomycosis	Cytology Biopsy Serology (see Chapter 111)	Geographic location markedly affects relative risk of each agent With blastomycosis, posterior segment signs are more dominant than anterior segment signs (Bloom et al., 1996) Concurrent systemic signs almost always occur with histoplasmosis With coccidioidomycosis, unilateral ocular infection can occur with no obvious systemic signs (Angell et al., 1987)
Cat > dog	Chorioretinitis, retinal detachment, optic neuritis, mild anterior uveitis	Cryptococcosis	Cryptococcal capsular antigen assay Cerebral spinal fluid serology	Posterior segment more affected Possible history of exposure to pigeon feces
Dog	Granulomatous posterior uveitis, exudative retinal detachment	Protothecosis	Culture Cytology Immunofluorescent assay	Rare Associated with hemorrhagic diarrhea Fatal to date
Cat	Mild anterior uveitis, iridal swelling, secondary glaucoma	Feline leukemia virus	ELISA	Intraocular and orbital masses with associated uveitis are more common than finding aqueous flare alone
Cat	Anterior uveitis, luxated lens, secondary glaucoma	Feline immunodeficiency virus	ELISA	Pars planitis Most common infectious agent associated with secondary lens luxation
Cat	Anterior uveitis, retinal detachment, keratic precipitates	Feline infectious peritonitis virus	No definitive test (see Chapter 112) Clinical signs, elevated serum immunoglobulins	More commonly seen in young than old cats with the "dry" form
Cat	Anterior uveitis, retinal hemorrhage	Hemoplasmosis (haemobartonellosis)	Cytology of blood smear Packed cell volume PCR	Ocular signs are mild Anemia is primary source of systemic illness
Cat	Anterior uveitis, conjunctivitis	Bartonellosis (tentative)	Western Blot ELISA PCR	Concurrent stomatitis gingivitis
Cat > dog	Anterior uveitis, keratic precipitates	Toxoplasmosis	Serology (immunoglobulins G and M)	Chorioretinitis less common History of hunting Rare chorioretinitis and optic neuritis in the dog
Dog	Anterior uveitis	*Neospora caninum*	Serology (see Chapter 116)	Primarily in puppies via transplacental infection Associated neurologic disease

>, More commonly affected than; *ELISA*, enzyme-linked immunosorbent assay; *PCR*, polymerase chain reaction.

TABLE 104-4

Systemic Diseases Associated with a Red Eye: Inflammation with a Mild Serous or Mucoid Discharge Consistent with Uveitis—*cont'd*

SPECIES	CLINICAL SIGNS	DISORDER	DIAGNOSTIC TESTS	COMMENTS
Dog	Anterior uveitis, glaucoma, retinal detachment	Vogt-Koyanagi-Harada syndrome	Skin biopsy	Depigmentation Akitas are the prototypical breed See Table 104-1
Dog	Alopecia, conjunctivitis	Leishmaniasis	Cytology of bone marrow or nodes Serology ELISA or PCR of bone marrow	Ocular lesions occur in 25% of cases (Pena et al., 2000) See Table 104-1
Dog	Anterior uveitis	*Anaplasma platys*	Serology (see Chapter 115)	Mild uveitis Hemorrhagic component is minimal
Dog	Anterior uveitis, hyphema, retinal hemorrhage and detachment	*Ehrlichia canis*, *Anaplasma phagocytophilum*	Serology (see Chapter 115)	Hemorrhagic component in anterior and posterior segment can be prominent See Table 104-5
Dog	Anterior uveitis, retinal hemorrhage, chemosis, conjunctivitis	*Rickettsia rickettsii*	Serology (see Chapter 115)	Signs similar to *E. canis* but less severe See Table 104-5
Dog	Anterior uveitis	*Borrelia burgdorferi*	Lyme Western blot ELISA PCR	Minimal documentation of associated ocular signs with Lyme disease (Cohen et al., 1990)
Dog	Corneal edema, anterior uveitis	Infectious canine hepatitis	Serology (see Chapter 112)	Reaction occurs 7-21 days postvaccination with canine adenovirus-1
Dog	Anterior uveitis	Dirofilariasis	Heartworm antigen	Mobile larva visualized in aqueous humor Removal via a limbal incision
Dog	Anterior uveitis, hyphema	Brucellosis	Serology (see Chapter 113)	More common in intact, breeding animals Zoonotic potential

TABLE 104-5

Systemic Diseases Associated with Ocular Hemorrhage

SPECIES	DISORDER	DIAGNOSTIC TESTS	COMMENTS
Coagulopathies			
Dog, cat	Clotting factor deficiencies	PT Activated PTT	Orbital, conjunctival, and retinal hemorrhages Hyphema von Willebrand disease most common in the dog
Dog, cat	DIC	Fibrin degradation products Antithrombin III Platelet count D-Dimer assay	Orbital, conjunctival, and retinal hemorrhages Hyphema DIC portends a guarded prognosis Look for primary cause

PT, One-stage prothrombin time; *PTT,* partial thromboplastin time; *DIC,* disseminated intravascular coagulation.

Continued

TABLE 104-5

Systemic Diseases Associated with Ocular Hemorrhage—*cont'd*

SPECIES	DISORDER	DIAGNOSTIC TESTS	COMMENTS
Dog, cat	Platelet abnormalities	Platelet count and function tests (e.g., buccal mucosal bleeding time)	Conjunctival and intraretinal hemorrhages Look for petechiae on any mucous membrane or skin
Dog, cat	Vitamin K–associated toxins	PT, PTT	Orbital, conjunctival, and retinal hemorrhages Hyphema History of rat poison ingestion
Infectious Agents			
Dog, cat	Bacterial septicemia	Culture Complete blood count	Conjunctival and retinal hemorrhages Animal usually febrile and depressed
Dog > cat	*Borrelia burgdorferi*	Lyme Western blot ELISA PCR	Retinal hemorrhages Mild uveitis and conjunctivitis See Table 104-4
Dog	*Ehrlichia canis, Anaplasma phagocytophilum*	Serology	Orbital, conjunctival, intraretinal, and subretinal hemorrhages Hyphema Acute phase associated with marked intraocular inflammation Chronic phase less robust See Table 104-4
Cat	Feline infectious peritonitis	Clinical signs Elevated serum immunoglobulins	Retinal hemorrhages Most common in kittens See Table 104-4
Cat	Hemoplasmosis	Blood smear PCR	Punctate retinal hemorrhages from anemia
Dog	*Rickettssia* spp.	PCR/serology	Petechiae of conjunctiva, iris, and retina Milder inflammation than noted with *E. canis*
Dog	*Toxocara canis*	Fecal flotation	Retinal hemorrhages Uncommon, but reported in active working dogs
Systemic Hypertension			
Dog, cat	All types of hypertension	See below	Primary differential diagnosis in old cats presenting with acute blindness May or may not have positive pupillary light reflexes Intraretinal, subretinal, vitreal, and conjunctival hemorrhages Hyphema
Dog > cat	Primary hypertension	BP	Diagnosis by exclusion
Cat > dog	Renal disease	BP Serum biochemistry panel Urinalysis	Polyuria/polydipsia Urinalysis important
Cat	Hyperthyroidism	BP Serum thyroid hormone assays	Weight loss in the presence of healthy appetite
Dog	Pheochromocytoma	BP Ultrasonography	Diagnosis may require exploratory laporotomy
Dog	Hyperadrenocorticism	Low-dose dexamethasone suppression test Adrenocorticotropic hormone simulation test	May resolve with control of disease

>, More commonly affected than; *ELISA,* enzyme-linked immunosorbent assay; *PCR,* polymerase chain reaction; *PCV,* packed cell volume; *BP,* blood pressure.

TABLE 104-5

Systemic Diseases Associated with Ocular Hemorrhage—*cont'd*

SPECIES	DISORDER	DIAGNOSTIC TESTS	COMMENTS
Immune-Mediated Diseases			
Dog > cat	Hemolytic anemia	Coombs' test Reticulocyte count Blood smear	Conjunctival, iridal, and retinal hemorrhages Middle-aged, spayed females overrepresented
Dog > cat	Thrombocytopenia	Platelet count	Conjunctival, iridal, and retinal hemorrhages Generally platelet count < 50,000/μL needed for petechiae to develop
Other Vasculopathies			
Dog, cat	Polycythemia	PCV Erythrocyte count	Primary or secondary forms
Dog, cat	Hyperviscosity syndrome	Elevated serum immunoglobulins Serum protein electrophoresis	Screen for malignant neoplasia (i.e., multiple myeloma), ehrlichiosis

TABLE 104-6

Systemic Diseases Associated with Cataract Formation

SPECIES	SEVERITY/LOCATION OF CATARACT	DISORDER	DIAGNOSTIC TESTS	COMMENTS
Dog	Immature to mature	Diabetes mellitus	Fasting serum glucose Urinalysis	Cataract typically rapid in onset Can occur even if diabetes appears controlled
Persian cats	Posterior subcapsular	Mannosidosis	See Chapter 23	Rare inborn error of metabolism
Dog, cat	Incipient to mature	Uveitis from any cause	See Chapter 96	Very common; progression and size are varible
Dog, cat	Multifocal punctate and linear	Hypocalcemia	Serum calcium and parathormone levels	Vision usually unaffected
Dog, cat	Incipient cortical; equatorial vacuoles to immature	Corticosteroid-associated	History of high dose and/or prolonged usage	Rare with either topical and parenteral use
Cat	Cortical and nuclear	Riboflavin deficiency	History of poor diet Serum riboflavin	Associated with a high-fat or raw fish diet

TABLE 104-7

Systemic Diseases Associated with Fundic Lesions with or without Visual Deficits

SPECIES	CLINICAL SIGNS	DISORDER	DIAGNOSTIC TESTS	COMMENTS
Cat	Tapetal hyper-reflectivity	Taurine deficiency	Plasma taurine levels	Progresses from a linear streak superior to the optic disc to generalized changes
Cat	Serous retinal detachment	Feline infectious peritonitis	No definitive test	See Table 104-4
Cat	Retinal tracks	*Cuterebra* spp.	Direct observation	Tracks are suspected larval migration
Cat, dog	Retinal detachment ± hemorrhage	Systemic hypertension	Blood pressure	Retina can attach and reattach, leading to altered reflectivity of fundus See Table 104-5
Dog	Normal retina (with vision loss)	Sudden acquired retinal degeneration	ERG	Central blindness or optic nerve disease are ruled out if ERG is extinguished Pupillary light reflexes are usually present
Dog	Subretinal granuloma	*Toxocara canis*	Fecal flotation	Lesions range from granulomas and retinal detachment to quiet areas of tapetal hyperreflectivity
Dog	Retinal detachment and depigmentation	Vogt-Koyanagi-Harada syndrome	Biopsy of skin lesions	See Table 104-4
Dog	Multifocal to diffuse chorioretinitis	Caine distemper	Serology	Associated conjunctival disease See Table 104-3
Dog, cat	Swollen optic papilla	Optic neuritis	Computed tomography, magnetic resonance imaging, cerebral spinal fluid analysis Normal ERG	Blind, quiet eye with fixed dilated pupils Retina may be normal in appearance
Dog, cat	Chorioretinitis, granulomatous retinal detachment, ± optic neuritis	Systemic mycoses, protothecosis, toxoplasmosis	Depends on suspected organism, serology	See Table 104-4
Dog, cat	Retinal hemorrhage ± detachment	Tick-borne diseases, coagulopathy, anemia, platelet dysfunction, metastatic neoplasia	Depends on etiology	See Tables 104-4 and 104-5

ERG, Electroretinogram.

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CHAPTER 105

Neuroophthalmology

Annajane B. Marlar

DISORDERS OF THE EYELIDS AND ADNEXA

Facial Nerve Paralysis

Definition

I. Facial nerve paralysis is a lack of motion of muscles innervated by motor branches of the facial or seventh cranial nerve (CN VII).
II. Paralysis can be complete or partial, depending on the extent of the lesion.

Causes

I. Lesions affecting either the facial nucleus (medulla) or individual branches of the facial nerve
II. Peripheral neuropathy: endocrine secondary to diabetes mellitus, hypothyroidism, or hyperadrenocorticism; myasthenia gravis
III. Trauma to the nerve
IV. Idiopathic forms
V. Inflammation: granulomatous meningoencephalitis (GME), otitis interna and media, polyneuritis
VI. Iatrogenic: most commonly after lateral ear canal resection, ear ablation procedures, orbital exploration, lateral canthotomy
VII. Toxins: botulism
VIII. Neoplasia

Pathophysiology

I. Lesions can occur anywhere along the course of the facial nerve.
   A. Facial nucleus: ventrolateral medulla
   B. Trapezoid body: close proximity to abducens nucleus and trigeminal nucleus and tract
   C. Internal acoustic meatus of the petrosal bone: close proximity to CN VIII
   D. Facial canal, stylomastoid foramen
   E. Near muscles of facial expression: ears, eyelids, nose, cheeks, lips
II. Other cranial nerves or central nervous system (CNS) signs may occur, depending on location of the lesion.
III. Lesions can be unilateral or bilateral, partial (paresis), or complete (paralysis).

Clinical Signs

I. Lesions of nucleus and nerve before termination in individual muscle groups
   A. Eyelid paresis and paralysis: absent or decreased menace reflex (CN II or VII lesion) and palpebral reflex (CN V or VII lesion), ± wide palpebral fissure
   B. Possible ear droop on affected side
   C. Lip droop to affected side ± drooling
   D. Abnormal position of philtrum of nose: pulled toward the normal side
   E. Hemifacial spasm
      1. Lip and nose are pulled caudally on affected side.
      2. Palpebral fissure is smaller.
   F. Possibly Horner's syndrome or vestibular signs if other cranial nerves are affected
   G. Keratoconjunctivitis sicca (KCS)
II. Lesions along individual branches to different muscle groups
   A. Auriculopalpebral nerve: paresis and paralysis of ear and eyelid
   B. Buccal nerves: paresis and paralysis of lips and nose, loss of depression of lower eyelid

Diagnosis

I. Observation of facial asymmetry and position of ears, nose, and lips
II. Abnormal or absent palpebral reflex (Table 105-1)
III. Abnormal or absent menace reflex from inability to blink
IV. Possibly low tear production on Schirmer tear test
V. Tests to determine underlying cause (see Chapters 23 and 25)
VI. Evaluation of other cranial nerves

Differential Diagnosis

I. Lid retraction from scarring or trismus
II. Conformational macroblepharon
III. Exophthalmos and proptosis

Treatment and Monitoring

I. No definitive treatment exists, except to correct any underlying causes.
II. Lateral canthal closure is considered in lagophthalmic animals or in animals in which neurotrophic keratitis or KCS is also present.

TABLE 105-1

Neuroophthalmic Examination

TEST	TECHNIQUE	PATHWAY/STRUCTURE ASSESSED	NORMAL RESPONSE
Menace response	Present a sudden visual stimulus to each eye without touching or causing air movement near animal (i.e., stimulating CN V); eyes may need to be covered to prevent stimulus from contralateral eye	CN II and CN VII CN VI may be involved if globe is retracted; this is only likely if CN VII deficit is present	Eyelids close in response to stimulus; this is a learned reflex and does not develop until 12-16 weeks of age
Visual motion detection	Objects with minimal scent are moved into the visual fields; each eye is tested individually as well as together; move or throw cotton ball in front of the animal	Retina, CN II, visual pathways including visual cortex and motor pathways	Animal follows or attempts to retrieve object; movement of eyes or head occurs; this technique may be used by owners to monitor vision in the home environment
Dazzle response	Shine a very bright light (fiberoptic is best) into each eye individually	Retina, CN II, visual pathways to the subcortical level, motor pathways	Normal response is closure of the eyelids and/or retraction of the globe; the animal may move to avoid the stimulus
Pupillary shape and symmetry (performed before dilation or PLRs)	From a distance in ambient and dim light, visualize both eyes at once; observe shape and size of the pupil, as well as position	By observing pupils, assess for dyscoria, anisocoria, strabismus, lid position; it is important to assess which is the normal vs. abnormal pupil	Pupils should be symmetrical and an appropriate shape for species
Direct PLR	In darkened room, shine a light directly into the eye and observe the movement of this pupil	Retina, optic nerve, optic tract, pretectal area, anteromedian nucleus (CN III)	As light is directed into the eye, the pupil constricts
Indirect (consensual) PLR	In darkened room, shine light into one eye and observe the pupillary response of the contralateral eye	As for direct PLR	As light is directed into one eye, the contralateral pupil constricts, sometimes to a lesser degree
Swinging flashing test	In darkened room, shine light into one eye; after a few seconds, direct the light source to the contralateral eye	Retina, optic nerve, and prechiasmal lesions This test is most useful in assessing lesions anterior to the optic chiasm	Test is positive (i.e., abnormal) if, when light shifts, stimulus is insufficient to maintain constriction or if pupil dilates under direct stimulation
Blink reflex	Gently touch lateral and medial palpebral fissure; it is important not to stimulate visual pathways instead of tactile pathways	CN V and CN VII Medial canthus: ophthalmic branch CN V Lateral canthus: maxillary branch CN V	Eyelids close in response to tactile stimulus; degree of eyelid closure depends on several factors (e.g., globe position)
Corneal reflex/ sensation	Without touching the eyelids, gently touch the unanesthetised cornea with a sterile cotton-tipped applicator; a Cochet-Bonnet aesthesiometer can also be used	CN V, CN VI, CN VII Ophthalmic branch CN V	The eyelids close and the globe is retracted; this test can be used to assess CN V in the absence of normal CN VII function
Mase testing	In both scotopic (dark) and photopic (light) conditions, the animal is tested with randomly placed obstacles	Entire visual pathway and motor pathways; particularly useful in testing for nyctalopia	Normal animal is able to avoid obstacles even in a dimly lit room; scotopic vision is better in small animals than humans

CN, Cranial nerve; *PLR*, pupillary light response.

Continued

TABLE 105-1

Neuroophthalmic Examination—*cont'd*

TEST	TECHNIQUE	PATHWAY/STRUCTURE ASSESSED	NORMAL RESPONSE
Visual placing	Carry the animal toward the edge of a table	Entire visual pathway and motor pathways to forelimbs	The visual animal will reach for the edge of the table prior to touching it
Vestibulo-ocular reflex/ oculocephalic reflex, doll's head reflex	Move the head in all directions and observe for movement of the globe	Assesses vestibular system and motor pathways to extrocular muscle (i.e., CN II, IV, VI)	Eyes follow the direction of head movement, so that anterior gaze remains parallel to nose; ocular movements are bilateral and symmetrical

III. Tear supplements can be used to decrease the risk of corneal erosion.
   A. Ointments or gels are preferable because of increased contact times.
   B. Applications are often required TID to QID.
IV. Acupuncture may benefit animals with idiopathic forms (Jeong et al., 2001).
V. In some instances, paresis and paralysis may resolve with time.

Protrusion of Third Eyelid

See Chapter 96.

Neurogenic Keratoconjunctivitis Sicca

See Chapter 97.

Fibrosing Strabismus

Definition

I. Fibrosing strabismus is a syndrome characterized by a convergent esotropia (medial or ventral strabismus).
II. It can lead to decreased vision in severe cases because of altered eye position.

Causes

I. Unknown
II. Seen in different breeds: shar-pei, Akita, white German shepherd dog

Pathophysiology

I. Selective fibrosing myopathy affecting certain extraocular muscles, particularly the medial rectus, ventral rectus, and ventral oblique
II. Rotation usually ventromedial

Clinical Signs

I. Severe unilateral or bilateral, medial and ventromedial rotation of the globe is noted.
II. With forced duction, the globe cannot be moved into normal position.

Diagnosis

I. Suggestive findings on ophthalmic examination and forced duction testing
II. Imaging of orbital soft tissues with ultrasonography, magnetic resonance imaging (MRI), and computed tomography (CT)
   A. To identify affected muscles
   B. To rule out other orbital abnormalities, such as loss of retrobulbar fat

Differential Diagnosis

I. True esotropia (Table 105-2)
II. Deviation of globe from retrobulbar disease

Treatment and Monitoring

I. Surgical exploration with incision of fibrotic bands is not very successful at correcting the condition.
   A. The condition usually recurs.
   B. When the condition recurs, it does so within a short period of time and continues to progress.
II. Prognosis for returning the eye to the normal position is guarded.

Neurotrophic Keratitis

Definition

I. A keratopathy that develops from damage to the ophthalmic, sensory branches of the trigeminal nerve (CN V)
II. Usually unilateral

Causes

I. Trauma (most common): after partial or complete proptosis of the globe
II. Inflammatory and infectious diseases: GME, feline herpesvirus 1
III. Neoplasia

Pathophysiology

I. Normal corneal homeostasis depends on normal innervation.

TABLE 105-2

Lesions Affecting Eye Position

CLINICAL SIGNS	ABNORMALITY
Divergent strabismus, ptosis, inability to rotate eye nasally, dorsally or ventrally (external ophthalmoplegia)	Complete lesion of occulomotor nerve/nucleus (CN III)
As above but with ipsilateral dorsal rectus dysfunction	Central lesion involving CN III nucleus
Dysfunction of dorsal oblique muscle: unable to rotate upper aspect of the eye toward the nose	Ipsilateral trochlear nerve or contralateral trochlear nucleus (CN IV)
Dysfunction of lateral rectus: medial strabismus	Ipsilateral abducens nerve (CN VI)
Dysfunction of retractor bulbi: exophthalmos and abnormal ocular motility	Ipsilateral abducens nerve or accessory abducens nucleus (CN VI)
Convergent strabismus and pendular nystagmus in cats	Abnormality in axonal projections to visual cortex: congenital; most common in Siamese or albino animals; no treatment required
Ventrolateral strabismus (sunset sign); other neurologic signs usually present	Hydrocephalus: congenital
Skew (unilateral) deviation (ventral or ventrolateral)	Ipsilateral peripheral vestibular disease
"Jerk" nystagmus: horizontal or rotatory with quick phase away from the side of lesion	Peripheral vestibular disease
Vertical or positional nystagmus: direction changes with head position	Central vestibular disease

CN, Cranial nerve.

II. Denervation of the cornea causes a loss in corneal sensation and often leads to chronic erosive disorders.

Clinical Signs

I. Decrease in corneal sensation (see Diagnosis and Table 105-1)
II. Recurring or unresponsive corneal erosions that are not painful
III. Cranial nerve deficits if other nerves are affected (especially facial nerve)

Diagnosis

I. Lack of corneal sensation is evaluated by touching a cotton-tipped applicator to the cornea.
   A. Perform this test before application of topical anesthetic.
   B. Expected response is blinking, retraction of globe, and/or movement of the third eyelid.
   C. Alternatively, a Cochet-Bonnet aesthesiometer is used to quantify the degree of corneal sensation.
II. Diffuse stippling of fluorescein retention often occurs in the cornea and early in the course.
III. Animals with decreased corneal sensation must be evaluated carefully for KCS and facial nerve paralysis and paresis.
IV. Perform other tests for isolating and identifying a cause.

Treatment and Monitoring

I. Institute appropriate treatment of corneal erosions with topical antibiotics (see Chapter 98).
II. Consider performing temporary or permanent canthoplasties to prevent recurrence of proptosis and to protect the cornea.
III. Administer appropriate therapy for KCS, if present (see Chapter 97).
IV. After proptosis, especially in eyes with trigeminal nerve deficits, topical corticosteroids are contraindicated because they often predispose to corneal erosions, even if fluorescein staining is negative before their use.
V. Prognosis for healing of these lesions is poor, and recurrences are common.

DISORDERS OF THE PUPIL

Afferent Mydriasis

Definition

I. Afferent mydriasis is a relative dilation of the pupil resulting from a lesion affecting the retina, the optic nerve (CN II), the optic chiasm, or, uncommonly, the optic tract.
II. Abnormalities in pupillary light response (PLR) and menace reflex depend on the extent and site of the lesion.
III. After dark adaptation, the pupil is almost maximally dilated.
IV. It may be unilateral or bilateral.
V. Afferent defects are often described as prechiasmal, chiasmal, or postchiasmal.

Causes

I. Retinal lesions
   A. Retinal degeneration and atrophy: inherited degeneration, taurine deficiency, glaucoma, toxicities
   B. Retinal detachment
   C. Chorioretinitis
   D. Sudden acquired retinal degeneration (SARD)
II. Optic nerve lesions
   A. Congenital lesions: hypoplasia, coloboma
   B. Neoplasia: meningioma, lymphoma, glioma
   C. Inflammatory disorders: GME, infections (particularly fungal), immune-mediated optic neuritis, toxoplasmosis
   D. Trauma: proptosis, surgical trauma after enucleation of opposite globe, or incision and drainage of retrobulbar space

III. Optic chiasm and optic tract lesions
  A. Congenital anomaly: hydrocephalus, hypoplasia of optic nerve
  B. Neoplasia: meningioma, lymphoma, masses involving pituitary or structures of the hypophyseal fossa
  C. Inflammation: GME, immune-mediated meningitis
  D. Infections: systemic mycoses, viruses (distemper), bacterial meningitis, toxoplasmosis and other parasites
  E. Trauma: head injury
  F. Vascular lesions

Pathophysiology

I. Afferent arm of pupillomotor control has been classified as either a two- or three-neuron pathway (Figure 105-1).
  A. Signals arising in the retinal photoreceptors synapse on the bipolar cells.
  B. Bipolar cells synapse on the ganglion cells (fibers from these cells compose the optic nerve).
  C. Pupillary light fibers pass through the lateral geniculate nucleus (LGN) to synapse in the pretectal nuclei.
    1. Information from the pretectal nuclei decussates again via the caudal commissure.
    2. Information then passes to the parasympathetic nucleus of oculomotor nerve III, which is located near the Edinger-Westphal nucleus.

II. Lesions anywhere along the pathway can interrupt the normal PLR.

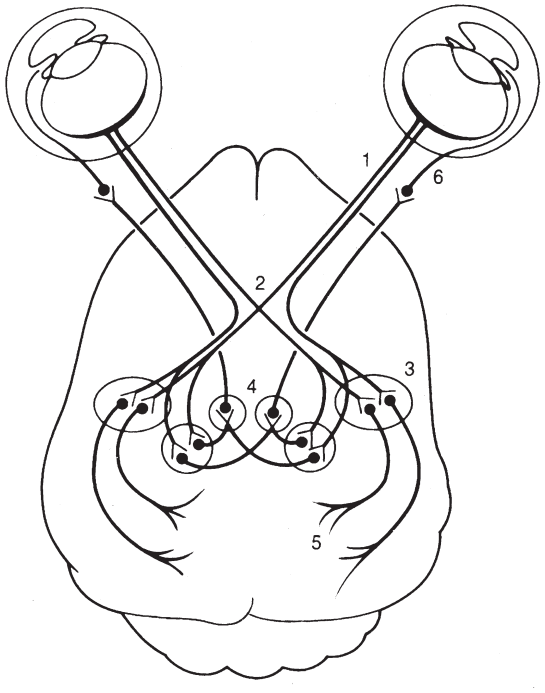

FIGURE 105-1 Pathways involved in pupillary light response (PLR) and vision. *1,* Optic nerve; *2,* optic chiasm; *3,* lateral geniculate nucleus (LGN); *4,* pretectal nucleus, near nucleus of Edinger-Westphal; *5,* optic radiation to occipital cortex; *6,* efferent, postganglionic component of parasympathetic innervation of the iris. *From Peiffer RL: Small Animal Ophthalmology: A Problem-Oriented Approach. 3rd Ed. WB Saunders, Philadelphia, 2001, p. 109; with permission.*

III. Fibers in the optic nerve carrying visual information synapse in the LGN and then travel on to the occipital cortex via the optic radiations.

Clinical Signs

I. Retinal lesions
  A. Variable menace response and visual deficits
  B. Diminished direct and consensual PLRs
  C. Positive swinging flashlight test (see Table 105-1)
  D. ± Visible fundic lesions
    1. Retinal detachment and/or retinal atrophy
    2. Chorioretinitis
    3. No lesions with SARD (see Chapter 102)

II. Optic nerve lesions
  A. Diminished direct and consensual PLRs
  B. Variable menace response and vision deficits
  C. Positive swinging flashlight test
  D. ± Funduscopic abnormalities
    1. Optic nerve swelling: papilledema, optic neuritis, elevated cerebrospinal pressure
    2. Hyperemic optic disc: optic neuritis
    3. Optic nerve cupping: coloboma or glaucoma
    4. Gray discoloration of optic nerve or small size: atrophy, hypoplasia

III. Optic chiasm lesions
  A. Diminished direct and consensual PLRs
  B. Variable menace response and vision deficits
  C. Possible systemic clinical signs: polyuria and polydipsia, polyphagia if lesion is pituitary in origin

IV. Optic tract lesions
  A. Variable direct and consensual PLRs, depending on the extent of the lesion
  B. Variable menace response and vision deficits (e.g., hemianopia)
  C. Other neurological signs depending on effect of the lesion on adjacent structures

Diagnosis

I. Complete ophthalmic examination
  A. Rule out intraocular or visible retinal and optic nerve disease.
  B. Include tonometry to rule out glaucoma.
  C. Afferent mydriasis is always accompanied by diminished or absent vision; visual deficits may be subtle to profound.

II. Neurological examination to evaluate for other deficits that aid in localization of lesion

III. PLR testing (see Table 105-1)
  A. With afferent lesions, both pupils dilate equally and maximally under dark adaptation.
  B. Because of unequal decussation of fibers at the chiasm and caudal commissure, dogs and cats may exhibit a physiological resting anisocoria.

IV. Swinging flashlight test
  A. Positive test is pathognomonic for retinal or prechiasmal lesions.

B. Lesions must be differentiated from pupillary escape—a normal phenomenon occurring when a normal pupil dilates slightly after the initial contraction as a result of adaptation of the retina.

V. Electrodiagnostics
   A. Electroretinogram (ERG) helps identify retinal diseases such as SARD or progressive retinal atrophy (PRA) (see Chapter 102).
   B. Visual evoked potentials (VEPs) are used to evaluate responses from ganglion cells to the occipital cortex.

VI. Advanced imaging techniques
   A. Ultrasonography allows visualization of the optic nerve and lesions affecting the retrobulbar area.
   B. MRI allows superior imaging of the optic nerve, chiasm, and optic tracts, as well as the brain.

VII. Cerebrospinal fluid analysis is indicated if optic pathway or CNS lesions are suspected.

Differential Diagnosis

I. Efferent mydriasis
II. Pharmacological blockade via iris sphincter paralysis (e.g., atropine)
III. Intraocular diseases
   A. Glaucoma
   B. Iris atrophy
   C. Early lens luxation
      1. Mild to moderate pupillary dilation with anterior position of lens
      2. ± Shallow anterior chamber

Treatment

I. Treat any underlying conditions (see Chapter 23).
II. Treatment of the pupillary abnormality alone is not warranted.

Monitoring of Animal

I. Prognosis depends on the underlying cause.
II. Monitor for additional ocular or neurological symptoms.

Efferent Mydriasis

Definition

I. Paralysis of the efferent parasympathetic pupillary pathway affects the iris sphincter and ciliary body.
II. Efferent mydriasis is also called *internal ophthalmoplegia*.

Causes

I. Orbital disease: trauma, space-occupying lesions, inflammation
II. Cavernous sinus syndrome (see Chapter 23)
III. Dysautonomia
IV. Midbrain or cerebellar lesions: infectious, inflammatory, anomalous, traumatic, neoplastic disorders
V. Pharmacologic blockade of iris sphincter: parasympatholytic agents (atropine, belladonna), sympathomimetics
VI. Idiopathic forms

Pathophysiology

I. Lesions along this two-neuron pathway affect the parasympathetic axons, with or without disrupting oculomotor nerve function to the extraocular muscles.
II. Cell bodies of the first-order neurons are located in the anteromedian nucleus at the rostral border of the oculomotor nucleus (CN III) and ventral tegmental area.
   A. Axons exit the mesencephalon in close proximity to the motor efferent fibers of the oculomotor nerve.
   B. Parasympathetic fibers travel superficially and medially.
   C. The fibers separate from motor efferent fibers just proximal to where they synapse within the ciliary ganglion.
III. Second-order or postganglionic parasympathetic fibers travel lateral to the optic nerve and become part of the short ciliary nerves (see Figure 105-1).

Clinical Signs

I. Mydriasis ipsilateral to lesion under normal lighting conditions
II. Normal vision and menace response in affected eye
III. Abnormal PLRs
   A. Affected eye: negative direct, positive indirect PLR
   B. Unaffected eye: positive direct, negative indirect PLR
IV. External ophthalmoplegia (see Table 105-2)
   A. It is a syndrome caused by lesions affecting the motor efferent fibers of the oculomotor nerve (CN III).
   B. It may occur if the lesion is proximal to the ciliary ganglion.
   C. Ipsilateral ptosis may occur but is often very subtle.
   D. Resting esotropia occurs from denervation of extraocular muscles innervated by CN III.

Diagnosis

I. Clinical ophthalmic examination
   A. Pupil on the affected side is dilated, with no direct PLR; however, a normal indirect PLR to the opposite eye is present.
   B. If internal ophthalmoplegia alone is seen, then the ophthalmic examination is otherwise normal.
   C. No visual deficit is detected.
   D. No history of pharmacological blockade of the iris sphincter is noted (e.g., atropine administration).
II. Neurologic examination
   A. Presence or absence of neurological deficits depends on the location of the lesion.
   B. Cavernous sinus syndrome often causes deficits in CNs IV, V, and VI.
   C. Other cranial nerve functions are usually normal if the lesion is confined to CN III.
III. Pharmacological testing (Table 105-3)
   A. To differentiate neurological lesions from iris sphincter disease
   B. To differentiate between preganglionic and postganglionic lesions

TABLE 105-3

Pharmacological Testing for Efferent Mydriasis

DRUG	MODE OF ACTION	FIRST-ORDER (PREGANGLIONIC) LESION	SECOND-ORDER (POSTGANGLIONIC) LESION	IRIS SPHINCTER DISEASE (INTRINSIC)
0.5% physostigmine	Indirect-acting parasympathomimetic	Constriction	No constriction	No constriction
0.1% pilocarpine	Direct-acting parasympathomimetic	No pupillary constriction	Constriction within 20 min	No constriction
2% pilocarpine	Direct-acting parasympathomimetic	Constriction within 20 min	Constriction within minutes	No constriction

Differential Diagnosis

I. Afferent mydriasis: vision deficit present
II. Dysautonomia: bilateral mydriasis, other ocular abnormalities (see Dysautonomia) with other systemic signs
III. Cerebellar disease: ± contralateral mydriasis
IV. Intraocular diseases
  A. Iris atrophy: no pupillary constriction with topical pilocarpine, other neurological signs absent
  B. Glaucoma: ruled out using tonometry, ophthalmic examination, and visual testing (see Chapter 100)
  C. Early lens subluxation: careful examination of anterior chamber depth and iris position usually diagnostic; ± elevations in intraocular pressure
  D. Posterior synechiae: visible adhesions between the iris and lens restricting iris movement
  E. Developmental anomalies of the iris sphincter: hypoplasia, coloboma, persistent pupillary membrane visible on examination of anterior segment

Treatment

I. Treatment is directed against any underlying neurological or orbital diseases.
II. If the mydriasis is caused by prior administration of parasympatholytic drugs, then consider discontinuing their use.
III. Dilute topical pilocarpine may be used for symptomatic relief in animals with dysautonomia (see later in this chapter).

Monitoring of Animal

I. Efferent mydriasis associated with focal CN III lesions may be permanent but is not life threatening.
II. Lesions of the midbrain and caudal brainstem warrant a guarded to grave prognosis.
III. Mydriasis from atropine and other parasympatholytic agents usually subsides within 7 to 14 days.
IV. Idiopathic efferent mydriasis may be transient and slowly resolve within several weeks.

Horner's Syndrome

Definition

I. Horner's syndrome is caused by a loss of sympathetic innervation to the eye and periorbita.
II. The causes are classified as central, preganglionic, or postganglionic.

Causes

I. Central (first-order) lesions
  A. Trauma
  B. Vascular diseases
  C. Neoplasia
  D. Inflammatory or infectious meningoencephalitides (e.g., GME, canine distemper)
II. Preganglionic (second-order) lesions
  A. Neoplasia
    1. Mediastinal lesions: lymphosarcoma, thymoma, metastatic tumors, anterior lung lobe tumors
    2. Cervical tumors: thyroid, parathyroid, soft tissue sarcomas
  B. Trauma
    1. Bite wounds to neck
    2. Automobile crashes with brachial plexus avulsion
    3. Surgical trauma
  C. Inflammation of cervical soft tissue structures adjacent to vagosympathetic trunk
  D. Abscess formation in soft tissues adjacent to neurons or ganglion
  E. Iatrogenic: jugular venipuncture or intravenous catheters
III. Postganglionic (third-order) lesions
  A. Idiopathic: common cause
  B. Middle ear disease: otitis media, petrositis
  C. Head trauma
  D. Neoplasia: middle ear, retrobulbar area
  E. Iatrogenic: bulla osteotomy, ear cleaning
  F. Cavernous sinus syndrome: vascular or neoplastic causes

Pathophysiology

I. Lesions may occur anywhere along the sympathetic efferent pathway.
II. First-order neurons develop as follows:
  A. Cell bodies reside in the hypothalamus and midbrain.
  B. Axons traverse the brainstem and spinal cord via the lateral tectotegmental spinal tracts.

C. They synapse with second-order neurons in the intermediate gray matter of the first three thoracic cord segments.

III. Second-order neurons exit the spinal cord via the thoracic spinal nerves.
   A. They travel with the sympathetic trunk across the cranial thorax.
   B. They continue through the cervicothoracic and middle cervical ganglion without synapsing and join the vagus nerve to form the vagosympathetic trunk.
   C. They synapse with third-order neurons in the cranial cervical ganglion.

IV. Third-order neurons arise in the cranial cervical ganglion (ventromedial to tympanic bulla), and their axons travel in close proximity to the internal carotid artery.
   A. They join the tympanic branch of the glossopharyngeal nerve (CN IX) in the middle ear.
   B. Axons travel from the middle ear through the cavernous sinus to join the ophthalmic branch of the trigeminal nerve (CN V).
   C. Axons enter the orbit through the orbital fissure and enter the globe via the long ciliary nerve.

Clinical Signs

I. Clinical signs ipsilateral to the lesion
II. Miosis and anisocoria more noticeable after dark adaptation
III. Third eyelid protrusion
   A. Passive: secondary to enophthalmos
   B. Active: denervation to smooth muscles of the third eyelid, particularly in the cat
IV. Enophthalmos
   A. Decrease in tone of smooth muscle encircling and within periorbital cone
   B. Allows increased retraction of globe by extraocular muscles, particularly retractor bulbi
V. Ptosis
   A. Secondary to denervation of Müller's muscle in the superior eyelid
   B. Rarely, a reverse ptosis (narrowing of palpebral fissure) if the inferior lid is involved
   C. Secondary to changes in globe position (enophthalmos)
VI. Possibly other signs associated with specific causes
   A. Laryngeal hemiplegia possible with lesions affecting second-order neurons
   B. CNS signs with first-order neuron disease
   C. Forelimb paralysis with anterior thoracic trauma
   D. Head tilt or facial nerve paralysis with middle ear disease

Diagnosis

I. Clinical history often indicates an acute onset and may identify an underlying cause (e.g., trauma, ear disease).
II. Careful ophthalmic and neurological examinations usually confirm the presence of Horner's syndrome.
   A. Three of the four ophthalmic signs are required (in the absence of other ophthalmic abnormalities that could produce these clinical signs).
   B. Perform a complete neurological examination to rule out other neurological deficits.
III. Thorough physical examination aids in the localization of any neurological and causative lesions.
IV. Pharmacological localization may be tried (Table 105-4).
   A. Controversy exists over the correct and most reliable testing protocols to use.
   B. Pharmacological testing may give helpful information but often yields inconsistent results.
   C. Denervation hypersensitivity of third-order neurons occurs after 7 to 14 days.
   D. Testing done in the absence of other ophthalmic manipulations (topical anesthetics and drugs affecting the pupils) is most reliable.
   E. Optimum minimal interval between applications of different test agents is 24 hours.
V. Other diagnostic aids include the following:
   A. Complete ear examination in postganglionic cases, ± fiber-optic scoping, myringotomy
   B. CT or MRI of the head and neck or radiography of the chest, depending on clinical signs
   C. Complete blood count, biochemistry profile, thyroid function tests
   D. Cerebrospinal fluid analysis for suspected central disease

TABLE 105-4

Pharmacological Testing for Horner's Syndrome

DRUG	MODE OF ACTION	CENTRAL LESION	PREGANGLIONIC LESION	POSTGANGLIONIC LESION
1% hydroxyamphetamine*	Indirect sympathomimetic—causes release of norepinephrine	Normal dilation	Normal dilation	No dilation
1% phenylephrine or 0.1% epinephrine	Direct-acting sympathomimetic	No dilation	No dilation	Dilation within 20 min
2.5% phenylephrine or 1% epinephrine	Direct-acting sympathomimetic	No dilation	Dilation within 20 min	Dilation within minutes

*This agent is no longer available commercially but can be compounded.

Differential Diagnosis

I. Third eyelid protrusion
  A. Ocular pain
  B. Enophthalmos
  C. Haw's syndrome
  D. Tetanus
  E. Dysautonomia
  F. Keratoconjunctivitis sicca
II. Miosis
  A. Ulcerative keratitis
  B. Anterior uveitis
  C. Drug-induced
  D. Spastic pupil syndrome (see later in this chapter)
  E. Central neurological lesions
III. Enophthalmos
  A. Ocular pain
  B. Decrease in orbital contents

Treatment

I. Treat any underlying cause.
II. Control of miosis in postganglionic lesions can be achieved using topical phenylephrine but is only recommended for those dogs in which vision is impaired by marked protrusion of the third eyelid.

Monitoring of Animal

I. Many postganglionic and idiopathic cases resolve spontaneously over a 6- to 8-week period.
II. If no cause is identified, then counsel owners to monitor for onset of other neurological signs.
III. Horner's syndrome associated with anterior thoracic lesions, brachial plexus injuries, and CNS disease is usually permanent.

Dysautonomia (Key-Gaskell Syndrome)

Definition

I. Key-Gaskell syndrome is characterized by a generalized failure of autonomic nerve function.
II. The disorder affects both sympathetic and parasympathetic systems.
III. The syndrome is most commonly recognized in the United Kingdom, but sporadic cases occur in the United States.
IV. Cats are affected most often in the United Kingdom, but dogs are affected more often in the United States.

Causes

I. The cause is unknown.
II. The syndrome closely resembles "grass sickness" in horses.
III. The disease does not appear to be contagious, but certain risk factors have been identified in dogs (Berghaus et al., 2001; Harkin et al., 2002).
  A. Young, outdoor dogs
  B. Rural location
  C. Dogs with access to pasture, farm ponds, and cattle
  D. Dogs consuming wildlife
IV. Previous theories that this syndrome is related to toxicity from flea products have been dismissed.

Pathophysiology

I. Necrosis and degeneration of autonomic ganglia and neurons occur and are most severe in acute to subacute cases.
II. Minimal inflammatory cellular infiltrates are noted.
III. CNS lesions involve a variety of locations.
  A. Various nuclei: CN III, V, VII, and XII; dorsal vagal nucleus; nucleus ambiguus
  B. Spinal cord ventral horn cells and intermediolateral gray matter
IV. Peripheral nervous system lesions are also widespread.
  A. Autonomic ganglia: both sympathetic and parasympathetic
  B. Dorsal root ganglia and ganglia of cranial nerves

Clinical Signs

I. Ophthalmic signs
  A. Keratoconjunctivitis sicca
  B. Bilateral third eyelid protrusion
  C. Mydriasis without visual deficits
  D. Occasional anisocoria
II. Systemic signs
  A. Dry mucous membranes
  B. Depression, anorexia, weight loss
  C. Constipation, fecal incontinence from decreased sphincter tone
  D. Megaesophagus with dysphagia, regurgitation, vomiting
  E. Possible bradycardia
  F. Dysuria, bladder atony

Diagnosis

I. Clinical history and physical examination findings are usually suggestive.
II. Pharmacological testing may be tried.
  A. Miosis occurs after topical administration of pilocarpine 0.05% to 0.1% or echothiophate iodide 0.06% (variable response in severe cases).
  B. Bethanechol 0.0375 mg/kg SC may result in voluntary urination.
III. Obtain a thoracic radiograph to evaluate for megaesophagus.
IV. Biochemistry, hematological findings, and urine tests are usually normal.
V. Definitive diagnosis requires histopathologic examination of autonomic ganglia.

Differential Diagnosis

I. Other causes of efferent mydriasis (see earlier in this chapter)
II. Other causes of third eyelid protrusion (see Chapter 96)
III. Other causes of KCS (see Chapter 97)

Treatment

I. Supportive therapy
  A. Parenteral nutrition, ± gastrostomy tube placement
  B. Manual bladder expression
  C. Fluid therapy

II. Topical ophthalmic pilocarpine (0.1% or 1%) or physostigmine (0.25%) BID to TID to stimulate pupillary constriction, as well as lacrimal and oronasal secretions
III. Bethanechol 2.5 to 5.0 mg PO BID to TID or 0.0375 mg/kg SC
   A. Monitor for denervation hypersensitivity to these drugs and adjust doses accordingly.
   B. Response often diminishes over time, requiring increased dose or change in route of administration (0.1 to 0.5 times normal dose).

Monitoring of Animal

I. Partial or full recovery is unlikely and may take months.
II. Abnormalities often persist, such as mydriasis, megaesophagus, and bladder atony.
III. Death from the disease or euthanasia is common.

Spastic Pupil Syndrome

Definition and Cause

I. Spastic pupil syndrome is a static or alternating anisocoria seen in cats with an absence of other neurologic deficits.
II. Feline leukemia virus infection is considered the cause.
   A. C-type viral particles are present in the ciliary ganglia and short ciliary nerves, suggesting direct viral invasion or an immunological reaction.
   B. Infiltration of these structures or iris stroma by neoplastic cells (lymphosarcoma) may also occur.

Clinical Signs

I. Anisocoria is noted over time and may alternate between eyes at various intervals.
II. Pupils may behave normally between episodes.
III. No other visual or iris abnormalities exist.

Diagnosis and Differential Diagnosis

I. Take a thorough history and perform a complete ophthalmic examination to rule out vision or iris disorders.
II. Also rule out Horner's syndrome and afferent PLR lesions.
III. Test for feline leukemia virus; may need repeated serology or testing of bone marrow.

Treatment and Monitoring

I. No treatment is available.
II. Prognosis is poor.
III. Other clinical signs of feline leukemia usually occur within a few years of diagnosis.

DISORDERS OF VISUAL PATHWAYS

Definition

I. Vision is decreased from lesions occurring in one or more of the structures involved in vision, such as the retina, optic nerve, optic chiasm, optic tracts, lateral geniculate body, rostral colliculus, optic radiation, parietal cortex, striate cortex, and extrastriate cortex.
II. Visual behavior relies not only on pathways that lead to processing of visual stimuli but also on the animal's ability to orient the eyes in such a way as to acquire those visual stimuli.
III. In animals, localization of more complex central visual deficits is often made difficult by the limitations of working with a nonverbal patient in conditions of varied stimuli and expected responses.
IV. It is important to note that a positive PLR is not indicative of vision.

Causes

I. Retina
   A. Retinal degenerations: PRA, SARD
   B. Retinal detachment
   C. Inflammatory disease, retinal toxins (see Chapter 102)
II. Optic nerve and chiasm
   A. Optic nerve hypoplasia, atrophy, coloboma
   B. Dysfunction from exposure to toxins (Table 105-5)
   C. Degeneration (e.g., glaucoma, trauma), inflammation, compression
   D. Anomalous misdirection of axons: Siamese cats, Belgian shepherd dogs
   E. Neoplasia
III. Optic tracts
   A. Inflammation, trauma
   B. Anomalies, vascular abnormalities
   C. Neoplasia
IV. LGN, rostral colliculus, optic radiation, visual cortices
   A. Inflammation, vascular disorders
   B. Drug-induced lesions, metabolic diseases
   C. Anomalous LGN abnormalities in albinos
   D. Anesthesia, certain toxicities
   E. Trauma, neoplasia

TABLE 105-5

Examples of Neuroophthalmic Toxicants

AGENT	NEUROOPHTHALMIC SIGNS
Cholinesterase inhibitors (e.g., carbamate, organophosphate)	Miosis
Ivermectin	Mydriasis, vision deficits, ± papilledema, ± retinal folding
Many plants (e.g., black locust, lantana, dogbanes)	Mydriasis
Metronidazole	Nystagmus
Sassafras	Mydriasis
Marijuana	Mydriasis
Cocaine	Mydriasis
Morphine	Miosis followed by mydriasis
Amphetamines	Mydriasis
Arsanilic acid	Blindness
Atropine	Mydriasis, decreased tear production

Pathophysiology

I. The afferent visual pathway involves multiple neurons as described previously (see Afferent Mydriasis and Figure 105-1).
II. Lesions may be bilateral or unilateral, partial, or complete.

Clinical Signs

I. Changes in visual behavior depend on the location and extent of lesions.
II. Wandering (pendular) nystagmus is indicative of a congenital or very early onset of blindness.
III. Retinal lesions are characterized by the following:
  A. Ipsilateral afferent mydriasis
  B. Abnormal menace and dazzle responses
  C. Visual deficits
  D. Funduscopic abnormalities in some conditions (e.g., PRA) but not in others (e.g., SARD)
IV. Optic nerve lesions often exhibit the following signs:
  A. Ipsilateral afferent mydriasis
  B. Visual deficits
  C. Abnormal menace response and dazzle response
  D. Ophthalmoscopic lesions in some cases: optic nerve atrophy, papillitis
  E. Possible cranial nerve deficits, other signs of orbital disease
V. Traits of optic chiasm lesions vary.
  A. Early rostral lesions cause decreased vision in the ipsilateral eye and progress to deficits in both visual fields (heteronymous).
  B. In some cases, other systemic abnormalities are present (e.g., polyuria, polydipsia) from expanding pituitary masses or other causes.
VI. Optic tract lesions have more subtle signs.
  A. Subtle or no anisocoria: dilated pupil contralateral to lesion
  B. Negative swinging flashlight test
  C. Contralateral homonymous visual field loss
VII. LGN lesions induce varying degrees of visual field deficits with normal PLRs.
VIII. Optic radiation lesions produce partial or complete vision loss with normal PLRs.
IX. Rostral colliculus lesions are characterized by partial or complete vision loss, visual deficits, and other neurological abnormalities.
X. With diffuse visual cortex disorders, menace response is usually absent.
  A. Changes in conjugate eye movement and vision may occur.
  B. The dazzle response is often positive, and PLRs are normal.

Diagnosis

I. Ophthalmic examination to identify vision, PLR, and other abnormalities
II. Neurological examination to elucidate cranial nerve and other deficits
III. Testing of oculomotor pathways via visual placing reactions, conjugate eye movements
IV. ERG to identify retinal disease
V. VEPs to detect postretinal lesions
VI. Diagnostic imaging to examine visual pathways
  A. MRI provides superior imaging of visual pathways and good delineation of CNS lesions.
  B. CT is good for localizing extracranial and intracranial nonocular disease.
  C. Ultrasonography is useful in imaging the retrobulbar space for compressive optic nerve lesions.
  D. Introduction of functional MRI may help to further delineate intracranial lesions.

Treatment and Monitoring

I. Treatment is aimed at any underlying cause.
II. Counseling the owner is recommended.
  A. Blindness, regardless of cause or reversibility, is traumatic for many owners.
  B. Visual impairment alone does not necessitate euthanasia of the animal.
  C. Alternative training techniques, such as scent training, voice commands, and/or clicker training, can help during the adjustment phase.
  D. Prognosis for return of vision from many conditions is guarded.
III. In many cases other neurological deficits are present or develop as the underlying disease progresses.

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CHAPTER 106

Introduction

Lynette K. Cole

GENERAL INFORMATION

I. Ear diseases are common in animals, with reported incidences of otitis externa between 10% and 20% in the dog and 2% and 10% in the cat (Logas, 1994).
II. Chronic recurrent otitis externa develops if any primary underlying dermatologic condition is not diagnosed and treated.
III. Infectious otitis media is common in dogs with chronic recurrent otitis externa and often prevents resolution of the otitis.
IV. End-stage otitis occurs after months or years of chronic, recurrent otitis externa and usually requires surgical intervention consisting of a total ear canal ablation and bulla osteotomy.
V. Clinical signs of otitis interna consist of a head tilt to the affected side, spontaneous horizontal or rotary nystagmus, and asymmetrical limb ataxia.
VI. Deafness may be either acquired or congenital, with both requiring electrodiagnostics to evaluate hearing objectively.

ANATOMY OF THE EAR

I. Pinna
  A. The auricular cartilage expands to form the pinna, with the skin of the concave portion of the pinna adhering tightly to this cartilage.
  B. The pinna has vastly different breed conformations in the dog, whereas, there is little breed variation in the cat.
  C. The pinna is a mobile structure designed to localize and collect sound waves and transmit them to the tympanic membrane.
  D. The cartilage of the pinna becomes funnel shaped at the opening of the external ear canal.
II. External ear canal
  A. The opening of the external ear canal is bounded by the helix (the free, slightly folded margin of cartilage at the base of the pinna) rostrally, the tragus laterally, and the antitragus caudally.
  B. The vertical ear canal runs for about 1 inch, extending ventrally and slightly rostrally before taking a medial turn and forming the horizontal ear canal.
  C. The horizontal ear canal is composed of auricular and annular cartilage. The deeper portion of the annular cartilage of the horizontal ear canal overlaps with the osseous external acoustic meatus and articulates via ligamentous tissue.
  D. The ear canal is lined by skin that contains sebaceous glands, ceruminous glands (modified apocrine glands), and hair follicles. These adnexal structures are more numerous in the vertical ear canal than the horizontal ear canal of the dog.
III. Middle ear
  A. The middle ear is composed of the air-filled tympanic cavity, which is connected to the nasopharynx by the auditory (eustachian) tube.
    1. The tympanic membrane closes off the tympanic cavity at the level of the external acoustic meatus.
    2. The tympanic cavity is divided into three portions and contains the three auditory ossicles.
  B. The tympanic membrane separates the external ear canal from the middle ear.
    1. It is a semitransparent membrane that is thin in the center and thicker at the periphery.
    2. It is divided into two sections—the small upper pars flaccida and the larger lower pars tensa.
    3. The pars flaccida is the pink, small, loosely attached region forming the upper quadrant of the tympanic membrane that contains small blood vessels.
    4. The pars tensa, a thin, tough, pearl-gray structure with radiating strands, occupies the remainder of the membrane.

5. The pars tensa is attached firmly to the surrounding bone by a fibrocartilaginous ring, known as the *annulus fibrocartilaginous,* which is in turn attached to the osseous ring of the external acoustic meatus by fibrous tissue.
6. The manubrium of the malleus attaches to the medial surface of the tympanic membrane.
7. The outline of the manubrium of the malleus (the stria mallearis) may be visualized when the tympanic membrane is viewed externally.

C. The tympanic cavity may be divided into three portions.
1. The epitympanic recess is the smallest of the three areas and is occupied by the head of the malleus and the incus at their articulation.
2. The tympanic cavity proper is adjacent to the tympanic membrane.
   a. The caudal portion of this region contains the cochlear (round) window.
   b. The auditory tube connects the nasopharynx to the rostral portion of the tympanic cavity proper.
   c. The promontory, which houses the cochlea, lies opposite the tympanic membrane.
3. The largest region of the tympanic cavity, the ventral portion, is contained within the tympanic bulla.

D. The three auditory ossicles—the malleus, incus, and stapes—are the bones that transmit and amplify air vibrations from the tympanic membrane to the inner ear.

E. The footplate (base) of the stapes is attached to the vestibular (oval) window, which is in direct contact with the perilymph fluid.

IV. Inner ear

A. The main functions of the inner ear are to transmit sound and maintain balance.

B. The inner ear consists of an osseous and membranous labyrinth.

C. The osseous labyrinth contains a fluid, perilymph, and encloses the membranous labyrinth, which contains its own fluid, endolymph.

D. The membranous labyrinth contains a series of fluid-filled ducts and chambers.
1. It has three semicircular ducts, each in a separate plane.
2. Each semicircular duct has an ampulla with a sensory crista.
3. The labyrinth also houses the utriculus and sacculus, which contain sensory maculae.
4. Both the maculae and cristae conduct impulses for balance via the vestibular nerve.
5. The most highly developed portion of the membranous labyrinth is the cochlear duct.
6. Within the cochlear duct lie the organ of Corti, tectorial membrane, vestibular membrane, and sensory cells, all of which are involved in the transduction and transmission of sound impulses via the cochlear nerve to the brain.

E. The bony labyrinth surrounds the membranous labyrinth and consists of a perilymphatic space or vestibule, three semicircular canals, and a spiral cochlea.

DISEASES OF THE EAR

I. The ear diseases have been divided into three chapters.

II. Diseases of the external ear pinna are discussed in Chapter 107.

III. Diseases of the middle and inner ear are covered in Chapter 108.

IV. Chapter 109 examines the subject of deafness.

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CHAPTER 107

Diseases of the External Ear and Pinna

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OTITIS EXTERNA

Definition

I. Otitis externa is an inflammation of the external ear canal.
II. Many times the pinna, middle ear, or both are also involved.

Causes

I. Causes of otitis externa are divided into predisposing, primary, and perpetuating factors.
II. Predisposing factors include anything that alters the delicate microenvironment of the external ear canal, allowing the canal to be overwhelmed by opportunistic or pathogenic microorganisms.
  A. Conformational abnormalities
    1. Gross anatomical variations
      a. Dogs with pendulous ears have significantly more otitis than dogs with erect ears.
      b. Dogs with congenital (e.g., Chinese shar-pei) or acquired (e.g., extraluminal neoplasias, abscessation) stenosis of the ear canal have increased incidence of otitis.
    2. Microanatomic variations
      a. Certain breeds, such as the Labrador retriever, American cocker spaniel, and English springer spaniel, have increased numbers of apocrine glands (ceruminous glands) and increased wax production.
      b. The aforementioned breeds and other heavily coated breeds (e.g., poodle, Lhasa apso) also have a higher density of compound hair follicles in the ear canal that allows for the excess accumulation of debris and wax in the canal.
      c. These microanatomical changes can lead to higher resident microbial populations and higher incidence of otitis externa compared with greyhounds and mongrel dogs.
  B. Ear canal epithelial compromise
    1. Increased moisture in the ear canal causes rehydration of corneocytes, maceration of the epidermis, and breakdown of the protective barrier (stratum corneum), allowing opportunistic microbes to colonize the ear canal and initiate otitis.
      a. Excessive wetting of the ear canal during bathing or swimming
      b. Chronic use of an aqueous-based ear cleaner
      c. High ambient humidity, temperature, and rainfall.
    2. Mechanical trauma to the ear canal leads to damage of the outer defenses of the otic epithelium and colonization by opportunistic pathogens.
    3. Overzealous ear cleaning with potent drying agents, use of cotton swabs or other objects to remove wax, and vigorous hair plucking are all potentially traumatic to the otic canal.
  C. Systemic diseases
    1. By impairing cell-mediated immunity, feline leukemia virus, feline immunodeficiency virus, canine parvovirus, and canine distemper virus predispose the ear to microbial overgrowth and subsequent otitis.
    2. Hyperadrenocorticism, hypoadrenocorticism, and diabetes mellitus are infrequently associated with otitis externa.
III. Primary factors directly cause otic inflammation.
  A. Parasites
    1. *Otodectes cynotis* is responsible for 50% of otitis externa cases in the cat and 5% to 10% in the dog, particularly in animals <1 year of age (Griffin, 1993).
      a. Otitis is secondary to direct irritation of ceruminous glands and sensitization of the host to the mite's salivary antigen.
      b. In cases of hypersensitivity, severe inflammation occurs with very few mites.
    2. *Demodex* spp. infestation can cause a severe ceruminous otitis in both dogs and cats, and otitis may be the first, only, or persistent sign of infestation.
    3. *Sarcoptes* spp., *Notoedres* spp., *Eutrombicula alfreddugesi,* hard ticks, fleas, flies, and lice mainly affect the pinna, although *Sarcoptes* spp. and *Notoedres* spp. can occasionally be found deep in the canal.
    4. The spinous ear tick, *Otobius megnini,* can cause severe, painful inflammation of the canal.
  B. Foreign bodies
    1. Grass awns, foxtails, dirt, and debris
    2. Dried medication, loose hair, and impacted wax

C. Hypersensitivity reactions
   1. The most common cause of persistent bilateral otitis externa in the dog
   2. Atopy
      a. Greater than 50% of atopic dogs have otitis externa at some time (Griffin, 1993).
      b. Otitis externa may be the first and only evidence of atopic disease.
      c. In uncomplicated cases of atopic otitis, only the pinnae and vertical canals are affected while the horizontal canals remain virtually normal.
   3. Food allergy
      a. Otitis externa may be present in up to 88% of food allergic dogs (Rosser, 1993).
      b. Otitis may be the first and only clinical sign.
      c. In uncomplicated cases, only the pinnae and vertical canals are affected.
   4. Contact allergy
      a. Contact allergy to topical therapy is suspected in any case that worsens or does not improve with appropriate therapy.
      b. Contact allergy also may occur from environmental allergens, such as wandering jew, jasmine, and various weeds.

D. Immune-mediated skin diseases
   1. Pemphigus foliaceus, Pemphigus erythematosus, discoid lupus erythematosus, systemic lupus erythematosus, Pemphigus vulgaris, bullous pemphigoid, and drug eruptions (both systemic and topical) may all develop otitis as part of their clinical manifestation.
   2. The pinnae are affected in addition to other parts of the body.

E. Disorders of keratinization
   1. They may cause severe ceruminous otitis.
   2. Idiopathic seborrhea and hypothyroidism are the most commonly diagnosed diseases.
   3. Other endocrinopathies or sex-hormone diseases (e.g., male feminizing syndrome, Sertoli or interstitial cell tumors, ovarian imbalance) may be associated with a ceruminous otitis externa, but are rarely diagnosed.

F. Neoplasia and polyps
   1. Intraluminal tumors usually cause unilateral otitis and are more common in older animals.
   2. Intraluminal neoplasia causes canal stenosis and direct inflammation via tumor ulceration and necrosis.
   3. Inflammatory polyps are a cause of recurrent unilateral otitis in cats, particularly those <2 years of age, and have also been identified in the dog,
   4. Neoplasms include sebaceous gland, basal cell, mast cell, and ceruminous gland tumors, as well as fibroma, fibrosarcoma, chondroma, chondrosarcoma, squamous cell carcinoma, and trichoepithelioma.

G. Miscellaneous diseases
   1. Juvenile cellulitis
   2. Zinc-responsive dermatosis
   3. Lethal acrodermatitis of bull terriers
   4. Papillomas

IV. Perpetuating factors prevent the resolution of otitis or worsen an already existing otitis externa.
   A. Bacteria
      1. Low numbers of commensal and potentially pathogenic bacteria are found in normal ears.
      2. The most common bacteria associated with otitis externa are *Staphylococcus intermedius, Pseudomonas* spp., *Enterococcus* spp., *Corynebacterium* spp., *Streptococcus* spp., *Proteus* spp., and *Escherichia coli*.
      3. Once alterations in the ear canal's microenvironment occur, the bacteria are able to proliferate unchecked and perpetuate the inflammatory reaction in the ear.
   B. Fungi
      1. *Malassezia* spp. are the most common fungal organisms found in both normal and inflamed ears.
         a. *Malassezia* spp. are extremely opportunistic and colonize the ear canal even if inflammation and maceration are mild.
         b. Yeast overgrowth produces ceruminous otitis more often than purulent otitis.
         c. Recurrent yeast otitis is often associated with underlying allergic disease (atopic dermatitis, food allergy).
      2. Other fungi and yeast that cause ear disease include *Candida* spp., *Aspergillus* spp., *Trichophyton* spp., and *Microsporum* spp.
   C. Otitis media: usually secondary to chronic otitis externa
   D. Chronic pathologic changes: proliferative changes important in the perpetuation of chronic otitis externa

Pathophysiology

I. A common pathway exists for the development of chronic otitis externa.
II. In the acute stage, the canal becomes erythematous and swollen; histologically there is hyperkeratosis and acanthosis of the epidermis, dermal vasodilatation and edema, and an increase in migration of inflammatory cells into the dermis and epidermis.
III. As inflammation continues, the apocrine glands hypertrophy and dilate, which leads to an increase in the production of cerumen and changes in its composition.
IV. If inflammation is left unchecked, the epidermis begins to fold and normal epidermal migration is inhibited and potentially reversed.
V. Increased epidermal thickness, increased glandular activity, and decreased epithelial migration lead to excessive wax production, keratinaceous debris buildup, and microbial overgrowth.
VI. Continued inflammation can result in calcification and/or ossification of the auricular cartilages, dermal fibrosis, and permanent stenosis of the ear canal lumen.

Clinical Signs

I. The most common signs of otitis externa are pruritus, pain, erythema, and swelling of the ears.

II. Common signs are head shaking or rubbing, periauricular excoriations and alopecia, or a head tilt toward the affected side (indicative of pain).
III. A discharge or foul odor is often present.
IV. Erythema of the pinna and vertical canal with an essentially normal horizontal canal is most commonly associated with uncomplicated allergic otitis externa.
V. Erosions and ulcerations of the ear canal may occur with gram-negative bacterial infections or contact dermatitis.
VI. Canal stenosis, palpable auricular calcification/ossification, and decreased hearing are common sequelae of chronic otitis.

Diagnosis

I. A complete dermatological and/or otic history and dermatological examination are essential.
II. Gross and microscopic otic examinations are performed.
  A. The presence of masses and the degree of erythema, erosion/ulceration, tissue hyperplasia, and exudation (color and odor) are noted.
  B. Cytological examination of the otic exudate is performed.
    1. Stains used include Gram stain, Wright-Giemsa stain, modified Wright-Giemsa stain (Diff-Quik), and new methylene blue.
    2. Cytological slides are examined for the presence of bacteria, yeast, fungal hyphae, parasites, white blood cells, cerumen, and neoplastic cells.
    3. The abundance and morphology of bacteria and yeast are evaluated, because normal ears contain a few yeast and a few gram-positive cocci.
  C. If the otitis externa is chronic or recurrent, if gram-negative rods are noted on cytology, or if otitis media/interna is suspected, a bacterial culture is submitted.
  D. Otoscopic examination is performed after the cytological examinations and cultures have been done.
    1. The animal may need to be sedated or anesthetized to accurately assess the horizontal canal and tympanic membrane (TM).
      a. Active or previous middle ear disease is suspected if the TM is ruptured or is discolored, thickened, or bulging (see Chapter 108).
      b. The presence of an intact TM does not rule out middle ear disease.
    2. In severe cases of otitis externa, 2 to 3 weeks of topical or systemic antiinflammatory medications (glucocorticoids), or both, may be required to reduce the inflammation before performing a proper otoscopic examination.
III. A definitive diagnosis may require further diagnostic tests or therapeutic trials.
  A. Fungal culture
  B. Skin scraping for parasitic diseases and trial scabicidal therapy
  C. Examination of skin scrapings or preparations for *Malassezia* spp.
  D. Allergy work-up: food elimination trial, intradermal skin testing, or in vitro blood testing
  E. Discontinuation of topical and/or systemic medications for suspected drug reactions
  F. Biopsy of ear masses or skin if neoplasia or immune-mediated disease is suspected
  G. Surgical intervention for suspected sex-hormone diseases
  H. Thyroid evaluation
  I. Ruling out any systemic disease that may manifest with ear involvement

Differential Diagnosis

I. Otitis externa is a condition and does not imply a specific disease; therefore multiple causes may be involved.
II. A differential diagnosis list is based on history and physical and cytological examinations.
III. A concurrent otitis media must be ruled out in chronic and recurrent otitis externa.

Treatment and Monitoring

I. In-hospital ear cleaning
  A. General concepts
    1. Essential for successful medical management of otitis externa
    2. Performed after cytological examination and culture of otic exudate
    3. Sedation or anesthesia needed in severe cases
    4. Topical or systemic antiinflammatory treatment (glucocorticoids) 7 to 14 days before cleaning severely inflamed ears
    5. Excessive hair clipped from the pinnae or the external ear canal initially
  B. Flushing solution
    1. The type depends on the degree of inflammation, characteristics of discharge, and status of the TM.
    2. After flushing with a potent solution, rinse out the canal well with saline or water, especially if the TM is absent.
  C. Equipment used
    1. Bulb syringes
    2. Red rubber feeding tubes (3 to 12 French) or 8 French polypropylene urinary catheters, open-ended male cat urinary catheters
    3. Straight and curved Buck curettes
    4. Surgical suction unit
  D. Assessment of TM
    1. Visual assessment
      a. It may not be possible in many cases of chronic otitis externa.
      b. Video otoscopes usually give a more complete view than standard hand-held otoscopes.
    2. Blind assessment of ruptured TM
      a. Buck curette catches on bony prominence on the ventral lip of the external auditory meatus
      b. Red rubber feeding tube tip disappears from view
      c. Excessive fluid use
      d. Animal swallows when fluid is instilled in ear
    3. Indications for myringotomy

a. In most cases of chronic otitis
b. Evidence of fluid or debris behind the TM
c. Abnormal TM

E. Hazards of deep ear cleaning
1. Ruptured TM
a. In many chronic cases, the TM is weak and ruptures easily during the flushing procedure.
b. This is not necessarily an unwanted side effect and often indicates an abnormal TM is present, requiring a myringotomy
2. Facial nerve paralysis, Horner's syndrome
3. Vestibular dysfunction, auditory dysfunction
4. Induction of contact irritant/allergy
5. Introduction of new pathogens

II. At-home flushing
A. Vital for the successful medical management of otitis externa
B. Flushing frequency
1. Depends on the harshness of the solution used
2. Severe bacterial otitis: TID initially
3. Yeast otitis: one to three times weekly
4. Decreases over several weeks to a maintenance level

III. Topical therapy
A. The number of applications per day (SID to QID) depends on the type of infection, severity of infection, and chronicity of the disease.
B. Commercially available veterinary otic medications are usually combination products containing glucocorticoids, antibiotics, and antifungal agents in either an ointment (oil) or solution/lotion (aqueous) base.
C. Use the lowest potency glucocorticoid that decreases the clinical signs of inflammation.
D. Antibacterial agents are selected based on cytological evaluation of otic exudate, and culture and susceptibility testing.
E. Antifungal agents are needed when significant numbers of yeast are seen cytologically.

IV. Systemic therapy
A. Systemic therapy is necessary in cases of recurrent or chronic (>3 months duration) otitis externa.
B. Systemic antibiotic therapy is based on bacterial culture and susceptibility testing.
C. Systemic glucocorticoid therapy is needed to decrease tissue inflammation and edema in severe or chronic cases.
1. Start with prednisone 0.5 to 2.2 mg/kg/day PO, and then reduce over 7 to 21 days.
2. How quickly the dose is reduced depends on the severity of inflammation, the chronicity of the otitis, the microbes present, and the underlying causes of the otitis.
D. Use antifungal agents such as ketoconazole 5 to 10 mg/kg PO SID or itraconazole 5 mg/kg PO SID for *Malassezia* spp. infections that do not resolve with topical therapy.

V. Surgical therapy
A. Lateral ear canal resection
1. Indications
a. Animals with otitis externa that relapse despite appropriate diagnostics and medical therapy
b. Animals with vertical ear canal stenosis (e.g., Chinese shar-pei)
c. To facilitate biopsy of small masses within the ear canal or removal of tumors of the lateral wall of the canal
d. As a temporary technique to aid surgical margin assessment for vertical canal resections done for neoplastic excision
e. Irreparable trauma to the lateral aspect of the vertical ear canal
2. Surgical technique
a. A perioperative antimicrobial, such as a first-generation cephalosporin, is used because aseptic surgical preparation of the ear is usually incomplete.
b. The skin incisions (parallel and beginning at the intertragic and tragohelicine incisures) are extended $1^1/_2$ times the length of the vertical portion of the ear canal below the base of the horizontal canal.
c. Connecting the incisions at their ventral-most margin allows elevation of a long rectangular skin flap attached to the top of the vertical ear canal.
d. Soft tissues are sharply dissected cranial and caudal to the vertical ear canal, staying very close to the cartilage to lessen hemorrhage.
e. The parotid salivary gland is separated from the vertical ear canal cartilage ventrally.
f. Parallel incisions are made in the cranial and caudal edges of the vertical ear canal, extending from each incisure ventrally to the level of the horizontal ear canal, so that the flap extends to the level of the ventral aspect of the horizontal ear canal.
g. Once the cartilage flap is incised, minor incision adjustments may be needed so the baffle plate will hinge completely ventrally, and create a smooth flat surface.
h. The cartilage flap is trimmed such that a "drain board" or "baffle plate" of about 1 to 1.5 cm is created.
i. Absorbable sutures are placed through the platysma muscle fascia near the ventral aspect of the skin incision to the underside of the cartilage flap (baffle plate) to help secure it in the ventral position.
j. The remainder of the incision is closed with monofilament nonabsorbable suture.
3. Postoperative care
a. Bandage the pinna over the head or use an Elizabethan collar to protect the incisions from self-inflicted trauma.
b. Opioid analgesia is required for at least 24 hours after surgery; nonsteroidal antiinflammatory drugs (NSAIDS), tramadol, and extended-release

morphine tablets can be prescribed for use at home for several days.
c. Tranquilization is helpful in some dogs to facilitate rest but is not a substitute for analgesia.
d. Prednisone 0.25 mg/kg PO BID, then tapered over 2 weeks, is beneficial in some dogs to lessen head shaking and pawing at the ears, but cannot be combined with NSAIDs.
e. Ear canal cleansing and topical medication is continued.
f. Antimicrobial therapy is continued and adjusted based on results of culture and susceptibility results.

B. Vertical canal resection
1. Indications
a. Aural tumors of the vertical ear canal
b. Irreparable traumatic injuries localized to the vertical canal
c. Dogs with otitis externa secondary to allergic skin disease (atopy) with severe proliferative changes that partially or totally occlude the vertical canal, yet spare the horizontal canal
d. Relapsing otitis externa: lateral ear resection simpler but some dogs with severe, proliferative vertical canal disease may benefit
2. Surgical technique
a. The surgical approach is by a T-shaped incision that extends approximately 1 cm below the horizontal ear canal.
b. Preserve as much skin as possible near the ear canal opening.
c. The incision encircles the top of the vertical ear canal at a level sufficient to remove the proliferative tissue or tumor within the vertical ear canal.
d. The perichondrium is identified and soft tissue dissection is continued around the vertical canal, releasing the proximal portion of the canal from the pinna while using care not to disrupt the auricular blood supply.
e. The facial nerve is not commonly encountered unless the dissection is deep, with resection of a portion of the horizontal canal, but it is important to understand facial nerve anatomy.
f. Transection of the vertical ear canal cartilage near the horizontal canal, or at the level of the annular ligament distally, releases the vertical canal.
g. Sufficient horizontal canal must remain for apposition of skin to close the surgical wound.
h. When aural tumors are resected, the level of the canal resection is determined by the margin of normal canal deep to the tumor.
i. When resection of the vertical ear canal is for benign proliferative disease, sufficient vertical canal is left to allow creation of medial (dorsal) and lateral (ventral) baffle plates to help prevent stenosis of the canal opening.
j. Apposition of soft tissues around the remaining horizontal canal is done by subcutaneous sutures where necessary to alleviate dead space, followed by simple interrupted sutures of monofilament, nonabsorbable suture to appose skin margins.
3. Postoperative care: identical to lateral ear resection

C. Total ear canal ablation and lateral bulla osteotomy (TECA-LBO)
1. Indications
a. End-stage otitis externa in which hyperplastic and inflammatory changes have obstructed the horizontal ear canal
b. Failed lateral or vertical ear canal resection
c. Neoplastic disease of the horizontal canal or the periphery of the ear canal
d. Congenital stenosis of the horizontal canal
e. Traumatic avulsion (with stricture) of the horizontal ear
f. Used in cats for the removal of neoplastic tissue or for infection secondary to inflammatory polyps
2. Surgical technique
a. Make a curvilinear incision (an upside-down L) starting at the anterior margin of the vertical ear canal, rather than the standard T-shaped incision, and extend caudally following the undulations near the incisures and curve ventrally and parallel over the caudal aspect of the vertical ear canal.
b. Extend the dissection to the perichondrium and retract the parotid salivary gland ventrally.
c. The vertical and horizontal ear canals are isolated by blunt and sharp dissection, staying close to the perichondrium.
d. The vertical canal is transected from the auricular cartilage close to the perichondrium to avoid the great auricular vessels that extend dorsally toward the tip of the pinna, and high enough to remove all proliferative tissue within the canal.
e. Dissection and excision of the entire ear canal is carried to the level of the external acoustic meatus, where it is released.
f. Palpate the mastoid process located caudal to the horizontal canal.
g. The facial nerve exits the skull at the stylomastoid foramen and turns ventrally and rostrally toward the auricular muscles, and the muscles of the eyelids and lip.
h. It is not necessary to isolate the facial nerve, but dissect carefully and avoid excessive pressure or too much traction on the nerve.
i. A lateral bulla osteotomy is created to aid removal of debris and exudate from the middle ear using an air drill or Leksell rongeur.
j. The bulla is curetted carefully to avoid damaging the bony labyrinth of the inner ear (vestibular and cochlear windows) located dorsally and medially.
k. Avoid the external carotid artery and the hypoglossal nerve traversing in the soft tissues ventral to the bulla.
l. Drains are not required for most TECA-LBO procedures, but Penrose or small closed-suction

drains may be used, depending on the surgeon's preference.

m. Wound closure is in three layers.
   (1) Absorbable suture is used to appose the attachments of the auricular muscles and subcutaneous tissues to close "dead space."
   (2) A continuous subcuticular pattern is used to appose the margins of the wound, taking care to avoid exposure of cartilage.
   (3) Nonabsorbable, monofilament suture is used to appose the skin.

3. Postoperative care
   a. The ear may be bandaged up over the dog's head or an Elizabethan collar used to prevent self-inflicted trauma.
   b. If drains are used, keep the animal in the hospital until they are removed.
   c. Give morphine 0.1 to 0.5 mg/kg SC every 3 to 4 hours, or as a continuous rate infusion at 1.5 mg/kg/24 hr, instilled in a 250-mL bag of normal saline and administered at a rate of 10 mL/hr IV for analgesia.
   d. Transdermal fentanyl patches, oxymorphone, and hydromorphone are alternatives.
   e. NSAIDs, tramadol, or extended-release morphine may be used or prescribed for home use.
4. Effect on hearing function
   a. Total ear canal ablation does not appear to cause complete deafness.
   b. After TECA-LBO, dogs can still hear, as measured by osseous conduction and air conduction to a level equal to preoperative levels.
   c. Total ear canal ablation performed for resection of neoplastic disease will impact hearing function, if the eardrum was intact before surgery, in the affected ear.

D. Ventral bulla osteotomy
1. Indications
   a. Debride inflamed, infected, or foreign debris from the tympanic bulla
   b. Removal of tumors, including inflammatory polyps in cats, or obtain tissue for culture and susceptibility testing or histopathologic evaluation
   c. Provide a route to achieve improved ventral drainage of exudate
   d. Treatment of otitis media with or without otitis externa
   e. Resolution of cholesteatomas (if ear canal is to be preserved)
2. Surgical procedure in the dog
   a. Surgery in large brachycephalic breeds such as the boxer or English bulldog can be difficult, because the thickness of the neck results in a deep surgical field.
   b. A paramedian incision is made between the angular process of the mandible extending caudally to the wings of the atlas.
   c. The tympanic bulla may be palpable between the angle of the mandible and the jugular process of the skull.
   d. Once the bulla is identified, the small overlying muscles are bluntly separated and the exposure is widened using a small Freer elevator.
   e. The tympanic bulla is penetrated using a Steinmann pin or a pneumatic drill, using care not to damage the dorsal aspect of the tympanic cavity.
   f. As the exposure is increased, remember that the oral cavity and pharynx are millimeters away and careless probing may penetrate the pharyngeal mucous membrane, resulting in contamination from oral flora.
   g. Epithelial lining is removed from the inner surfaces of the bulla with a small curette, taking care not to curette or damage structures of the dorsal wall of the tympanic cavity and in the region of the promontory.
   h. Drains may not be required; however, a simple Penrose drain may be used to allow dependent drainage from the tympanic cavity, or ingress–egress drains may be placed if deemed necessary.
3. Surgical procedure in the cat
   a. When the ventral portion of the bulla is removed, the partitioning septum within the feline osseous bulla is exposed.
   b. The polyp is removed by traction and gentle curettage to remove the polyp base.
   c. Portions of the polyps that extend on a stalk through the eardrum into the ear canal may be removed by pulling the polyp into the middle ear, or by avulsing the polyp from the ear canal before ventral bulla osteotomy.
   d. Remember that small, sympathetic branches cross the promontory, and damage to them frequently (nearly 50%) results in postoperative Horner's syndrome.
   e. The dorsal and medial aspects of the middle ear are not aggressively curetted, because the auditory ossicles, cochlear window, and vestibular window are contained within the mesotympanum and epitympanic recess.
   f. Care is also taken not to remove too much of the vertical walls of the osseous bulla, as ingrowth of fibrous scar within the tympanic cavity can disrupt ossicle function and affect hearing.
4. Postoperative care
   a. A nonadherent, absorptive bandage is applied to protect the incision and the drain (if used).
   b. Antimicrobial therapy (based on culture and susceptibility) is used for 2 to 4 weeks, especially if there is associated otitis externa.
   c. Drains are usually removed in 3 to 5 days.
   d. Analgesic therapy, as for other ear surgeries, can be tailored based on the invasiveness of surgery.

DISEASES OF THE PINNA

Pinnal Dermatoses

Dawn E. Logas

See Table 107-1.

Aural Hematoma

Jamie R. Bellah

Definition and Causes

I. An aural hematoma is the accumulation of serosanguineous fluid or blood within the pinna.
II. Trauma to the pinna from scratching or shaking the head is the primary cause.
III. Aural hematomas may be associated with otitis externa, or the ear canal may be completely normal.
IV. A primary or secondary, immune-mediated component has been suggested but remains controversial.

Clinical Signs

I. A firm or fluctuant swelling involves small regions to nearly the entire pinna.
II. There may be concurrent otitis externa.
III. It may be painful when acute.
IV. The pinna becomes firm and scarred, with a cauliflower appearance, if the hematoma is left untreated.

Diagnosis

I. History and clinical signs usually diagnostic
II. Aspiration of serosanguineous fluid
III. No fluid if the hematoma is chronic, organized

Differential Diagnosis

I. Neoplasia
II. Abscessation
III. Generalized pinnal edema

Treatment

I. Simple aspiration is the most conservative treatment and relieves acute pain, but recurrence is common.
II. Surgical drainage decreases pain and reduces likelihood of recurrence; several methods are available.
   A. Silastic drain placement
      1. Use heavy sedation (narcoleptic) or general anesthesia.
      2. Infiltrate lidocaine at the dorsal-most and ventral-most boundaries of the swelling.
      3. A stab incision is made at both locations and the fluid is drained.
      4. Using a straight mosquito hemostat, a small-diameter (3 to 4 mm) Silastic drain is pulled through the cavity and sutured at each opening.
      5. The ear may be bandaged over the head.
   B. Teat cannula placement
      1. Make a stab incision at the most dependent aspect of the hematoma (relative to the ear being in a normal position), and on the concave or inner surface of the ear.
      2. Remove the screw cap from a teat cannula and make two holes in the collar of the cannula using a 19-gauge needle.
      3. Introduce the cannula into the hematoma through the stab incision.
      4. Secure the cannula with a suture placed through the skin and the collar.
      5. A second suture may be placed through the skin around the end of the tube.
   C. Closed suction catheter system
      1. Make a stab incision in the most dependent region.
      2. Cut the luer-lock tip off a butterfly catheter and fenestrate 1 to 2 cm near the end of the tube.
      3. Insert the fenestrated end into the cavity and affix the catheter to the ear by a finger-snare suture.
      4. Insert the needle of the butterfly catheter into a red-top Vacutainer; change as needed.
   D. Incisional drainage
      1. Usually reserved for more chronic or organized hematomas.
      2. General anesthesia is required.
      3. An incision (straight or S-shaped) is made into the hematoma on the concave side of the ear.
      4. Organized blood clots and fluid are removed.
      5. Full-thickness mattress sutures are placed parallel to the vasculature of the pinna (parallel to the long axis of the pinna), so blood supply is not compromised.
   E. Carbon dioxide (CO_2) laser procedure
      1. The laser is used to make three or four circular skin incisions of 3 to 7 mm in diameter.
      2. The hematoma is drained and lavaged.
      3. Nonabsorbable sutures are placed through small stents (i.e., cut segments of IV tubing or other suitable material), and through the cartilage while avoiding penetration of the haired surface of the pinna (convex surface).
      4. Alternatively the ear is not sutured.
      5. Home care consists of application of warm compresses to the ear for 5 to 10 minutes BID and removal of soft scabs as they form, to encourage drainage.
      6. If sutures are used, they are removed in 7 days; weekly examination is recommended.
III. Treat any underlying causes with proper medical therapy.
   A. Antimicrobial therapy is based on concurrent diseases and culture and susceptibility test results.
   B. Prednisone 0.25 mg/kg PO BID and tapering over 3 weeks helps relieve pruritus, head shaking, and self trauma.

Monitoring of Animal

I. Silastic drain or cannula techniques
   A. Instruct owners to keep the opening of the drain or cannula free of debris or clots and to milk out fluid as it accumulates.

TABLE 107-1

Dermatoses of the Pinna

DISEASE	AREAS AFFECTED	CLINICAL SIGNS	DIAGNOSIS	TREATMENT
Actinic (solar) dermatitis	1	A,B,C,D	Biopsy	Limit sun exposure, sunscreen
Alopecia areata	2	B	Biopsy	No treatment
Atopy	2	A	Skin test, blood test	Desensitization vaccine, topical glucocorticoids, cyclosporine
Bullous pemphigoid/pemphigus vulgaris	3	E	Biopsy	Immunosuppressive drug therapy
Cold agglutinin disease	2	D,E	Biopsy, positive 4° C Coombs' test	Systemic glucocorticoids, surgery
Congenital alopecia	2	B	Other disorders excluded	No treatment
Contact dermatitis	1	A,B,C,D,E	Provocative exposure	Avoidance of cause, pentoxifylline
Cutaneous lupus erythematosus	3	B,D,E	Biopsy	Topical and systemic glucocorticoids, tetracycline and niacinamide, tacrolimus
Deep/subcutaneous mycotic disease	3	E,F	Biopsy, culture	Systemic antifungal therapy
Demodicosis	2	A,B,C,D	Skin scrape	Local—no treatment Generalized—amitraz, ivermectin, milbemycin
Dermatomyositis	2	A,B,D,E	Muscle, skin biopsy; EMG	None, pentoxifylline
Dermatophytosis	2	A,B,C,D	Culture	Topical antifungal agents and systemic griseofulvin, ketoconazole, terbinafine, or itraconazole orally
Ear margin dermatosis	1	A,B,D,E	Other disorders excluded	Topical antiseborrheic therapy
Fly strike	1	A,C,D	Clinical signs	Fly control, topical glucocorticoids
Food allergy	2	A	Food trials	Avoidance of allergen
Frostbite	2	D,E	Clinical signs	Warm area, surgery
Hypothyroidism	3	B,D	T_4, free T_4, and TSH	T_4 supplementation
Insect-induced granuloma	3	A,B,D,F	Biopsy	Avoidance of insect repellants
Juvenile cellulitis	3	A,B,D,E	Biopsy	Glucocorticoids ± antibiotics
Keratinization disorder	2	B,D	Other disorders excluded, biopsy	Topical antiseborrheic therapy, vitamin A, glucocorticoids
Lichenoid-psoriasiform dermatitis of springer spaniels	1	A,C,D	Biopsy	None, ± antibiotics
Linear granuloma	3	E,F	Biopsy	Systemic glucocorticoids
Neoplasia	2	F	Biopsy	Surgery, chemotherapy
Pattern baldness	2	B	Biopsy, other disorders excluded	Melatonin
Pemphigus foliaceus, erythematosus	3	C,D	Biopsy	Immunosuppressive drug, topical glucocorticoids
Periodic alopecia	1	B	Other disorders excluded	No treatment
Pinnal alopecia	1	B	Other disorders excluded	No treatment
Proliferative thrombovascular necrosis	1	E	Biopsy	Surgery, ± pentoxifylline
Sarcoptiform mange	2	A,B,D	Skin scrape, response to therapy	Lime sulfur, ivermectin, selamectin
Sebaceous adenitis	3	A,B,C,D	Biopsy	Topical baby oil/propylene glycol soaks; systemic fatty acids, retinoids, cyclosporine
Squamous cell carcinoma	1	A,B,D,E	Biopsy	Surgery

1, Pinna affected only; *2,* pinna and sometimes other body areas affected; *3,* pinna and other body areas affected; *A,* erythema; *B,* alopecia; *C,* pustule/papules; *D,* scale/crust; *E,* ulcer/scar; *F,* nodule; *T4,* thyroxine; *TSH,* thyroid-stimulating hormone; *EMG,* electromyogram.

TABLE 107-1

Dermatoses of the Pinna—*cont'd*

DISEASE	AREAS AFFECTED	CLINICAL SIGNS	DIAGNOSIS	TREATMENT
Staphylococcal folliculitis	3	C,D	Biopsy, response to therapy	Antibiotics
Sterile eosinophilic pinnal folliculitis	1	C,D	Biopsy	Topical and systemic glucocorticoids
Subcorneal pustular dermatosis	3	C,D	Biopsy	Dapsone
Systemic lupus erythematosus	3	B,D,E	Biopsy, work-up for systemic disease	Immunosuppressive drug therapy
T-cell lymphoma	3	A,E,F	Biopsy	Chemotherapy
Vasculitis	2	D,E	Biopsy, work-up for underlying disease	Immune-modulating drugs, pentoxifylline
Zinc-responsive dermatosis	3	A,D	Biopsy	Zinc supplementation

   B. Drains or cannulas are removed in 3 weeks and the wounds heal by second intention.
   C. Antimicrobials are not used routinely.

II. Incisional technique
   A. Sutures are removed in 10 to 14 days.
   B. Antimicrobials are not used routinely.
   C. Disfigurement of the pinna may occur.

III. Complications of aural hematoma treatment
   A. Pinnal contracture caused by organized hematomas or sutures placed with excessive tension
   B. Disfigurement of the pinna
   C. Hematoma recurrence
   D. Pinnal necrosis secondary to improper suturing or tight bandaging

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CHAPTER 108

Diseases of the Middle and Inner Ear

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OTITIS MEDIA

Definition

I. Otitis media is defined as inflammation of the middle ear.
II. Otitis media is an important cause of recurrent otitis externa.

Causes

I. Infectious causes
  A. The most frequent cause is a bacterial infection (Cole et al., 1998).
    1. Most common bacterial isolates: *Staphylococcus intermedius, Pseudomonas aeruginosa*
    2. Other less common isolates: *Corynebacterium* spp., *Enterococcus* spp., *Proteus* spp., β-hemolytic streptococcus, *Citrobacter* spp., non–group D streptococcus, *Escherichia coli, Lactobacillus* spp., anaerobes
  B. Yeast may be a significant pathogen (isolated alone in 23.7% of ears in dogs with otitis media) (Cole et al., 1998).
  C. Otitis media appears to be uncommon in the cat.
II. Noninfectious causes
  A. Congenital diseases (Gregory, 2000): palatine defects (secondary cleft palate)
  B. Trauma
  C. Neoplasia, polyps
    1. Tumors are usually malignant when found in both the ear canal and tympanic bulla.
    2. If the tumor is present only in the tympanic bulla, 33% are malignant in dogs and up to 50% are malignant in cats (London et al., 1996).
    3. Inflammatory polyps are common in the cat, but are relatively uncommon in the dog.
  D. Foreign bodies
  E. Primary secretory otitis media
    1. It is reported in the Cavalier King Charles spaniel (Stern-Bertholtz et al., 2003).
    2. Principal signs are moderate to severe pain in the head or cervical region, neurological signs (ataxia, facial paralysis, nystagmus, head tilt), otic pruritus, otitis externa, and fatigue.
    3. In most cases, a bulging but intact tympanic membrane (TM) was observed.
    4. After myringotomy, a highly viscous mucus plug may be removed with ear forceps or a suction catheter.
    5. Removal of the mucus plug and flushing the middle ear may need to be repeated up to six times for resolution.
  F. Otoliths (mineral opacities within the tympanic bullae)
    1. Rarely reported in dogs as an incidental finding radiographically or with signs of vestibular disease (Ziemer et al., 2003)
    2. Significance unknown

Pathophysiology

I. Route of inflammation and infection
  A. Otitis media occurs as a direct extension from an existing otitis externa through a ruptured TM.
    1. The presence of an intact TM does not rule out otitis media, because the defect in the membrane may have healed.
    2. In dogs with infectious otitis media, 71.1% have an intact TM (Cole et al., 1998).
  B. Less common routes include extension through the eustachian tube or hematogenous dissemination.
II. Potential factors involved in the pathogenesis of otitis media
  A. The mucociliary system in the eustachian tube drains the middle ear of mucus, debris, and bacteria (Edwards et al., 1992).
  B. Blockage of the eustachian tube may result in the inability to clear these secretions and produce a sterile otitis media.
  C. A surface tension–lowering substance has been found in the canine eustachian tube (Birken and Brookler, 1972).
    1. Infection diminishes production of the surface tension–lowering substance.
    2. The eustachian tube is then more resistant to opening, resulting in a serous otitis media.

Clinical Signs

I. Signs of otitis externa may be seen, including discharge from the external ear canal, pawing or rubbing the affected ear, head shaking, and pain.
II. Facial nerve paralysis or paresis is possible.
  A. It is characterized by drooping of or inability to move the ear or lip, drooling of saliva, and decreased or absent palpebral reflex.

B. Facial neuropathy secondary to otitis media has been reported in 21.5% of dogs and 18.8% of affected cats (Kern and Erb, 1987).
C. Cocker spaniels with facial neuropathy are more likely to have otitis media as the underlying cause, as compared to other breeds (Kern and Erb, 1987).

III. Injury to the facial nerve may result in ipsilateral keratoconjunctivitis sicca (KCS).
IV. Horner's syndrome results from injury to the sympathetic nerve as it courses through the middle ear.
A. Horner's syndrome is characterized by ptosis, miosis, enophthalmos, and protrusion of the third eyelid.
B. Horner's syndrome secondary to otitis media occurs in 26.9% of cats and 2.7% of affected dogs (Kern et al., 1989).
V. Otitis media may lead to otitis interna.
A. Clinical signs of otitis interna include horizontal nystagmus, asymmetrical ataxia, head tilt, circling, falling, or rolling toward the affected side.
B. In dogs with peripheral vestibular disease, as many as 49% have concurrent otitis media/interna (Schunk and Averill, 1983).

Diagnosis

I. Examinations to perform
A. Complete physical examination of lymph nodes, oral cavity, and nasopharyngeal region
B. Dermatological examination to evaluate for underlying diseases (e.g., parasites, allergy, keratinization disorders, autoimmune disease)
C. Neurological examination to evaluate for signs suggestive of facial nerve paralysis/paresis, nystagmus, KCS, and vestibular disease
D. Otoscopic and video otoscopic examination of the external ear canal and TM
1. Otoscopic examination is performed using a hand-held otoscope.
2. Video otoscopy using an otoendoscope, camera, light source, and monitor may also be performed.
3. If the ears are ulcerated, hyperplastic, or stenotic, 2 to 3 weeks of topical or systemic glucocorticoids, or both, are often necessary before the otic examination.
4. The normal TM is translucent and concave.
5. Otitis media is suspected if the TM is ruptured, bulging, opaque, or cloudy.

II. Specific diagnostic tests: see Table 108-1
III. Laboratory tests
A. Cytological examination, as well as culture and sensitivity testing, is useful.
1. It is uncommon to find identical organisms or isolates when concurrent otitis externa and otitis media are diagnosed (Cole et al., 1998).
2. Obtain samples from both the horizontal ear canal and middle ear.
B. Biopsy any mass found in the vertical ear canal, horizontal ear canal, or middle ear, and submit tissue for histopathologic evaluation.

Differential Diagnosis

I. The early stages of otitis media may be overlooked, and it is important to recognize that otitis media is present in 50% to 82.6% of dogs with chronic otitis externa (Spreull, 1964; Cole et al., 1998).
II. Rule out other causes of Horner's syndrome, facial nerve paralysis/paresis, and peripheral vestibular disease.

Treatment

I. Goals of treatment
A. It is important to clean the ear for evaluation of the TM.
B. If the TM is ruptured, obtain samples for cytology and culture from the middle ear cavity.
1. When using the hand-held otoscope, pass a small sterile culture swab (Calgiswab Type 1; Hardwood Products, Guilford, Me.) through a sterile otoscopic cone attached to a hand-held otoscope into the middle ear cavity to obtain samples.
2. If the video otoscope is used, an open-ended Tom cat urinary catheter attached to a 12-mL syringe is passed through the port on the otoendoscope into the middle ear cavity to obtain samples.
3. Once the samples have been obtained, flush the middle ear repeatedly with sterile saline to remove any exudate and any residual ceruminolytic agent.
C. If the TM is intact but abnormal, a myringotomy is required (see later).
D. Once the ear is clean, treat infections systemically, topically, or both, based on results from cytology and culture and susceptibility testing.

II. Ear flushing
A. Deep ear flushing is best performed under general anesthesia.
B. Soak the ear canal for 10 minutes with a ceruminolytic cleaner, then flush with sterile isotonic saline, first with a bulb syringe and then with an 8 French polypropylene urinary catheter attached to a 12-mL syringe passed through an otoscopic cone.
C. Once the exudate and debris are removed from the ear canal, evaluate the TM with an otoscope or video otoscope.
D. Some ceruminolytic agents may be ototoxic (Mansfield et al., 1997) and are avoided or thoroughly flushed out with sterile saline if the TM is ruptured.

III. Myringotomy
A. It is indicated if the TM is intact but abnormal, in order to obtain samples for cytological examination and culture, to flush the middle ear, and allow the middle ear to drain.
B. Make an incision into the caudoventral quadrant of the TM.
1. This procedure can be performed with a small, sterile culture swab (Calgiswab Type 1, Hardwood Products, Guilford, Me.) passed through a sterile otoscopic cone attached to a hand-held otoscope.
a. Submit the first swab for culture; insert a second swab to obtain material for cytological evaluation.

TABLE 108-1

Diagnostic Techniques Available for Otitis Media

DIAGNOSTIC TEST	PURPOSE	TECHNIQUE PERFORMED	ABNORMAL FINDINGS
Plain radiographs	Visualize changes in tympanic bulla, external ear canal, middle and inner ear	Views performed include dorsoventral, right and left lateral obliques, open-mouth rostral-caudal (best view for evaluation of tympanic bullae)	Suggestive findings include thickening or lysis of bulla, sclerosis and proliferation, or lysis of petrous temporal bone Abnormal radiographs suggest otitis media Normal radiographs do not rule out otitis media
CT	Same as radiographs	Serial radiographic images obtained with CT scanner	Abnormallities are same as with radiographs; however, CT appears to be a more sensitive indicator of otitis media compared to plain radiographs (Love et al., 1995)
MRI	Same as radiographs	Uses radio waves in combination with a strong magnetic field to create concise images of internal organs and tissues	Fluid in the tympanic bulla appears hyperintense on T2-weighted images and is isointense with brain tissue on T1-weighted images T1 and T2 are intrinsic tissue characteristics and are representative of the relative content of water molecules moving throughout the intracellular and extracellular structures Its limitation compared to CT is that it is poor for evaluation of osseous changes
Ultrasonography	Detection of fluid in the tympanic bulla	Ultrasound probe is placed on the skin overlying the tympanic bulla	To date, this procedure has been performed only in cadavers (with water introduced via myringotomy into the tympanic bulla) and in live dogs with no evidence of otitis; the presence of fluid in the tympanic bulla could be differentiated from gas with the ultrasound The fluid-filled tympanic bulla was visible as an oval-shaped, anechoic region while the gas-filled tympanic bulla created a reverberation artifact, causing an acoustic shadow obscuring deeper areas (Dickie et al., 2003)
Pneumotoscopy	Used to judge the mobility (compliance) of the tympanic membrane and determine presence or absence of fluid in the middle ear	A hand-held, diagnostic-head otoscope with a pneumatic bulb attachment is inserted into the horizontal ear canal The tympanic membrane is visualized, and air is blown against the membrane with the pneumatic bulb in a pulsatile fashion while observing the motion of the tympanic membrane	Lack of movement (compliance) of the tympanic membrane indicates possible fluid in the middle ear or thickened tympanic membrane, suggestive of otitis media Normal compliance does not rule out otitis media
Impedance audiometry			
Tympanometry	Used to indirectly measure air pressure in the middle ear and compliance of the tympanic membrane, and estimate external ear canal volume	Requires a middle ear analyzer	A flat tympanogram suggests middle ear effusion, a severely scarred tympanic membrane, or, if associated with increased ear canal volume, a perforated tympanic membrane An abnormal tympanogram suggests otitis media; however, a normal tympanogram does not rule out otitis media

CT, Computed tomography; *MRI*, magnetic resonance imaging.

Continued

TABLE 108-1

Diagnostic Techniques Available for Otitis Media—*cont'd*

DIAGNOSTIC TEST	PURPOSE	TECHNIQUE PERFORMED	ABNORMAL FINDINGS
Acoustic reflex	This reflex protects the inner ear from damaging levels of noise A normal acoustic reflex results in a change in compliance of 0.02 mL or greater as the stimulus intensity is increased	A middle ear analyzer is used to measure the decrease in compliance of the tympanic membrane when a loud noise is introduced to the ear	An acoustic reflex less than the normal range in conjunction with an abnormal tympanogram is suggestive of otitis media A normal acoustic reflex does not rule out otitis media
Positive contrast canalography	Evaluates the patency of the tympanic membrane by infusing positive contrast medium into the ear canal of anesthetized dogs (Trower et al., 1998)	Precontrast and postcontrast bulla radiographs are performed	Contrast material in the bulla indicates tympanic membrane rupture Lack of contrast material in the bulla does not rule out a ruptured tympanic membrane

b. Flush the middle ear repeatedly with sterile saline using an open-ended Tom cat urinary catheter passed through the sterile otoscopic cone.

2. If using a video otoscope, pass an open-ended Tom cat urinary catheter attached to a 12-mL syringe through the port on the otoendoscope and use it to make the myringotomy incision.
   a. Flush saline into the middle ear cavity, aspirate it back, and culture the fluid.
   b. Then flush the middle ear repeatedly with saline through the open-ended Tom cat urinary catheter.

IV. Systemic antimicrobial, antifungal agents
   A. The choice of antibiotic is based on cytology and culture and susceptibility results.
   B. Certain systemic antibiotics (primarily aminoglycosides) can be ototoxic and must be used cautiously.
   C. If yeast otitis media is present, consider an antifungal agent, such as ketoconazole or itraconazole at 5 mg/kg PO SID.
   D. Administer antibiotics or antifungal agents for at least 3 to 6 weeks, or until the infection resolves.

V. Topical antibacterial, antifungal agents
   A. With topical medications, concentrations are achieved in the ear 100 to 1000 times higher than when the drug is given systemically.
   B. An antibiotic considered resistant on culture and susceptibility may be efficacious if administered topically, but use caution when administering topical otic preparations in an ear with a ruptured TM.

VI. Systemic prednisone
   A. Dose: 0.5 to 1 mg/kg PO SID, then tapered
   B. To reduce hyperplasia and stenosis of the ear canal

VII. Topical glucocorticoids
   A. They are available in combination products or as the sole agent in otic preparations.
   B. They are indicated for hyperplasia and stenosis of the external ear canals.

VIII. Topical cleaning and drying agents
   A. These are used to keep the external ear clean by removing exudate, and numerous products are available.
   B. Most products contain some type of acid, sometimes in combination with isopropyl alcohol, to dry the ear canal.
   C. Even though chlorhexidine (0.2%) is not considered ototoxic (Merchant et al., 1993), these products must be used with great caution in ears with a ruptured TM.

IX. Surgical management
   A. Surgical intervention is required in unresponsive or recurrent cases of otitis media.
   B. Surgery is indicated if middle ear polyps, neoplasia, foreign bodies, or osteomyelitis of the tympanic bulla are present.
   C. The surgical techniques used depend on which specific condition is present (see Chapter 107).

Monitoring of Animal

I. Otoscopic examination
   A. Perform with a hand-held otoscope or video otoscope at each reevaluation.
   B. Monitor healing of the TM.
   C. Reevaluate every 2 weeks until infection has resolved.
   D. Repeat ear flushing under general anesthesia as needed to keep the ear canal clean of otic exudate.

II. Cytology and culture

A. Perform a cytological examination of exudate from the external ear canal at each reevaluation to monitor response to treatment.
B. Also, submit a culture of external ear canal exudate if the infection worsens or is nonresponsive to treatment.

III. Neurological signs
A. Horner's syndrome and facial nerve paralysis/paresis may persist even after the infection has cleared.
B. Treat exposure keratitis from facial nerve paralysis or KCS with artificial tears, lubricating eye ointments, or topical cyclosporine (see Chapter 97).

IV. Complications and sequelae
A. Chronic otitis media
1. Occurs if infection does not completely resolve
2. Associated with persistent otic discharge and pain on palpation of the bulla

B Aural cholesteatoma or epidermal cyst
1. Epidermal-lined cavity containing keratinous debris
2. May develop in the middle ear of dogs secondary to chronic otitis media

C. Osteomyelitis of the petrous temporal bone
1. Signs of peripheral vestibular disease may develop.
2. Sensorineural hearing loss is common.

D. Meningitis, intracranial abscess, or meningoencephalitis (Spangler and Dewey, 2000)
E. Possible complications of the ear flushing or myringotomy procedure
1. Horner's syndrome
2. Facial nerve paralysis/paresis
3. Vestibular disturbances, deafness

OTITIS INTERNA

Michael Podell

Definition

I. Otitis interna is an inflammatory condition of the structures of the inner ear.
II. Clinical signs arise with disruption of the peripheral vestibulocochlear nerve (cranial nerve VIII) input to the central nervous system.
III. Labyrinthitis is inflammation of the membranous labyrinth housing the vestibular receptors of the inner ear.

Causes

I. Infectious causes
A. Bacteria
1. Extension from the middle ear
a. *Staphylococcus* spp.
b. *Streptococcus* spp.
c. *Proteus* spp.
d. *Pseudomonas* spp.
e. *E. coli*
f. *Enterococcus* spp.
2. Hematogenous infection: less common

B. Fungal agents
1. Extension from the middle ear
a. *Malassezia* spp.
b. *Candida* spp.
c. *Aspergillus* spp.
2. Hematogenous infection
a. *Aspergillus* spp.
b. *Blastomyces* spp.
c. Other systemic mycoses

C. Rickettsial diseases: *Ehrlichia canis,* causing vasculitis in the dog

II. Noninfectious causes
A. Idiopathic, congenital disease
1. Signs from birth
2. Most common in purebred dogs: Doberman pinscher, German shepherd dog, English cocker spaniel, beagle
3. Cats: Burmese, Siamese

B. Idiopathic, acquired diseases
1. "Old dog" vestibulitis
2. Feline vestibulitis

C. Metabolic disorders
1. Hypothyroidism
2. Hypercortisolism

D. Traumatic and compressive events
1. Foreign body penetration
2. Blunt trauma
3. Polyp formation

E. Toxicity
1. Mitotane *(Lysodren)*
2. Aminoglycosides

Pathophysiology

I. Infectious diseases
A. Direct extension of infection from the middle ear is the most common mechanism for the development of otitis interna.
1. Invasion through the round window
2. Secondary to osteomyelitis of the petrous temporal bone

B. A hematogenous source is most likely with rickettsial and systemic fungal organisms.

II. Noninfectious diseases
A. Idiopathic vestibular disease has no identified etiology; pathologic changes include abnormalities in endolymphatic fluid absorption, production, or circulation, as well as inflammatory neuritis.
B. Inflammatory polyps in cats originate within the middle ear or auditory (eustachian) tube and are secondary to chronic inflammation.

Clinical Signs

I. Goals in evaluation of clinical signs
A. Determine whether the vestibular disease is peripheral or central (Schunk, 1988).
B. Determine whether the peripheral disease is unilateral or bilateral.
C. Determine whether another systemic illness is present

TABLE 108-2

Differentiation of Normal versus Pathologic Nystagmus

NYSTAGMUS	FUNCTION	TEST	DESCRIPTION
Normal			
Oculovestibular reflex (doll's eye reflex)	To maintain visual fixation on stationary points as the body rotates	Horizontal movement of head and/or body with a rigid neck to elicit quick and slow eye movements	Tonic phase = slow deviation of eyes away from the turn Saccadic phase = quick deviation of eyes toward the turn
Postrotatory nystagmus		Initiate rapid rotation of animal (acceleration)	Quick phase is in the direction of rotation
		Maintain constant velocity of rotation	No nystagmus
		Stop rotation of animal rapidly (deceleration)	Quick phase is opposite the direction of rotation
Pathologic	Arises from an imbalance in resting extraocular muscle tone owing to asymmetrical input from the vestibular nuclei	Direct observation and placing head in different positions	Temporal phase *Spontaneous:* sustained (constant) *Positional* Direction phase *Horizontal*: side-to-side eye movements *Vertical*: perpendicular eye movements relative to head position Direction changing Fatigability *Nonfatigable*: no decrease in velocity *Fatigable*: decreases in velocity with time or position

II. Essential signs of peripheral vestibular disease caused by otitis interna
  A. Changes in head posture
  B. Gait changes
  C. Nystagmus
    1. Nystagmus is an involuntary rhythmic oscillation of the eyes, with either pendular movements or quick (i.e., jerk) and slow phases that occur in any plane.
    2. The direction of the jerk nystagmus is described according to the quick phase.
    3. Determine if abnormal vestibular nystagmus is present (Table 108-2).
  D. Associated with other neurological deficits
III. Unilateral peripheral vestibular disease
  A. Typically acute onset of dramatic signs
  B. Presence of many of the described clinical signs (Table 108-3)
  C. May be confused with an epileptic seizure if thrashing or struggling noted during the acute episode
  D. Often misdiagnosed as a stroke
IV. Bilateral peripheral vestibular disease
  A. Acute to subacute onset
  B. No normal or pathologic nystagmus: loss of oculovestibular reflex pathognomonic
  C. No head tilt
  D. Symmetrical ataxia
  E. Wide head excursions to both sides
V. Central vestibular disease (see Table 108-3)
  A. Subacute to chronic onset
  B. Paradoxical central vestibular disease
    1. Head tilt is opposite the side of the lesion owing to injury of the caudal cerebellar peduncle.
    2. Remaining clinical signs are all ipsilateral to the lesion.
VI. Signs of infections
  A. Infections occur most commonly in the dog.
  B. Any age, gender, or breed may be affected, although cocker spaniels and long-eared dogs are more commonly affected.
  C. Extension of disease into the inner ear is most commonly seen in cases of recurrent otitis externa and media.
  D. Signs of unilateral peripheral disease are typical.
  E. Signs of central vestibular disease may occur from focal extension into the central nervous system (Sturges et al., 2006).
    1. Often associated with cranial nerves V (trigeminal), VII (facial), and VIII (vestibulocochlear) deficits
    2. Focal lesion situated at the cerebellopontine angle
VII. Signs of congenital disease
  A. Unilateral peripheral vestibular signs from birth

TABLE 108-3

Signs Associated with Peripheral versus Central Unilateral Vestibular Disease

CLINICAL ABNORMALITY	PERIPHERAL SIGNS	CENTRAL SIGNS
Head position	Head tilt toward lesion	Head tilt toward lesion Exception: central paradoxical vestibular disease with head tilt away from lesion
Nystagmus	Sustained Most common = horizontal to rotatory Fast phase away from lesion Does not change direction Positional Usually seen with recovery Rotary to upbeat Delayed onset Short duration Fatigable (see Table 108-2) Abnormal postrotatory nystagmus Rotation in the direction *opposite* the side of the lesion results in depression of postrotatory nystagmus	Sustained Pure vertical, horizontal, or rotary Fast phase to or away from lesion Direction changing Positional Most common Pure vertical or horizontal Rapid onset Persistent duration Nonfatigable
Gait	Asymmetrical ataxia Circling, falling toward lesion No paresis No proprioceptive deficits	Asymmetrical ataxia Circling, falling toward lesion Ipsilateral hemiparesis Ipsilateral proprioceptive deficits
Strabismus	Positional, ventral	Positional, ventral
Cranial nerve involvement	VII ipsilateral to lesion	Cerbellopontine angle = V, VII, VIII Others possible: VI, IX, X, XII
Pupillary changes	Horner's syndrome ipsilateral to lesion	Changes present with rostral brain stem lesions
Mental status	Alert but disoriented	Changes in arousability Disorientation

B. Also smaller stature, failure to thrive
C. Multiple littermates possibly affected

VIII. Signs of idiopathic canine ("old dog") vestibulitis (Schunk and Averill, 1983)
A. Median age of onset 12.5 years and typically >10 years
B. No breed predisposition
C. Peracute onset of clinical signs
D. No history of trauma or recent otitis externa
E. Typically "pure" unilateral peripheral vestibular signs
1. No other cranial nerve deficits
2. No paresis or proprioceptive deficits
3. Consistent sustained, horizontal to rotatory nystagmus with the fast phase opposite the head tilt
F. Bilateral vestibular disease less common

IX. Signs of idiopathic feline vestibulitis (Burke et al., 1985)
A. Median age of onset 4 years and typically <7 years
B. Peracute onset of clinical signs
C. Possibly more common in summer months
D. Unilateral or bilateral disease

Diagnosis

I. Infectious diseases
A. History is often suggestive.
1. Prior history of chronic otitis externa and/or media
2. Acute (days) to subacute (weeks) onset of unilateral peripheral vestibular signs
3. Failure to improve with current medical treatment
B. Initial diagnostic procedures are similar to those described for otitis media and include the following:
1. Otoscopy or video otoscopy
2. Cytological examination of exudate and middle ear fluid
3. Culture of exudate and middle ear fluid
4. Schirmer tear test
C. Imaging is a very important tool.
1. Tympanic bullae radiography
a. Specific test but not very sensitive, and may miss subtle and early lesions
b. Insensitive method in detecting extent of disease process
c. Requires general anesthesia
d. The least expensive diagnostic tool
2. Computed tomography (CT)
a. Highly sensitive and specific test that detects bone and soft tissue changes associated with otitis media extending to otitis interna

b. Less sensitive test to detect extension of disease into the brainstem
c. Requires general anesthesia

3. Magnetic resonance imaging (MRI) (Garosi et al., 2001)
a. Highly sensitive and specific test that detects soft tissue changes associated with otitis media extending to otitis interna
b. Diagnostic test of choice for detecting extension into the brainstem and to rule out other causes of vestibular disease
c. Requires general anesthesia and is the most expensive modality

D. Cerebrospinal fluid analysis is indicated in certain circumstances.
1. Indications
a. Presence of brain involvement on imaging studies
b. Presence of central vestibular disease in the face of otitis media or interna
c. Presence of multifocal central nervous system disease
2. Potential contraindications
a. Coagulopathies
b. Potential brainstem herniation if mass detected with imaging

E. Ventral bulla osteotomy with debridement, culture and sensitivity, and biopsy may be both therapeutic and diagnostic.

F. Serological testing is indicated if rickettsial or fungal agents are suspected.

II. Noninfectious diseases
A. History
1. Determine whether any trauma has occurred.
2. Determine prior signs of upper respiratory disease, especially if inflammatory polyps are suspected in cats.
3. Onset is most often acute.

B. Diagnostic procedures
1. Congenital, nontraumatic peripheral vestibular disease: otoscopic exam
2. Idiopathic vestibular disease
a. It is important to rule out underlying causes of infectious disease, as described previously.
b. Hypothyroidism is always ruled out in older dogs (Jaggy et al., 1994).
3. Trauma: radiographic or CT imaging
4. Polyp formation
a. Examine ear and oropharynx under sedation.
b. Evaluate behind the soft palate.
c. CT or MRI is helpful.

Differential Diagnosis

I. Other causes of peripheral vestibular disease
A. Neoplasia
1. Peripheral nerve sheath tumors
2. Meningioma
3. Lymphosarcoma
4. Bone-related tumors
5. Carcinomas

B. Polyneuropathy
1. Endocrine disease: hypothyroidism
2. Toxicities
3. Degenerative forms

C. Vestibulotoxic agents
1. Aminoglycoside antibiotics
2. Mitotane *(Lysodren)*
3. Diuretics
4. Heavy metals
5. Antineoplastic agents (cisplatin)

II. Causes of central vestibular disease
A. Neoplasia
1. Cerebellopontine angle tumors
a. Involve cranial nerves V (trigeminal), VII (facial), and VIII (vestibulocochlear) on the same side, along with central vestibular signs
b. May cause paradoxical central vestibular disease
2. Meningioma
3. Choroid plexus tumors: papilloma or carcinoma
4. Ependymoma
5. Invasive peripheral nerve sheath tumor
6. Pituitary-dependent hyperadrenocorticism with macroadenoma

B. Inflammatory disorders
1. Infectious diseases
a. Canine distemper virus
b. Feline infectious peritonitis
c. Rocky Mountain spotted fever
d. Fungal diseases
e. Protozoal infections: *Neospora caninum* (dogs), *Toxoplasma gondii* (cats)
2. Immune-mediated diseases
a. Granulomatous meningoencephalitis
b. Steroid-responsive meningoencephalitis
c. Vasculitis

C. Metabolic diseases
1. Hypothyroidism
2. Pituitary-dependent hyperadrenocortisolism

D. Drug toxicity: metronidazole

III. Other causes of cranial nerve disease
A. Facial nerve disorders
1. Idiopathic facial neuritis: loss of blink reflex, unilateral or bilateral
2. Hemifacial spasm: facial nerve irritation from inflammation or physical trauma (e.g., postsurgical)
3. Peripheral nerve sheath tumor
4. Myasthenia gravis
a. Bilateral decrease in blink reflex
b. May worsen with repetitive testing of the blink reflex
5. Otitis media without interna

B. Trigeminal nerve disorders
1. Idiopathic neuritis
a. Acute onset of dropped jaw and pain around the zygomatic arch
b. May be associated with Horner's syndrome

2. Peripheral nerve sheath tumor: asymmetrical temporalis muscle atrophy

C. Horner's syndrome
1. Idiopathic form: Horner's syndrome without any other neurological deficits
2. Otitis media without interna
3. Cranial mediastinal neoplasia

Treatment

I. Infectious diseases
A. Appropriate antimicrobial drug therapy
1. Optimal selection of antibiotic is based on culture and susceptibility testing.
2. Long-term treatment of 3 to 6 weeks is recommended for bacterial otitis interna.
3. Systemic antifungal therapy is based on cytological examination, culture, or positive serology testing.
4. Topical therapy alone is inadequate.

B. Debridement of mass or fluid removal via ventral bulla osteotomy
1. Indicated for recurrent otitis interna with otitis media, or if there is significant inflammatory tissue accumulation
2. Helps to improve healing

C. Corticosteroid therapy: contraindicated

II. Noninfectious diseases
A. Congenital form
1. Supportive care to maintain normal growth is most important.
2. No known therapy alters the clinical outcome.

B. Acquired disorders
1. Supportive care is critical during the acute phases of vestibular disease.
a. Provide adequate hydration.
b. Provide adequate nutritional support.
c. Provide appropriate environment to prevent decubital ulcers and recumbency-induced pneumonia.
2. Corticosteroid therapy is contraindicated for any of the idiopathic vestibular syndromes.
3. Treat any endocrine imbalance appropriately.
4. Bulla osteotomy is indicated for polyp resection and traumatic injury associated with middle ear hemorrhage (see Chapter 107).

III. Antivertiginous therapy
A. Anecdotally, certain drugs reduce the effect of vertigo or dizziness.
1. Meclizine *(Antivert)* 0.5 mg/kg PO BID
2. Diazepam *(Valium)* 0.1 to 0.2 mg/kg PO SID to BID
3. Acepromazine 1 mg/kg PO SID for possible nausea control

B. A dark, quiet room with minimal visual stimulation also helps minimize vertigo.
C. Over time, gradual institution of exercise on flat surfaces allows the vestibular system to start to compensate.
D. Caution must be used around stairs until a full recovery is present.

Monitoring of Animal

I. Immediate hospital or home care
A. Hydration status and nutritional intake are carefully monitored to prevent dehydration and malnutrition, especially in the older animal.
B. Prevent self-injury from excessive rolling or falling.
C. Monitor for gastric dilatation–volvulus in dogs with excessive rolling.

II. Recovery period
A. Improvement of clinical signs is usually seen during the first week after treatment of bacterial otitis interna.
B. Improvement of clinical signs is usually seen during the first 2 weeks after the onset of idiopathic vestibular disease, but may take several weeks to stabilize.
C. Rapid recovery from clinical signs occurs with appropriate treatment of hypothyroidism.

III. Residual signs
A. Mild to moderate head tilt may persist indefinitely.
B. Positional, direction-changing nystagmus may be present during the recovery period from unilateral vestibular disease.
C. Decreased oculovestibular eye movements are also possible.
D. Permanent facial nerve paresis or paralysis may occur with concurrent otitis media.

IV. Recurrence
A. Recurrent episodes of infectious otitis interna are most common with chronic bacterial otitis media.
B. Recurrent episodes of idiopathic vestibular disease are uncommon.

V. Prognosis
A. Infectious otitis interna
1. Fair to excellent with appropriate antimicrobial therapy
2. Worse for fungal infections

B. Noninfectious otitis interna
1. Excellent for acquired idiopathic vestibular disease
2. Fair for congenital idiopathic vestibular disease
3. Excellent for polyp- or trauma-induced disease, with adequate surgical correction

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CHAPTER 109

Deafness

Michael Podell

Definition

I. Deafness is the loss of normal hearing function.
II. Deafness can be classified as follows:
  A. Conductive hearing loss is the result of failure of sound energy to be transmitted to mechanical energy in the outer and middle ear structures.
  B. Sensorineural hearing loss is the result of loss of electrical energy transfer from the cochlear sensory receptors or cochlear nerve.
  C. Central-mediated hearing loss is the failure to process auditory information at the level of the brain.
  D. Presbycusis is an age-related hearing loss that is not associated with a specific pathologic process.

Causes

I. Conductive hearing loss
  A. Outer ear diseases
    1. Otitis externa with reduction in ear canal volume
      a. Acute: fluid, debris, medication accumulation
      b. Chronic: stenosis
    2. Ear wax impaction
    3. Foreign body
    4. Neoplasia
    5. Trauma: iatrogenic (ear canal ablation) or blunt
    6. Tympanic membrane (TM) perforation
  B. Middle ear diseases
    1. Aural atresia
    2. Ossicular chain dysfunction: disarticulation, fusion
    3. Otitis media
    4. Otosclerosis
    5. Foreign body
    6. Inflammatory polyp, neoplasia
II. Sensorineural hearing loss
  A. Congenital, hereditary deafness is seen most commonly in dog and cat breeds with white pigmentation or blue eyes (Strain, 2004).
    1. It is the most common cause of deafness in dogs.
    2. It is typically present at birth, but may be progressive as the animal matures.
    3. Numerous purebred dogs are affected, including the Dalmatian, Australian blue heeler, English setter, Argentine dogo, bull terrier, Australian shepherd dog, Jack Russell terrier, and Cavalier King Charles spaniel (Hayes et al., 1981; Strain, 1999).
    4. White-coated, blue-iris cats and dogs may be also affected.
    5. Female Dalmatians may be predisposed (Wood and Lakhani, 1998).
  B. Acquired or age-related forms also occur.
    1. Ototoxicity from chemical or noise-induced toxic changes to the inner or outer hair cells (Mansfield, 1990)
      a. Approximately 200 ototoxic drugs and chemicals have been identified.
      b. In most cases, the hearing loss is irreversible and often progressive, even after cessation of exposure to the toxic agent.
      c. Common ototoxic agents include the following:
        (1) Aminoglycoside antibiotics, polymyxin B, erythromycin
        (2) Loop diuretic agents
        (3) Cisplatin, salicylates
        (4) Topical antiseptics: chlorhexidine, iodine
        (5) Heavy metals
        (6) Otic ceruminolytic agents
    2. Otitis interna
    3. Trauma: petrous temporal bone fractures, hemorrhage
    4. Neoplasia
    5. Presbycusis: individual or combined degeneration of cochlear, sensory, neural, strial structures

Pathophysiology

I. Normal hearing function (Hall, 1997)
  A. Sound waves travel to the outer ear, are transmitted through the external ear canal to the external auditory meatus, and are received by the TM.
    1. The TM resonates to convert the sound waves into mechanical energy.
    2. Vibrations of the TM set the bones of the middle ear (malleus, incus, and stapes) into motion.
  B. The mechanical energy is amplified over 20 times in the bony ossicles of the middle ear by the time the energy is transmitted to the oval window, just before entering the inner ear.
    1. Movements of the oval window initiate pressure waves in the perilymph within a structure of the cochlea called the *scala vestibuli*.

2. The fluid wave energy is then transferred into the scala tympani, where the basilar membrane of the scala tympani begins to vibrate as a result of this fluid wave energy transfer.
3. Sitting firmly attached to the basilar membrane is the organ of Corti, a specialized receptor organ.
   a. The organ of Corti is composed of neuroepithelial hair cells and several types of supporting cells.
   b. The rocking motion of the basilar membrane moves the organ of Corti, causing a shearing motion of the small stereocilia sitting on top of the hair cells.

C. When the shearing force produces a deflection of stereocilia toward the taller stereocilia, the cell becomes depolarized, generating an electrical impulse that is synaptically transmitted to the auditory nerve fibers.

D. As the basilar membrane becomes shorter with each turn of the cochlea, it vibrates at a different frequency relative to its width.
1. Low-frequency sound is detected near the base, and high-frequency sound near the apex of the cochlea.
2. Dogs can hear sounds from a low frequency of 2 Hz to a high frequency of 47 kHz.

II. Conductive hearing loss

A. Failure to transform sound waves to mechanical energy

B. Diseases that create an obstruction of air (sound waves)
1. Fluid accumulation
2. Tissue proliferation from chronic inflammation
3. Mass effect

C. Diseases that prevent mechanical energy from forming
1. Loss of compliance of the TM
2. Loss of mobility of the ossicular chain
3. Loss of connection of the ossicular chain onto the oval window

D. Presbycusis: age-related event where conduction no longer occurs

III. Sensorineural hearing loss

A. In dogs carrying the merle or piebald gene, the deafness arises from loss of hair cells secondary to degeneration of the cochlear blood supply (stria vascularis)
1. Hearing loss is permanent and usually complete by 3 weeks of age, but may progress later in life.
2. Unilateral deafness is twice as prevalent as bilateral deafness (Wood and Lakhani, 1998).

B. Deafness in breeds carrying the piebald gene is neither a dominant nor a recessive trait (Strain, 1999).
1. Deaf dogs can produce normal offspring and normal-hearing dogs can produce deaf offspring.
2. Blue eyes, white coat color, or a deaf parent are phenotypic risk factors (Strain, 2004).
3. Evidence exists that congenital, hereditary deafness is a polygenic trait with incomplete penetrance or expression (Cargill et al., 2004).

Clinical Signs

I. History with congenital, hereditary forms

A. Signs are present soon after birth.

B. Puppy does not respond to environmental noises.
1. Failure to wake up with rest of litter
2. Failure to respond to noises from people, toys, and so forth
3. Startles easily

C. Unilaterally deaf dogs often go undetected or may exhibit difficulty localizing sound.

D. Progressive hearing loss may occur in certain breeds as they mature over several years, such as the Cavalier King Charles spaniel (Podell, 1999).

II. History with acquired forms

A. Acute-onset deafness
1. May be the result of a chronic, progressive disease pattern that goes unnoticed
   a. Otitis externa, media, interna
   b. Presbycusis
   c. Procedure or manipulation of the ear canal in older animals that raises the hearing threshold to a level of noticeable hearing loss (e.g., dental, ear cleaning procedures)
2. Association with aminoglycoside antibiotic treatment
3. Known trauma
4. Postoperative total ear canal ablation

B. Chronic-onset deafness
1. Preceding history of recurrent otitis externa, media, interna
2. Progressive pattern of altered behavior: not following commands or responding to auditory cues
3. Failure to be aroused from sleep

III. Physical examination findings with congenital, hereditary forms

A. Usually the physical examination is normal.

B. Animals with a developmental anomaly of the brain may have neurological deficits and changes in cranial structure (e.g., domed skull with hydrocephalus).

C. Certain purebreed dogs may have multiple congenital anomalies that are detected at the time of the examination.
1. An example is Alport syndrome in Dalmatians and bull terriers (Hood et al., 2002).
2. Alport syndrome is an inherited disease characterized by hematuria, renal failure, and deafness.
3. The cause is a genetic mutation that alters type IV collagen that translates into a lamellated glomerular basement membrane.
4. The disease is progressive over the first 2 years of life in dogs.

D. Concurrent congenital peripheral vestibular disease may be associated with deafness and is reported in Doberman pinschers (Wilkes and Palmer, 1992).

IV. Physical findings with acquired forms

A. Concurrent signs of ear disease may be present.

B. Physical examination findings may be normal with age-related changes.

C. Concurrent peripheral vestibular disease may be present.

V. Caveats

A. The accuracy of the historical information for the onset and progression of acquired hearing loss is often poor owing to the wide frequency range detected by dogs, and their ability to compensate with other sensory modalities.
B. Unilateral deafness is very difficult to detect accurately with historical or physical examination findings.
C. The most accurate method of confirming hearing loss is with specific diagnostic testing.

Diagnosis

I. Rule out causes of otitis externa and media (see Chapters 107 and 108).
II. Behavioral audiometry requires active participation from the animal.
  A. Both conscious and reflexive responses can be monitored with this sensitive, but less specific, test of hearing loss.
    1. Conscious responses are obtained in conditioned dogs to determine the tonal range of hearing; however, this type of testing is unrealistic in a clinical setting.
    2. Reflexive testing is used to try to determine an "absolute" positive response.
      a. Caution must be used in the interpretation of reflexive responses because many dogs are attuned to vibratory motions that occur with most startle reaction tests.
      b. Significant hearing loss may be present even in the face of a positive response.
  B. Unilateral deafness is difficult to detect with this method.
III. Impedance audiometry is a noninvasive, objective means of evaluating the integrity of the middle ear utilizing tympanometry and acoustic reflex testing.
  A. Tympanometry is the measurement of changes in eardrum compliance (mobility) as pressure in the external ear is changed.
  B. Tympanometry provides an indirect measurement of the air pressure in the middle ear and the degree of compliance of the TM, and an estimate of the external ear canal volume.
  C. The acoustic reflex is the involuntary action of the middle ear in response to a sound stimulus (Sims, 1988).
    1. When a loud noise is introduced into a normal ear, the muscles in the middle ear contract reflexively, thus decreasing the compliance of the ear.
    2. The purpose of this reflex is protection of the inner ear from damaging levels of noise through attenuation of high-intensity sounds.
    3. All measurements are tested at the pressure at which maximum compliance occurs.
    4. The reflexes are elicited by pure tones presented at frequencies of 2000 to 4000 Hz and intensities ranging from 70 to 110 dB in 5- to 10-dB increments delivered through the probe for ipsilateral reflexes and through an earphone for contralateral reflexes.
    5. An acoustic reflex less than the normal range, in conjunction with an abnormal or normal tympanogram, indicates otitis media or retrocochlear pathology, respectively.
IV. Evoked potential audiometry measures the electrical manifestation of the brain's reception of, and response to, an external stimulus (Sims, 1988).
  A. Auditory evoked responses (AERs) are signal-averaged recordings of brain activity in response to acoustic stimuli.
  B. AERs have the advantage of providing objective, quantifiable data that do not require the animal's cooperation and are highly resistant to the effects of sedatives and anesthetic agents.
  C. Evoked potential audiometry measures very specific components of the auditory pathway.
    1. Several types of AER can be recorded, depending on the time over which the response to the stimulus is averaged.
    2. Early-latency (0 to 10 msec) components are the result of activation of peripheral receptor, nerve, and brainstem structures, and thus are often referred to as a brainstem auditory evoked response (BAER) (Figure 109-1).
  D. The BAER test can be used to characterize both conductive and sensorineural deafness.
    1. Changes in latency onset, amplitude, and interval between waveforms can be analyzed to evaluate for site-specific pathology of the auditory pathway.
    2. Either clicks (2 to 4 kHz) or frequency-specific tones can be introduced as acoustic stimuli.
    3. Exposure to specific tones at varying intensities (tone burst BAER) provides the ability to distinguish hearing loss at specific frequencies.
    4. Requirements for the tests differ.
      a. Click BAER testing often can be done in awake, lightly restrained dogs.

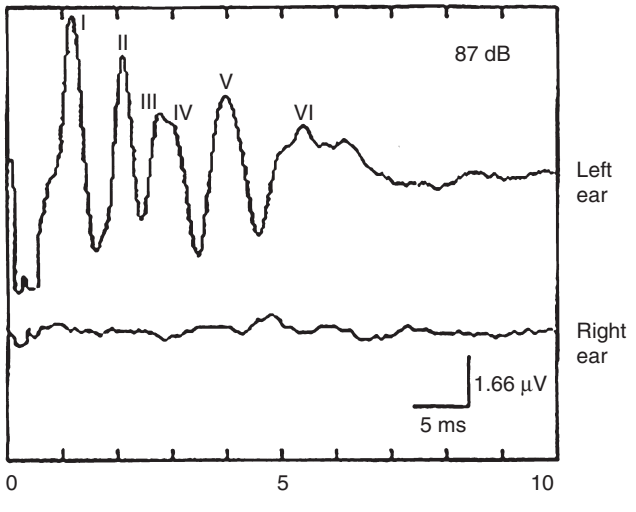

FIGURE 109-1 Early-latency brainstem auditory evoked response testing in a unilaterally (right ear) deaf 8-week-old male Jack Russell terrier. This recording is an example of congenital/hereditary sensorineural deafness from birth.

b. Tone-burst BAER testing requires sedation and a sound-attenuated room.

5. The BAER test is the preferred test for congenital deafness screening in animals, owing to its high sensitivity and ease of administration.

V. Otoacoustic emissions (OAEs) are spontaneous or acoustic-stimulated sounds generated within the normal cochlea (Lonsbury-Martin et al., 1997).
   A. These sounds can be measured when the middle ear and cochlea are functioning normally.
   B. The reemitted sounds of OAEs are thought to originate from active feedback of sound energy into the cochlea, a function attributed to outer hair cells.
   C. A decrease in amplitude of OAEs is found in pathologic conditions that result in loss of outer hair cells, such as noise exposure, anoxia, and aminoglycoside intoxication.
   D. Measurement of OAEs provides increased sensitivity and specificity in establishing the degree and type of hearing loss.
   E. Two types of otoacoustic emissions are commonly evaluated.
      1. Transient evoked OAEs are produced by presenting a broad-band "click" to the ear and measuring the magnitude of the emissions.
      2. In distortion product OAEs, two tones of overlapping frequencies are used to stimulate the basilar membrane.
   F. Measurement of OAEs requires sedation and a sound-attenuated room, which are only available in audiology laboratories at this time.

Differential Diagnosis

I. In young dogs, developmental diseases of the brain with abnormal behavior or failure to respond appropriately to auditory stimuli must be considered.
   A. Hydrocephalus
   B. Lissencephaly
   C. Storage disorders
II. Age-related behavior changes may occur in older pets who no longer respond to normal owner commands or interactions; although these animals may appear deaf, they no longer are processing the hearing information.
III. Forebrain neoplasia with behavioral disturbances in older animals may be mistaken for age-related deafness.

Treatment

I. Treatment of reversible conditions
   A. Appropriate antimicrobial agents for infectious otitis externa, media, interna
   B. Removal of accumulated ear wax or other debris
   C. Removal of inflammatory tissue from ear canal
II. Improving hearing with hearing aids
   A. Bone-anchored hearing aids may be useful in restoring hearing function in dogs with bilateral total ear canal ablation and lateral bulla osteotomy (Sommerlad et al., 1999).
   B. Hearing aids that are seated in the ear canal to amplify sound for partial sensorineural deafness are not well tolerated in the dog or cat.
III. Conditions with no available treatment
   A. Congenital, hereditary deafness
   B. Presbycusis
IV. Animal–owner behavioral modifications (Becker, 1998)
   A. Owners can develop hand signals to train their dogs.
   B. Identify the dog as being deaf, via either collar or tags.
   C. Bright, reflective markings may be used when the dog is outside, to alert others (i.e., cars) to the dog.

Monitoring of Animal

I. A return of hearing function is most likely to be seen with resolution of inflammatory or infectious diseases.
II. Preventive measures include the following:
   A. Congenital, hereditary forms
      1. Stop the breeding of lines that produce deaf offspring.
      2. Early screening of breeds with a predisposition for hereditary deafness is strongly recommended.
      3. Auditory evoked response (BAER) screening of sire, dam, and all puppies after 7 weeks of age is recommended.
   B. Acquired forms
      1. Systemic aminoglycoside dosages must be adjusted according to renal function to reduce the total time of peak serum concentration that may cause ototoxicity.
      2. Do not use topical agents with the potential for ototoxicity.
III. Repeated auditory screening is performed in any dog thought to have hearing loss, but is not completely deaf.
IV. Normal auditory screening with an evoked potential test may warrant further diagnostic testing to evaluate for central-mediated disease, especially in older dogs.

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CHAPTER 110

Introduction

Lynn Guptill

GENERAL CONSIDERATIONS

I. Infectious diseases remain an important component of daily veterinary practice.
   A. Recognized diseases such as leptospirosis and ehrlichiosis are reemerging and being redefined.
   B. Pathogens "new" to companion animals in the United States are being recognized, such as leishmaniasis in foxhounds and other dogs.
   C. For pathogens previously considered "minor," a broader understanding is developing.
      1. Bartonellosis is increasingly recognized in cats and dogs.
      2. Increased recognition of methicillin-resistant *Staphylococcus aureus* (MRSA) infections is occurring in cats and dogs.
   D. "Traditional" pathogens persist (e.g., rabies virus, parvovirus, canine distemper, feline leukemia, feline immunodeficiency, and feline infectious peritonitis viruses).
II. Concepts of antibiotic use are being reexamined.
   A. Increased awareness and concerns about multiple antibiotic-resistant strains of bacterial pathogens
   B. Increased awareness and analysis of antimicrobial use in large veterinary hospitals
   C. American Veterinary Medical Association (AVMA) guidelines for antibiotic use (www.avma.org/scienact/jtua)
III. Vaccination protocols and concepts are continually revised.
   A. "Core" and "noncore" vaccine protocols and exposure risks are being redefined for individual animals.
   B. Reexmaination of the duration of vaccine-induced immunity is causing vaccination frequency to be reconsidered.
   C. Vaccines are changing, with new recombinant vaccines and DNA vaccines either in use or being developed.
   D. Vaccine-associated adverse event characterization has improved.

Changes in Exposure

I. Cats and dogs are exposed to an increasingly diverse set of infectious diseases.
   A. Increased proximity of homes and recreational areas to wildlife reservoirs
   B. Introduction of organisms and vectors through travel of people, pets, and livestock
II. Immunocompromised owners and their pets require special consideration.
   A. Pets are an important source of comfort and should be retained by immunocompromised individuals.
   B. Although uncommon, it is possible for pets to transmit zoonotic and opportunistic pathogens to immunocompromised people.
   C. Veterinarians, clients, and physicians are working together to address the following:
      1. Understanding the true potential for transmission of zoonotic and opportunistic pathogens
      2. Developing plans for choice of and care of pets by immunocompromised clients

NEW DIAGNOSTIC TECHNIQUES

I. Polymerase chain reaction (PCR) tests are available commercially and other molecular diagnostic tools are increasingly available.
II. Veterinarians must realize both the advantages and shortcomings of these tests.
   A. Difficult-to-culture pathogens (e.g., *Bartonella* spp. in endocarditis lesions) are detected.
   B. Species and strains are identified and reclassified.
      1. Better characterization of *Ehrlichia* spp., *Anaplasma* spp., and *Neorickettsia* spp.
      2. Better characterization of the hemoplasma and *Babesia* spp.

C. Nucleic acid detected and/or amplified by PCR does not necessarily indicate the organism is viable or responsible for the disease state.
D. False-positive results occur from contamination.
E. False-negative results can occur from degradation of nucleic acids in tissue specimens.

SUMMARY

I. Infectious diseases remain an important component of veterinary practice, and the understanding of infectious agents, pathogenesis, and epidemiology continues to develop.
II. The chapters in this section have been updated to address what the authors consider the most important infectious diseases encountered in dogs and cats in the United States.

CHAPTER 111

Systemic Mycoses

Joseph Taboada

BLASTOMYCOSIS

Definition

I. Blastomycosis is a systemic, fungal infection that usually originates in the lungs and then disseminates to the lymphatics, skin, eyes, bones, and other organs.
II. Young, male, large-breed dogs (especially sporting breeds and hounds) living near water are at increased risk; most affected animals live within one-quarter mile of water.
III. Dogs have been used as a sentinel animal for human disease, because the incidence in dogs is approximately 10 times higher.
IV. Cats are rarely infected.

Cause

I. Blastomycosis is caused by the dimorphic fungus *Blastomyces dermatitidis*.
II. *Blastomyces dermatitidis* characteristics are as follows:
    A. In tissue or when cultured at 37° C, the organism is a thick-walled yeast (5 to 20 μm) that usually has a single bud attached to the mother cell by a broad base.
    B. When cultured at 25° C, the organism grows as a white, cottony mold that may become tan as it ages.
    C. Colonies grow slowly and contain branching septate (1 to 2 μm) mycelia that form round to pyriform-shaped (2 to10 μm) conidia, resembling the microconidia of *Histoplasma capsulatum.*
III. *Blastomyces dermatitidis* is probably a soil saprophyte, but the natural reservoir remains unidentified.
    A. It is often grown from wet, acidic, or sandy soil containing decaying wood, animal feces, or other organic enrichment.
    B. Moisture is important for growth and transmission; therefore the organism is primarily endemic along the Mississippi, Ohio, Missouri, Tennessee, and St. Lawrence rivers; in the southern Great Lakes; and in the southern mid-Atlantic states.

Pathophysiology

I. Infection occurs most commonly via inhalation of infective conidia from the environment, but direct inoculation may rarely result in localized cutaneous disease.
II. Blastomycosis is not a contagious disease; however, it is an occupational hazard to laboratory workers and veterinary personnel when handling infective materials or cultures.
    A. Activities that disrupt the soil, such as digging or construction, may also play a role in the aerosolization of spores.
    B. Point sources of exposure within enzootic areas are important in establishing infections.
III. After inhalation, conidia are phagocytized by alveolar macrophages and transformed from the mycelial phase to the yeast phase, which induces a marked suppurative to pyogranulomatous response.
    A. Phagocytized yeast are then transported into the pulmonary interstitium, where access is gained to the lymphatic and vascular systems.
    B. Hematogenous and lymphatic dissemination results in multisystemic disease.
    C. Although dissemination may affect any organ system, the lymph nodes, eyes, skin, bones, subcutaneous tissue, and prostate gland are commonly affected in dogs.
    D. The skin, subcutaneous tissue, eyes, central nervous system (CNS), and lymph nodes are often affected in cats.
IV. Incubation period varies in dogs from 5 to 12 weeks.
V. Immune response determines the severity of clinical disease.
    A. Antibody production occurs in most cases, with higher serological titers found in severe disseminated disease (Klein et al., 2000).
    B. Recovery is probably dependent on cell-mediated immune responses.
        1. Adequate immune response may result in mild respiratory disease that resolves spontaneously or may result in disease in other organ systems without apparent pulmonary involvement.
        2. A poor or weak immune response results in severe pulmonary and disseminated disease.

Clinical Signs

I. High-risk breeds include the blue tick coonhound, pointer, and Weimaraner (Rudmann et al., 1992).
    A. Male dogs are affected more than females.
    B. Large-breed dogs are affected more than small breeds.
    C. Any age dog can be affected, with the highest incidence occurring at 1 to 5 years.
II. Clinical findings are variable.
    A. Nonspecific signs such as anorexia, depression, weight loss, cachexia, and fever (about 40%) are common.

B. The lungs are the portal of entry for organisms; thus pulmonary signs are seen in up to 85% of dogs (Arceneaux et al., 1998).
   1. Signs range from cough and mild respiratory distress to severe dyspnea.
   2. Hypoxemia results in cyanosis in the most severely affected cases.
C. A dry, hacking cough is common with compression of primary bronchi from enlargement of perihilar lymph nodes, and from bronchointerstitial and alveolar disease.
D. Rapid, shallow respiratory efforts are occasionally caused by pleural effusion and pleuritic pain.
E. Chylothorax and solid pulmonary masses are uncommon.
F. Cranial vena caval syndrome may result from anterior mediastinal disease (Howard et al., 2000).

III. Diffuse lymphadenopathy occurs in up to 60% of dogs (Arceneaux et al., 1998).

IV. Cutaneous signs occur in 30% to 50% of dogs and are commonly noted in cats (Arceneaux et al., 1998).
   A. Skin lesions are usually single or multiple papules, nodules, or plaques that may ulcerate and drain a serosanguineous to purulent exudate.
   B. Large abscesses occasionally occur, especially in cats.
   C. Paronychia is common in dogs, so the feet and nail beds should be examined closely.

V. Ocular involvement is noted in 20% to 50% of the cases, with approximately 50% of affected dogs having bilateral involvement (Brooks et al., 1991; Arceneaux et al., 1998).
   A. Posterior segment disease usually occurs first and may progress to endophthalmitis, panophthalmitis, or secondary glaucoma.
   B. Posterior segment disease includes chorioretinitis, retinal detachment, subretinal granulomas, or vitreitis.
   C. Optic neuritis is occasionally seen.
   D. Anterior segment disease is usually secondary to posterior segment disease.
      1. It includes anterior uveitis, conjunctivitis, keratitis, and episcleritis.
      2. Secondary glaucoma is common in dogs with anterior segment disease.
   E. Long-term effects on vision can be severe.
      1. Dogs with only focal chorioretinitis have a better prognosis for vision than those with anterior segment disease or endophthalmitis (Brooks et al., 1991).
      2. It is unlikely that dogs with severe visual impairment will regain vision even after appropriate therapy.

VI. Lameness is noted in up to 25% of dogs (Arceneaux et al., 1998).
   A. Osteomyelitis is noted in 10% to 15% of dogs, usually involving the epiphyseal regions below the elbow or stifle (as a single lesion).
   B. Paronychia may cause pain and lameness.
   C. Monoarthritis or polyarthritis is a rare cause of lameness.

VII. Reproductive system is affected in approximately 10% of dogs (Arceneaux et al., 1998).
   A. Orchitis is seen in 16% of intact male dogs (Arceneaux et al., 1998).
   B. Prostatitis or mastitis is seen in <5% of dogs.

VIII. The CNS is affected in <5% of dogs; a higher percentage of cats have CNS involvement.
   A. CNS signs are dependent on the location of lesions.
   B. CNS involvement may occur without obvious clinical signs.

IX. Other potential sites of infection include liver, spleen, kidneys, bladder, and nasal cavity; the gastrointestinal (GI) tract is rarely affected.

X. Feline blastomycosis is uncommon.
   A. Most clinical signs seen in dogs may also occur in cats.
   B. Large abscesses are more common.
   C. Neurological signs are more common.
   D. CNS involvement is an important risk factor for recurrence in cats.

Diagnosis

I. Hematological and serum biochemistry findings
   A. Results of hematological examination are often normal, but mild nonregenerative anemia and mature neutrophilia or neutrophilia with a mild left shift may be seen.
   B. Hypoalbuminemia and hyperglobulinemia are the most consistent biochemical abnormalities.
   C. Mild to moderate hypercalcemia is noted in <10% of cases.

II. Radiographic findings (Arceneaux et al., 1998).
   A. Interstitial patterns are observed in about 70% of dogs, and include nodular interstitial (41%), diffuse interstitial (24%), and bronchointerstitial (5%) forms.
   B. Alveolar or mixed interstitial/alveolar patterns can occur (20%).
   C. Tracheobronchial lymphadenopathy may be noted (30%).
   D. Mediastinal (8%) or solitary pulmonary masses (8%) are uncommon.
   E. Pleural effusion (7%) may obscure the pulmonary parenchyma.
   F. Pneumothorax (1%) is rare.
   G. Bone lesions occur in about 12% of cases (Arceneaux et al., 1998).
      1. Most bony lesions (66%) are solitary osteomyelitis lesions.
      2. Most lesions (75%) occur in the extremities.
         a. Lesions are osteolytic and typically at the ends of the long bones.
         b. The forelimbs are affected more than the hind limbs.
         c. Most extremity lesions are below the elbow or stifle.
      3. Periosteal proliferation and soft tissue swelling is noted in about 50% of lesions.

III. Organism identification

A. Cytological findings from tissue are as follows:
   1. Suppurative or pyogranulomatous inflammation is present, often with thick-walled yeast (5 to 20 μm in diameter, 0.5 to 0.75 μm wall) that bud to form daughter cells from a broad base.
   2. The yeast cells lack a capsule, helping to differentiate them from *Cryptococcus* spp.
   3. Infected skin yields organisms in about 80% of impression smears, skin scrapings, or fine-needle aspirates (FNA) of nodular lesions.
   4. Vitreal aspirates yield organisms from most affected, blind eyes.
   5. Lymph node aspirates yield organisms approximately 60% of the time.
   6. Bone and lung aspirates, transtracheal washes, and bronchoalveolar lavage yield organisms <50% of the time.
   7. FNAs of focal parenchymal lesions of the lungs yield organisms more often than transtracheal washes or bronchoalveolar lavage.
   8. Urine sediment, prostatic washes, or peritoneal lavage rarely reveal organisms.
   9. Organisms are occasionally identified in the stool of dogs with pulmonary disease (Baumgardner and Paretsky, 1997).

B. Histopathological findings are as follows:
   1. Purulent to pyogranulomatous lesions with broad-based organisms are usually apparent.
   2. Special stains (periodic acid–Schiff [PAS], Gridley's fungal, Gomori methenamine silver) demonstrate the organisms best in tissue.

C. Fungal culture and identification are as follows:
   1. They are not needed for definitive identification in clinical cases.
   2. Mycelial growth on Sabouraud's dextrose agar may require 1 to 4 weeks at 37° C, whereas growth occurs on blood or brain-heart infusion agar in 1 to 2 weeks at 25° C.
   3. Culturing the organisms from the environment is rarely achieved (Baumgardner and Paretsky, 1999).

IV. Serology

A. Antibody response
   1. It is used primarily when a high degree of probability exists or repeated attempts fail to demonstrate the organisms.
   2. Agar-gel immunodiffusion (AGID) test is most commonly used.
      a. It detects antibodies directed against the fungal organism (sensitivity 41% to 90%, specificity 90%).
      b. It may be negative in early disease, and some dogs fail to develop a serologic titer.
      c. It is not useful in following response to therapy.
      d. There is a low prevalence of antibodies in unaffected dogs living in endemic areas.

B. Antigen detection
   1. A highly sensitive, competitive, enzyme-linked immunosorbent assay (ELISA) has been developed to detect *B. dermatitidis* antigen in urine (Shurley et al., 2005).
   2. Specificity has not been critically evaluated.

Differential Diagnosis

I. Other multisystemic granulomatous, neoplastic, and immune-mediated diseases

II. Skin involvement
   A. Bacterial diseases: actinomycosis, mycobacteriosis, botryomycosis, brucellosis, or *Rhodococcus equi* infection
   B. Mycotic and related diseases: cryptococcosis, coccidioidomycosis, sporotrichosis, basidiobolomycosis, phaeohyphomycosis, hyalohyphomycosis, eumycotic mycetoma, dermatophytic mycetoma, protothecosis, pythiosis, lagenidiosis, nodular leishmaniasis
   C. Noninfectious pyogranulomatous diseases: foreign body reaction, idiopathic nodular panniculitis, sebaceous nodular adenitis, and canine cutaneous sterile pyogranuloma/granuloma syndrome
   D. Neoplasia: squamous cell carcinoma, cutaneous T-cell lymphoma, cutaneous histiocytosis
   E. Miscellaneous diseases: systemic lupus erythematosus, systemic vasculitis, cutaneous embolic disease

III. Ocular involvement
   A. Fungal disease: cryptococcosis, coccidioidomycosis, geotrichosis, histoplasmosis, aspergillosis
   B. Neoplasia: lymphosarcoma, metastatic tumors
   C. Other diseases: protothecosis, brucellosis, toxoplasmosis, neosporosis, leishmaniasis

IV. Lymph node involvement
   A. Lymphosarcoma
   B. Other fungal infections, rickettsial diseases, brucellosis
   C. Mycobacteriosis, protothecosis, leishmaniasis

V. Bony involvement
   A. Primary or metastatic neoplasia
   B. Other fungal or bacterial osteomyelitis

Treatment

I. Spontaneous recovery from systemic blastomycosis rarely occurs in dogs, so symptomatic animals are always treated.

II. Itraconazole is the preferred treatment (Legendre et al., 1996).
   A. Give dogs 5 mg/kg PO BID for the first 3 to 5 days, then 5 mg/kg PO SID for 2 to 3 months or until active disease has subsided.
   B. Cats may require 5 mg/kg PO BID or 10 mg/kg PO SID.
   C. Itraconazole oral solution has more consistent bioavailability in cats.
   D. Response may be minimal in the initial 1 to 2 weeks of treatment.
   E. Drug-induced side effects include the following:
      1. Increased liver enzymes may indicate hepatocellular damage or only enzyme induction.
         a. Mild to moderate increases in serum alanine transaminase (ALT), aspartate transaminase (AST), and alkaline phosphatase (ALP) activities

occur in about 50% of treated animals, especially at a dose of 10 mg/kg.
b. Therapy is discontinued if liver enzyme elevations are marked or if they are accompanied by anorexia, vomiting, or abdominal pain.
c. Therapy can be reinstituted at a lower dose following a return to normal liver enzyme levels.
2. Anorexia is the most common side effect.
a. It is dose-related and more common in cats.
b. Cyproheptadine 2 mg PO SID to BID or oxazepam 2 to 3 mg PO SID to BID may be used as appetite stimulants in cats.
3. A dose-dependent cutaneous vasculitis (ulcerative skin lesions with appearance similar to a recurrence of blastomycosis) is seen in about 7% of dogs receiving 10 mg/kg.
4. Fearful behaviors (e.g., hiding, submission) are rare complications in dogs.

F. Itraconazole does not cross the blood–brain, blood–ocular, or blood–prostatic barriers well, but it is still effective in some CNS, ocular, and prostatic infections.
G. It concentrates well in the skin, making it highly effective in treating cutaneous infections.
H. Severely ill or hypoxemic dogs may have a better outcome if they are treated initially with itraconazole and amphotericin B in combination, or with IV fluconazole or itraconazole.
1. Worsening respiratory signs may occur in the first few days after beginning treatment.
2. Dexamethasone (0.25 to 0.5 mg/kg IV SID for 2 to 3 days) may improve prognosis for dogs with severe respiratory disease whose hypoxemia worsens after starting treatment.

III. Fluconazole is less expensive, but typically not as effective as itraconazole.
A. Give dogs or cats 2.5 to 5 mg/kg PO, IV SID for one month beyond complete clinical remission.
B. It does not require a low gastric pH for maximal bioavailability and is not affected by the presence or absence of food.
C. Fluconazole is excreted in the urine; crosses the blood–brain, blood–ocular, and blood–prostatic barriers well; and may be the preferred treatment for urinary tract, prostatic, and CNS infections.
D. Side effects are similar to those of itraconazole.

IV. Ketoconazole is another choice.
A. Give dogs or cats 5 to 15 mg/kg PO BID for a minimum of 3 months (with food, not concurrently with antacids).
B. Response rates are much lower and relapses are higher, and dogs generally must be treated for a longer periods.
C. Anorexia, vomiting, hepatotoxicity, and adrenal insufficiency are more likely.

V. Amphotericin B is used in selected cases.
A. It has good efficacy against blastomycosis, but nephrotoxicity is the primary limiting side effect.
B. Amphotericin B lipid complex *(Albecet)* is recommended in combination with itraconazole or fluconazole for severely affected or hypoxemic cases.
1. It allows higher total doses to be used and reduces nephrotoxicity compared to the less expensive deoxycholate salt of amphotericin B.
2. Recommended dose in dogs is 1 to 2 mg/kg IV QOD to a total dose of 12 to 24 mg/kg (Krawiec et al., 1996).
C. Deoxycholate salt of amphotericin is less expensive but more toxic.
1. Nephrotoxicity is the primary limiting factor.
2. Fever is another major side effect and is usually ameliorated by pretreatment with nonsteroidal anti-inflammatory drugs.
3. Other side effects include thrombophlebitis, hypokalemia, distal renal tubular acidosis, hypomagnesemia, cardiac arrhythmias, and nonregenerative anemia.
4. Reconstitute with 5% dextrose in water and infuse IV over 10 to 15 minutes or over 1 to 6 hours.
5. The longer infusion rates or pretreatment saline diuresis reduce the likelihood of nephrotoxicity.
6. Dosage is 0.5 mg/kg (dog) or 0.25 mg/kg (cat) IV QOD to a total dose of 4 mg/kg (total dose of 8 mg/kg if amphotericin B is the sole treatment).
7. Renal function is monitored before each treatment, and therapy is discontinued if azotemia (blood urea nitrogen >50 mg/dL, creatinine >3 mg/dL) develops.
8. Calcinosis cutis is occasionally noted (Gortel et al., 1999).
D. Efficacy of amphotericin B when combined with itraconazole is equal to that of itraconazole alone in most dogs.

Monitoring of Animal

I. Initial in-hospital monitoring includes daily vital signs, body weight measurements, and physical and/or ocular examinations.
II. Monthly examinations during therapy also include a serum biochemistry profile.
III. After 2 months of itraconazole therapy, consider whether to discontinue the drug.
A. Discontinue therapy if the animal is outwardly normal, there is no evidence of active ocular disease, and thoracic radiographs have improved substantially.
B. Thoracic radiographs often continue to improve after discontinuing therapy.
C. If doubt exists concerning the presence or absence of active disease, the animal is treated for an additional month.
IV. If fluconazole is used, treatment is continued at least 1 month beyond complete clinical remission.
V. After discontinuing therapy animals are reevaluated at 3 and 6 months for evidence of relapses.
VI. Prognosis for dogs and cats with blastomycosis is good.

A. Approximately 50% to 75% of dogs treated with either itraconazole or a ketoconazole–amphotericin B combination respond completely to therapy.
B. Dogs most often die of severe respiratory disease and hypoxemia; however, dogs that survive the first 10 days of therapy usually do well.
C. Hypoxemia and involvement of three or more body systems warrant a poor prognosis.
D. Relapse occurs in 15% to 20% of treated dogs, usually in the first 6 months.
E. CNS signs on relapse are common in cats.
F. Relapses are treated similarly to any new infection.

HISTOPLASMOSIS

Definition

I. Histoplasmosis is a systemic, fungal infection that usually originates in the lungs or GI tract and then disseminates to the lymphatics, liver, spleen, bone marrow, eyes, and other organs.
II. Cats are more susceptible than dogs.
III. Dogs and cats <4 years old are at an increased risk, but any age can be affected.
IV. No apparent sex predilection exists in dogs.
V. Pointers, Brittany spaniels, and Weimaraners are overrepresented.

Cause

I. It is caused by the dimorphic fungus *Histoplasma capsulatum*.
II. *H. capsulatum* characteristics are as follows:
A. In tissue or when cultured at 30° to 37° C, the organism is a yeast and is usually found intracellularly.
B. When cultured at 25° C, the organism grows as a white cottony or buff-brown mold that requires 7 to 10 days for growth.
III. *H. capsulatum* is a soil saprophyte that survives in a wide range of moistures and temperatures.
IV. Nitrogen-rich soil (containing bird or bat guano) appears ideal for its growth.
V. *H. capsulatum* is endemic to most temperate and subtropical regions of the world and mostly occurs in the central United States along the Mississippi, Ohio, and Missouri rivers.

Pathophysiology

I. Infection occurs most commonly via inhalation or ingestion of infective conidia from the environment.
A. Inhalation is probably the primary route of infection.
B. Ingestion of conidia may occur in dogs.
II. After inhalation or ingestion, conidia transform from the mycelial phase to the yeast phase and are phagocytized by cells of the macrophage-monocyte system, where they grow as facultative intracellular organisms.
A. Hematogenous and lymphatic dissemination results in multisystemic disease.
B. Although dissemination may affect any organ system, the lungs, GI tract, lymph nodes, liver, spleen, bone marrow, eyes, and adrenal glands are commonly affected in dogs.
C. Lungs, liver, lymph nodes, eyes, and bone marrow are most commonly affected in cats.
III. Incubation period is 12 to 16 days in dogs.
IV. The immune response determines the severity of clinical disease.
V. Subclinical infection is probably common.
VI. Point-source outbreaks of disease are usually associated with exposure to areas heavily contaminated with *Histoplasma* spp. (e.g., chicken coops, bat habitats, starling roosts).

Clinical Signs

I. Feline histoplasmosis
A. Signs are usually insidious in onset and nonspecific (e.g., depression, anorexia, fever, pale mucous membranes, weight loss).
B. Pulmonary signs (e.g., dyspnea, tachypnea, abnormal lung sounds) are seen in about 50% of animals, but coughing is uncommon.
C. Hepatomegaly, splenomegaly, or lymphadenopathy is seen in about one third of animals.
D. Ocular signs include eyelid granulomas, retinal pigment proliferation, retinal edema, granulomatous chorioretinitis, anterior uveitis, panophthalmitis, and optic neuritis; retinal detachments and secondary glaucoma are uncommon.
E. Lameness in one or more limbs may occur from lytic bone lesions and soft tissue swelling.
F. Cutaneous lesions consisting of multiple small nodules that either ulcerate, drain, or crust over are uncommon.
G. Oral and lingual ulcerations are atypical manifestations; icterus is occasionally seen with hepatic involvement.
II. Canine histoplasmosis
A. Subclinical infection is probably common following inhalation of organisms.
B. GI signs occur most commonly.
1. Large intestinal diarrhea with tenesmus and passage of mucus and fresh blood is common in early stages of the disease.
2. Small intestinal diarrhea, possibly voluminous and associated with malabsorption or protein-losing enteropathy, may be apparent with progressive disease.
C. Elaboration of inflammatory mediators may cause nonspecific signs of fever, anorexia, depression, and severe weight loss.
D. Abnormal lung sounds with or without coughing, tachypnea, or dyspnea are seen in <50% of dogs.
E. Splenomegaly, hepatomegaly, and lymphadenopathy occur occasionally.
F. Oral ulceration, lameness from bony involvement, neurological signs, nodular skin disease, ocular involvement, and adrenal insufficiency are less common.

Diagnosis

I. Hematological and serum biochemistry findings
   A. Normocytic normochromic nonregenerative anemia is the most common change and results from chronic inflammation, GI blood loss, or bone marrow infection.
   B. Neutrophilia and monocytosis are often seen, but total leukocyte counts are variable.
      1. Neutropenia or pancytopenia are unusual occurrences, especially in cats.
      2. Organisms are rarely seen within monocytes, neutrophils, or eosinophils.
   C. Thrombocytopenia caused by increased platelet utilization or destruction is common.
   D. Hypoalbuminemia is the most consistent biochemical abnormality, especially in cats.
   E. Increased serum ALT, AST, ASP, and total bilirubin concentrations indicate hepatic involvement.
   F. Hypercalcemia may occur, especially in cats.

II. Radiographic findings
   A. Thoracic radiography often shows a diffuse interstitial or linear interstitial pattern that may coalesce into a nodular interstitial pattern, although alveolar infiltrates are rare.
   B. Hilar lymphadenopathy is common in dogs but unusual in cats.
   C. Calcified pulmonary infiltrates or hilar lymph nodes usually indicate inactive disease.
   D. Bony lesions of the distal appendicular skeleton, especially carpal and tarsal bones, are rarely seen.
   E. Pleural or abdominal effusions are occasionally seen.

III. Organism identification
   A. Cytological examination may reveal organisms in mononuclear phagocytic cells.
      1. Some organisms are released from infected cells during slide preparation and are seen as free organisms on slides stained with a Wright-Giemsa stain.
      2. Evidence of pyogranulomatous inflammation may exist with numerous intracellular small, round to oval yeast cells (2 to 4 μm in diameter, basophilic center) with a light halo caused by shrinkage of its cell wall during fixation.
      3. In cats, aspirates from bone marrow and lymph nodes, or cells from tracheal washes or bronchoalveolar lavage, are most likely to yield organisms.
      4. In dogs, cells from rectal scrapings or biopsies; aspirates from bone marrow, liver, lymph nodes, or spleen; or cells from tracheal washes or bronchoalveolar lavage are most likely to yield organisms.
      5. Buffy coat smears, cerebrospinal fluid (CSF), aspirates of lytic bone lesions, or aspirates and impression smears of nodular skin lesions may also yield organisms.
   B. Histopathologic findings are as follows:
      1. Pyogranulomatous lesions with multiple intracellular organisms are usually seen.
      2. Special stains (PAS, Gridley's fungal, Gomori methenamine silver) best demonstrate organisms in tissue.
   C. Fungal culture and identification are as follows:
      1. It is not needed for definitive identification.
      2. Buff-brown mycelial growth on Sabouraud's dextrose agar usually takes 7 to 10 days at room temperature, whereas yeast produces white, moist colonies on blood agar at 30° to 37° C.
      3. Attempts at culture are not advised because of the potential public health risk.

IV. Other tests
   A. Serology is presently an ineffective method of diagnosis; both false-positive and false-negative results occur commonly.
   B. Cats with histoplasmosis are typically negative for feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV).

Differential Diagnosis

I. Blastomycosis or other systemic fungal diseases
II. Other GI diseases
   A. Large intestinal disease: see Chapter 34
   B. Small intestinal disease: see Chapter 33

Treatment

I. Treatment is similar to that described for blastomycosis, although azole antifungal usage is not as well-studied.
II. Longer treatment times are probably needed with the azole antifungals, but such treatment times are variable depending on the severity of the infection and the response of the animal.
III. Pulmonary disease may be self-limiting, but antifungal treatment is recommended because of the potential for chronic dissemination.
IV. Feline histoplasmosis is treated as follows:
   A. Itraconazole 5 mg/kg PO BID for at least 2 to 4 months is the treatment of choice (Hodges et al., 1994).
      1. Bioavailability of capsules is variable, and doses up to 10 mg/kg PO BID may be required in some cats.
      2. Bioavailability of the oral solution is better, and 10 mg/kg/day is adequate.
   B. Ketoconazole is effective in about one third of cats.
   C. Fluconazole may be effective, but it has not been studied well.
   D. Amphotericin B may be added to the treatment protocol in severely affected cats.
V. Canine histoplasmosis requires the following:
   A. Itraconazole 10 mg/kg PO SID is the preferred treatment.
   B. Ketoconazole is effective, but amphotericin B is added in fulminant cases.
   C. Amphotericin B may also be added to itraconazole in dogs with severe, disseminated disease.
   D. Fluconazole has not been well studied but may be effective.
   E. Corticosteroids may be indicated in dogs with airway obstruction secondary to hilar lymph node enlargement (Schulman et al., 1999).

Monitoring of Animal

I. Resolution of clinical signs is the best means of monitoring therapy.
II. Initially, in-hospital monitoring includes daily vital signs, body weight measurements, and physical and/or ocular examinations.
III. Monthly examinations also include a serum biochemistry profile.
IV. Treatment is continued for 1 month beyond complete resolution of clinical signs.
V. Animals are reevaluated 3 and 6 months after discontinuing therapy to assess for relapses.
VI. Serological evaluation is not useful in monitoring response to therapy or evaluating for relapse.
VII. Prognosis is variable.
  A. Prognosis is good for dogs with only pulmonary signs.
  B. Dogs with GI or severe disseminated signs have a guarded prognosis.
  C. The prognosis is fair to good for cats treated with itraconazole, although long-term therapy may be required.
  D. Severely debilitated cats have a guarded prognosis.

COCCIDIOIDOMYCOSIS

Definition

I. Coccidioidomycosis (Valley fever, San Joaquin Valley fever) is a systemic fungal infection that typically originates in the lungs and may disseminate to the lymphatics, bones, and other organs.
II. Dogs are affected more often than cats.
III. Young, large- and medium-sized male dogs kept outdoors are most commonly affected, with the likelihood of infection decreasing with advancing age.
IV. Boxers, pointers, Australian shepherds, beagles, Scottish terriers, Doberman pinschers, and cocker spaniels may be at an increased risk (Davidson, 1995).
V. No breed or sex predilection occurs in domestic cats (Greene and Troy, 1995).
VI. Epizootics occur in endemic areas when drought conditions are followed by periods of rain, dust storms, earthquakes, or other conditions that spread soil-derived arthrospores into the air.

Cause

I. It is caused by the geophilic, dimorphic fungus *Coccidioides immitis*.
II. *C. immitis* characteristics are as follows:
  A. In tissue or when cultured at 37° C, the organism grows as large spherules that gradually enlarge to 20 to 200 μm.
  B. Endospores are produced by cleavage from the wall of the spherule.
  C. In the environment or when cultured at 25° C, the organism grows as a mycelium that forms square to rectangular (2 to 4 μm by 3 to 10 μm) multinucleate arthrospores.
III. *C. immitis* is a soil saprophyte that is restricted to the lower Sonoran life zone.
  A. It grows only in areas with sandy alkaline soils, semiarid conditions, high summer and moderate winter temperatures, and low geographic elevations (sea level to a few hundred feet).
  B. It is endemic to the desert southwest (parts of California, Arizona, Texas, New Mexico, Nevada, Utah) and to Mexico, Central America, and parts of South America.

Pathophysiology

I. Infection is usually via inhalation of infective arthrospores from the environment or direct inoculation of arthrospores into the skin.
  A. During periods of high temperatures and low rainfall, the mycelia lie dormant below the soil surface.
  B. Following periods of rain, the organism then returns to the surface, sporulates, and releases large numbers of arthrospores that are disseminated by the wind.
  C. After drought periods, large numbers of arthrospores may be released, resulting in disease epidemics.
  D. Dust storms or earthquakes may cause aerosolization of arthrospores and disease epidemics.
  E. Coccidioidomycosis is not a contagious disease.
II. Inhalation of <10 arthrospores produces clinical disease.
  A. After inhalation, arthrospores move from peribronchial tissues to the subpleural area; spherules then form and produce endospores, which become more spherules.
  B. Respiratory signs result from the endospore formation and subsequent inflammation.
  C. Hematogenous and lymphatic dissemination is uncommon and results in multisystemic disease.
  D. Although dissemination may occur to any organ system, areas most commonly affected are the bones, joints, spleen, liver, kidneys, heart, reproductive organs, eyes, brain, and spinal cord.
  E. In cats, the skin is often affected.
  F. Rarely, primary cutaneous infections occur after a penetrating injury (Plotnick et al., 1997).
III. The incubation period varies from 1 to 3 weeks in dogs.
IV. The immune response determines the severity of clinical disease.
  A. Recovery is dependent on cell-mediated immunity, but a humoral response is present in most dogs living in endemic areas.
    1. An adequate immune response results in subclinical or mild respiratory disease that resolves spontaneously; most cases in dogs and cats are probably subclinical.
    2. A poor immune response allows severe pulmonary and disseminated disease to develop.
  B. It is unknown whether recovered dogs and cats are immune.

Clinical Signs

I. Most affected dogs and cats probably show no or only mild respiratory signs before mounting an effective immune response.

II. Disseminated feline coccidioidomycosis is uncommon (Greene and Troy, 1995).
  A. Cats are more resistant to infection when compared with dogs.
  B. No age, sex, or breed predisposition exists.
  C. Clinical findings are variable because of the multisystemic nature of the disease, and signs of disease are often present for <1 month before diagnosis.
  D. Nonspecific signs of depression, anorexia, fever, and weight loss are common.
  E. Pulmonary signs (e.g., dyspnea, tachypnea, abnormal lung sounds) occur in about 25% of cats.
  F. Skin lesions (e.g., draining lesions, subcutaneous masses, abscesses) are seen in >50% of cats, and localized lymphadenopathy is noted in one third of these cats.
  G. Lameness develops in approximately 20% of cats.
  H. Ocular involvement (e.g., granulomatous chorioretinitis with retinal detachment, uveitis, panophthalmitis) occurs in approximately 10% of cats.
  I. CNS involvement is uncommon.
III. Disseminated canine coccidioidomycosis often occurs in dogs <4 years of age (Green and Troy, 1995).
  A. Males are affected twice as often as females.
  B. The clinical findings are related to the severity of pulmonary involvement and the extent of systemic dissemination.
    1. Clinically inapparent infection is common following inhalation of organisms.
    2. When clinical signs develop, they are often present for 1 to 6 months before the initial diagnosis.
  C. The most common presenting complaint is a chronic cough.
  D. Prolonged intermittent fever, anorexia, depression, and weight loss are also common.
  E. Lameness associated with osteomyelitis and painful periarticular swelling is common.
    1. The appendicular skeleton is affected about 3 times more often than the axial skeleton.
    2. Multiple osseous lesions may be seen in many dogs.
    3. The distal portion of long bones is affected most commonly.
  F. Approximately 20% of dogs have cutaneous lesions characterized by nodules, abscesses, ulcers, and draining tracts.
    1. Skin lesions usually occur as an extension from an infected osseous lesion.
    2. Primary skin and subcutaneous infections following direct cutaneous inoculation in dogs are rare.
    3. Regional lymphadenopathy associated with cutaneous or osseous lesions is common, but generalized peripheral lymphadenopathy is unusual.
  G. Rarely visceral organ involvement may result in icterus, renal failure with renomegaly, or GI signs.
  H. Cardiac involvement may result in right- or left-sided heart failure, pericardial effusion, arrhythmias, and syncope.
  I. Seizures, ataxia, behavioral changes, and coma have been associated with CNS involvement.
  J. Ocular lesions often involve both the posterior and anterior segments, but they are not as common as with other systemic fungal infections.
    1. Anterior segment disease (iritis, granulomatous uveitis) is usually an extension of posterior segment disease.
    2. Glaucoma occurs in almost half of affected eyes.
    3. Granulomatous chorioretinitis, with or without retinal detachment, is common but may not be apparent because of the severity of the anterior segment disease.
    4. Lesions are usually unilateral, but bilateral disease may develop.

Diagnosis

I. Hematological and serum biochemistry findings
  A. A mild normocytic, normochromic nonregenerative anemia is common.
  B. Moderate neutrophilia, usually with a left shift, and monocytosis are often seen.
  C. Hypoalbuminemia and hyperglobulinemia are consistent abnormalities.
  D. Increased serum ALT, AST, ALP, and total bilirubin concentrations indicate hepatic involvement.
  E. Azotemia and hyperphosphatemia may indicate renal involvement.
  F. Hypercalcemia may occur.
II. Radiographic findings
  A. Numerous abnormalities may be found on thoracic radiographs.
    1. Hilar and central lung regions often reveal an ill-defined, diffuse, interstitial, or peribronchiolar pattern.
    2. Involvement of peripheral regions and alveolar infiltrates are uncommon.
    3. Hilar lymphadenopathy is seen in approximately 80% of dogs.
    4. Mediastinal widening as a result of mediastinal lymph node enlargement is less common.
    5. Pleural involvement (pleural thickening, effusion) is seen in almost 65% of dogs.
  B. Osseous lesions consisting of periosteal and endosteal new bone formation and osteolysis are noted in approximately 20% of dogs.
    1. Bones of the distal appendicular skeleton are affected about 3 times more frequently than bones of the axial skeleton.
    2. The distal diaphysis, metaphysis, and epiphysis are affected most often.
    3. Multiple osseous lesions are usually evident.
    4. Hypertrophic osteopathy may occur secondary to pulmonary or hilar lymph node involvement.
III. Cytological findings
  A. Fewer spherules make cytological demonstration difficult.
  B. Exudates from draining skin lesions and pleural fluid are the most likely to yield organisms.
  C. Tracheal washes or bronchoalveolar lavage samples, lymph node aspirates, or aspirates from affected tissue may also yield organisms.

D. Bone aspirates do not usually yield organisms.
E. Spherules appear as large (20 to 200 μm), round, double-walled structures with endospores.
1. The walls appear refractile, on wet preparations or potassium hydroxide (KOH) preparations.
2. They stain blue when hematoxylin and eosin (H&E) stain is used.
3. They stain deep red to purple with PAS, whereas the endospores stain bright red.
4. They stain purple-black with Papanicolaou stain, whereas the cytoplasm stains yellow and the endospores stain red-brown.

IV. Histopathological findings
A. A biopsy is more likely than cytological examination to demonstrate organisms.
B. Multiple samples are taken when biopsying bone to increase the likelihood of finding organisms.
C. Special stains (PAS, Gridley's fungal, or Gomori methenamine silver) best demonstrate the organisms.

V. Fungal culture and identification
A. *C. immitis* grows readily on a wide variety of agars at room temperature as a white, cotton-like mold that changes to tan or brown with age.
B. Arthrospores from cultures are highly infectious.

VI. Serological evaluation
A. It is used in dogs and cats from endemic areas to make a presumptive diagnosis when clinical signs are suggestive but organisms cannot be demonstrated.
B. Precipitin antibodies are thought to represent immunoglobulin (Ig) M and are detectable 2 to 4 weeks after initial infection.
1. The precipitin test may become negative after 4 to 5 weeks and then positive again in those animals in which dissemination has occurred.
2. False-negative results may occur in early infections, fulminant disease, chronic infections, and immunosuppressed animals.
C. Complement-fixing (CF) antibodies are thought to represent IgG and are detectable shortly after precipitin antibodies.
1. An AGID test is used as a screening test for CF antibodies.
2. The CF titer generally increases with the severity of disease.
3. Low titers (<1:16) may indicate early, very chronic, localized or past infections.
4. Titers >1:32 are suggestive of active, disseminated disease.
5. Higher titers are generally seen in more severe disease.

Differential Diagnosis

Rule out blastomycosis or other systemic fungal diseases.

Treatment

I. Ketoconazole 5 to 15 mg/kg PO BID or itraconazole 5 to 10 mg/kg PO SID is the preferred treatment.
A. Fluconazole or ketoconazole are generally used, because they are less expensive than itraconazole.
B. Treatment is continued for at least 2 months beyond clinical remission, often for at least 6 to 12 months.
C. Itraconazole treatment may allow for a shorter course of treatment, but limited studies exist in dogs.
D. Chronic low-dose therapy beyond the initial treatment period may be necessary to keep some animals in remission.

II. Coccidioidomycosis is less responsive to amphotericin B than the other systemic fungal infections.

Monitoring of Animal

I. Resolution of clinical signs is the best means of monitoring response to therapy.
II. Initial in-hospital monitoring include daily vital signs, body weight, and physical and/or ocular examinations.
III. Monthly examinations also include a serum biochemistry profile to evaluate liver enzyme activities for animals receiving azole antifungals.
IV. Cataracts may occur in dogs on long-term (>12 months) ketoconazole.
V. Animals are reevaluated 3 and 6 months after discontinuing therapy to assess for relapse.
VI. Serological evaluation has been used to monitor response to therapy and to evaluate for relapses.
A. CF titers may stay elevated for >1 year following therapy.
B. CF titers should be <1:16 when therapy is discontinued.
C. CF titers often increase with relapses.

VII. Prognosis is variable.
A. The prognosis is good for animals with only pulmonary signs.
B. The prognosis is guarded with disseminated disease; although most animals respond well initially, relapse is common when treatment is discontinued.
C. The prognosis is poor with CNS involvement or involvement of multiple bones.
D. If untreated, disseminated disease is usually fatal.

CRYPTOCOCCOSIS

Definition

I. Cryptococcosis is an opportunistic, systemic, fungal infection of worldwide significance that usually originates in the nasal cavity, paranasal tissues, or lungs and is then disseminated to the skin, eyes, or CNS.
II. Cats are most commonly affected.
III. Unlike the other systemic mycoses, it does not follow any specific geographic boundaries.

Causes

I. It is caused most commonly by *Cryptococcus neoformans* and *Cryptococcus gattii.*
II. *C. neoformans* is the species that most commonly causes clinical disease in cats and is usually associated with pigeon droppings or other avian habitats.
A. *C. gattii* is geographically more restricted and is associated with bark and leaf litter of certain Eucalyptus trees in tropical and subtropical environments.

B. In tissues and cultures, the organism is a variably sized yeast (3.5 to 7 μm), with a large heteropolysaccharide capsule (1 to 30 μm thick).
C. Temperature-sensitive strains may produce hyphae within nasal tissues.
D. The organism primarily reproduces by budding from a narrow base.
E. Under controlled laboratory conditions, the organism undergoes sexual reproduction, but most infections are thought to be caused by environmental exposure to the yeastlike phase.

III. Pigeons are thought to be the most important vector of *C. neoformans.*
A. *C. neoformans* can be found in high numbers in pigeon roosts, barn lofts, hay mows, and along cupolas and cornices where pigeons often sit.
B. In the desiccated state, the organism may be ≤1 μm in size and may survive up to 2 years.
C. Direct exposure to sunlight or soil quickly kills the organism.

IV. *C. neoformans* may be found in nasal washings from dogs and cats as an incidental finding but may also progress to clinical disease.

Pathophysiology

I. Infection is most commonly via inhalation of yeast organisms from the environment.
A. Most yeast are probably too large to be inhaled directly into the lungs but tend to settle in the nasal passages.
B. Small, desiccated forms of the yeast are infective and can be inhaled directly into the small airways and alveoli.

II. After inhalation, nasal, paranasal sinus, or pulmonary granulomas form.
A. Dissemination may occur by direct extension or by hematogenous spread.
1. Direct extension through the cribriform plate to the CNS or to the paranasal soft tissues or skin is common.
2. Although dissemination to any organ can occur, the skin, eyes, and CNS are most commonly affected.
B. Lesions often exist as either granulomatous inflammation with few organisms or as gelatinous masses of organisms with little inflammation.
C. The capsule surrounding the cryptococcal organism contributes to its pathogenicity by inhibiting phagocytosis, plasma cell function, and leukocyte migration.

III. The immune response determines the severity of clinical disease.
A. Antibodies are not protective.
B. Recovery is dependent on cell-mediated immunity.
1. Immunosuppression has not been an apparent problem in infected cats and dogs.
2. An association with FeLV and FIV infections in cats appears unlikely (Flatland et al., 1996).
3. Prolonged glucocorticoid use may be a predisposing factor.

IV. Cryptococcosis is not a contagious disease.

Clinical Signs

I. Feline cryptococcosis
A. No apparent breed or sex predilection exists.
B. Clinical findings are usually related to upper respiratory, cutaneous, ocular, or CNS involvement.
C. Depression and anorexia are common in chronic cases, but fever is uncommon.
D. Upper respiratory signs related to nasal cavity involvement are seen in 50% to 80% of cats.
1. Sneezing and unilateral or bilateral mucopurulent nasal discharge, ± blood, are typically seen.
2. Proliferative soft tissue masses or ulcerative lesions within the nasal passage or on the bridge of the nose are seen in approximately 70% of cases with upper respiratory involvement (Malik et al., 1992).
3. Nasopharyngeal granulomas resulting in snoring, stertor, and inspiratory dyspnea are occasionally seen (Malik et al., 1997a).
E. The lungs are affected less often than in the other systemic mycoses.
F. Oral ulcerations are occasionally seen.
G. The skin and subcutaneous tissues are affected in approximately 30% to 50% of cats (Malik et al., 1992).
1. Papules or nodules are the primary lesions; multiple lesions are typical, and larger lesions are usually ulcerated.
2. Regional lymphadenopathy is common.
H. The eyes are affected in 20% to 25% of cats, especially those with CNS involvement.
1. Granulomatous chorioretinitis, with or without exudative retinal detachment, is the most common lesion and may lead to a panophthalmitis.
2. Optic neuritis may cause acute blindness.
3. Anterior uveitis is present in some cats.
I. CNS involvement is reported in approximately 25% of cats (Gerds-Grogan and Dayrell-Hart, 1997; O'Brien, et al, 2004).
1. Behavioral changes, seizures, circling, and ataxia occur.
2. Head pressing, cranial nerve (CN) deficits, and paresis may also occur.
J. Hematogenous spread from the respiratory tract may result in lameness (osteomyelitis), renal failure, and generalized lymphadenopathy.

II. Canine cryptococcosis
A. Large-breed dogs <4 years of age are most commonly affected.
B. The American cocker spaniel, Labrador retriever, Great Dane, border collie, boxer, Dalmatian, German shepherd dog, and Doberman pinscher are overrepresented.
C. Clinical findings are most often related to CNS, upper respiratory, ocular, or cutaneous involvement.
D. Depression and anorexia are common, but fever is uncommon.
E. CNS involvement occurs in approximately 50% to 80% of dogs (Berthelin et al., 1994a, 1994b).
1. The brain is most often affected, but involvement of the spinal cord may also occur.

2. Neurological signs include mental depression, vestibular syndrome, ataxia, CN deficits (especially CN V, VII, and VIII), seizures, paresis, blindness, hypermetria, and cervical pain.
3. Most dogs with CNS involvement have other affected organ systems.

F. Upper respiratory tract or perinasal tissues are affected in approximately 50% of dogs (Malik et al., 1995).
1. Caudal nasal passages and frontal sinuses are affected more commonly than are the rostral nasal passages.
2. Respiratory signs include upper airway stridor, nasal discharge and sneezing, epistaxis, and firm swellings on the bridge of the nose or periorbitally.

G. Eyes or periorbital tissue are affected in approximately 20% to 40% of dogs.
1. Granulomatous chorioretinitis, with or without exudative retinal detachment, is the most common lesion and can lead to panophthalmitis.
2. Retinal hemorrhage or retinal scarring may be seen.
3. Optic neuritis may cause acute blindness.
4. Anterior uveitis is less common than posterior segment disease.

H. The skin is affected in approximately 10% to 20% of dogs.
1. Subcutaneous nodules with ulcerative draining lesions are typical.
2. The head, footpads, nail beds, and oral mucous membranes are common sites.

I. Proliferative lesions in the external ear canals, and direct extension from the ear canals to the CNS may occur.

J. Multiorgan dissemination is common, may be subclinical, or may result in clinical signs.

Diagnosis

I. Hematological and serum biochemistry findings.
A. They are often normal, but mild nonregenerative anemia and mature neutrophilia, with a left shift, may be seen.
B. Serum biochemistry findings are usually normal.

II. CSF analysis
A. CSF pressure and protein levels are often increased, and a mixed mononuclear and neutrophilic pleocytosis is common.
B. Organisms are seen in approximately 90% of dogs with CNS involvement.

III. Radiographic findings
A. Thoracic radiographs are usually normal, but a nodular to interstitial lung pattern, pleural effusion, and tracheobronchial lymphadenopathy can occur.
B. Nasal radiographs may demonstrate increased soft tissue density and bony destruction in the nasal passages and frontal sinuses.

IV. Organism identification
A. Cytological testing is the quickest and easiest means of identifying cryptococcal organisms.
1. Nasal swabs, exudate from cutaneous lesions, or aspirates from soft-tissue masses, subretinal lesions, or vitreous often reveal organisms.
2. Organisms may not be apparent in approximately 25% of animals (Medleau and Barsanti, 1990).
3. The organism's thin wall and large capsule, as well as its budding from a narrow base, help differentiate it from *Blastomyces* spp.

B. Histopathological findings are as follows:
1. Nodular to diffuse granulomatous lesions or areas of degeneration with limited inflammation are seen in infected tissue, and yeastlike organisms are usually numerous.
2. Special stains (PAS, Gridley's fungal, and Gomori methenamine silver) best demonstrate the organisms.
3. Mucicarmine stains demonstrate the organism's capsule.

C. Fungal culture can also be used for identification.
1. The organism can be cultured from infected tissue, exudate, CSF, urine, joint fluid, and blood if sufficient samples are submitted.
2. Yeastlike growth occurs in 2 to 42 days on Sabouraud's dextrose agar.
3. Hyphae rarely grow, even at 37° C.

V. Serology
A. It is very useful when cytological testing fails to demonstrate organisms.
B. Latex agglutination (LA) detects cryptococcal capsular antigen and is the preferred test.
C. Commercially available LA tests can be used on serum, urine, or CSF.
1. CSF is the preferred sample in animals with neurological signs.
2. Serum is the preferred sample in animals with other signs.

D. False-negative LA antigen titers may occur with localized disease.
E. False-positive LA antigen titers are uncommon and are usually related to technique or interfering substances, such as rheumatoid factor.
F. LA antigen titer tends to correlate well with the extent of disease and may be used to evaluate the effectiveness of treatment (Malik et al., 1996b).
G. Sensitivity and specificity are both 90% to 100%.
H. Detection of serum or CSF antibodies is not a useful diagnostic tool.

Differential Diagnosis

I. Other upper respiratory diseases: primary nasal neoplasia, nasal aspergillosis, other nasal fungal infections, nasal foreign body, chronic viral sinusitis in cats, oronasal or oroantral fistula, tooth root abscess

II. CNS disease: toxoplasmosis (primary differential in cats)

III. Cutaneous disease: see differential diagnoses for Blastomycosis

IV. Ocular disease: see differential diagnoses for Blastomycosis

Treatment

I. Fluconazole 2.5 to 10 mg/kg PO BID is effective and may be the preferred treatment in cats, because it causes fewer side effects and is less expensive than amphotericin B. (O'Brien et al., 2006).

A. Fluconazole is the least expensive means of treatment and may require the fewest months of therapy.
B. Cats with CNS involvement are probably more effectively treated with protocols that contain amphotericin B.

II. Itraconazole 10 mg/kg PO SID or divided BID is also effective in cats and dogs, but treatment time is longer (mean >8 months) (Medleau et al., 1995; O'Brien et al., 2006).
III. Amphotericin B is the most effective drug in vitro against the various cryptococcal isolates.
A. Amphotericin B lipid complex (2 mg/kg IV 3 times per week for 12 treatments) is recommended as the form of the drug that will reduce toxicity and allow for the highest cumulative amounts to be administered (see under Blastomycosis).
B. Amphotericin B is synergistic with flucytosine 25 to 50 mg/kg PO QID, and the combination is useful in CNS infections.
1. CSF concentrations of flucytosine approach those of serum.
2. Cryptococcal organisms may rapidly develop resistance to flucytosine, so it has limited efficacy as a single treatment agent.
3. Toxicity to flucytosine includes ulcerative drug eruptions of the skin (especially of the face and mucocutaneous junctions), enterocolitis, leukopenia, and thrombocytopenia.
4. The dose of flucytosine is decreased in animals with advancing renal failure.
C. Amphotericin B in combination with azole antifungals or flucytosine has been used to successfully treat feline and canine cryptococcosis.
D. Amphotericin B (deoxycholate formulation) can be used SC in a protocol that has been shown to reduce toxicity and costs associated with administration.
1. When given SC, amphotericin (0.5 to 0.8 mg/kg) is diluted in 0.45% saline/2.5% dextrose solution (400 mL for cats, 500 mL for dogs <20 kg; 1000 mL for dogs >20 kg) and administered 2 to 3 times per week.
2. This protocol may allow for larger cumulative doses of amphotericin because of reduced toxicity.
3. Amphotericin B has been used SC to reduce nephrotoxicity; concentrations >20 mg/L cause local irritation.

IV. Ketoconazole (10 to 30 mg/kg PO BID) is slightly less effective.
V. Large lesions, especially those affecting the bridge of the nose, often require surgical reduction before medical therapy.

Monitoring of Animal

I. Resolution of clinical signs is the best means of monitoring response to therapy.
II. In-hospital monitoring includes daily vital signs, body weight, and physical and/or ocular examinations.
III. Monthly examinations include a serum biochemistry profile to evaluate liver enzyme activities for animals receiving azole antifungals and LA antigen titer.
IV. Treatment is continued until clinical signs have resolved and LA antigen titers are negative or have been low and stable for several months.
A. LA antigen titers that drop after treatment indicate that the treatment is having an effect.
1. A tenfold drop at the end of 2 months indicates a favorable prognosis.
2. No change in titer after 2 months may indicate the need for a change in treatment.
B. LA antigen titer is also monitored after discontinuing treatment.
1. An increasing titer indicates that clinical relapse is likely.
2. A low-positive titer that does not increase is seen in some cats that are clinically cured.

V. Animals are reevaluated 3 and 6 months after discontinuing therapy to assess for relapses.
VI. The prognosis is good for cats with extraneural disease; however, cats with FeLV or FIV may require longer therapy.
VII. The prognosis is guarded for dogs with any form of the disease and for cats with CNS involvement.

PYTHIOSIS AND LAGENIDIOSIS (OOMYCOSIS)

Definition

I. Pythiosis is an uncommon infectious disease in dogs and cats.
II. Most infections occur in dogs; cats are only rarely infected.
III. It occurs mainly in tropical and subtropical areas of the world.
IV. In the United States, it occurs primarily along the Gulf of Mexico, mostly in southern Louisiana, Texas, Alabama, and Florida, but cases in the eastern, western, and midwestern states are being reported more frequently.

Causes

I. Pythiosis is caused by a protistan member of the Oomycetes class, *Pythium insidiosum,* which is evolutionarily more closely related to algae than to true fungi.
II. *P. insidiosum* grows in tissues and the environment as thick-walled, septate hyphae.
III. In an aquatic environment, it produces motile zoospores.
IV. *Lagenidium* spp. is the cause of a similar disease in dogs (Grooters, 2003).

Pathophysiology

I. The infective stage is thought to be the motile zoospore.
A. Zoospores are released into a warm water environment, where they are able to chemotactically orient themselves toward certain aquatic plants and animal hair.
B. They enter the host through damaged skin or mucous membranes.

II. *P. insidiosum* is considered to be a true pathogen rather than an opportunist because immune suppression is not a prerequisite for infection.

III. Three forms of pythiosis include cutaneous disease (most common in cats), GI disease (predominantly in dogs), and rare multisystemic disease.
IV. In the GI form of the disease, any part of the GI tract may be affected, but the stomach and proximal small intestine are affected most commonly.
  A. Occasionally only the mesenteric lymph nodes are affected.
  B. Diffuse to irregular transmural thickening of a segment (5 to 25 cm) of the GI tract, with variable irregular mucosal ulceration occurs.
V. Arterial thrombosis and arterial disruption from growing *Pythium* spp. and the inflammatory processes may occur, and probably account for rare cases of multisystemic involvement.

Clinical Signs

I. Canine GI pythiosis
  A. Male, large-breed (especially hunting breeds) dogs <3 years old are most likely to be infected.
  B. Vomiting, pronounced weight loss, and a palpable abdominal mass are typical clinical findings.
  C. Other signs may include regurgitation if the esophagus is involved, diarrhea if the distal small intestine is affected, or hematochezia if the colon is involved.
  D. Presentation is often late in the disease, because affected dogs usually remain bright and alert.
  E. Signs of systemic illness occur when intestinal obstruction, infarction, or perforation occur.
II. Canine cutaneous pythiosis
  A. Cutaneous disease is less common than the GI disease.
  B. The German shepherd dog may be predisposed.
  C. Cutaneous lesions may occur anywhere.
    1. Slightly pruritic, poorly defined nodules that soon become ulcerated are typical.
    2. Multiple tracts may drain a serosanguineous or purulent exudate.
    3. Rarely, they are complicated by GI involvement.
  D. Dogs with cutaneous pythiosis rarely have systemic involvement.
III. Canine lagenidiosis is characterized by cutaneous signs that are similar to pythiosis.
  A. Affected dogs usually have systemic involvement.
  B. Great vessels, sublumbar and inguinal lymph nodes, lungs, the cranial mediastinum, and the pulmonary hilus are often involved.
IV. Feline pythiosis is rare.
  A. Most cats have cutaneous disease.
  B. Nasal and retrobulbar disease may also be seen.

Diagnosis

I. Hematological and serum chemistry findings are usually normal.
II. Radiographic and ultrasonographic findings are variable.
  A. An abdominal mass with or without an obstructive pattern may be seen on abdominal radiographs.
  B. Esophagitis induced by *Pythium* spp. may result in megaesophagus.
  C. Ultrasonography may reveal markedly thickened intestinal or gastric walls with loss of the normal layered pattern.
III. Organism identification involves the following:
  A. Histologically, a presumptive diagnosis can be made based on the morphological examination of the hyphal organisms and the inflammatory response pattern.
    1. A pronounced granulomatous or eosinophilic inflammatory response is seen.
    2. *Pythium* spp. and *Lagenidium* spp. do not stain well on H&E–stained sections.
    3. Gridley-stained or Gomori methenamine silver–stained sections are best used to identify hyphae.
    4. An immunohistochemical staining technique is also useful in identifying hyphal organisms, such as *Pythium* spp., and for differentiating them from *Lagenidium* spp. or other Zygomycetes.
  B. Fungal culture and identification are as follows:
    1. *Pythium* spp. is relatively easy to culture on a variety of fungal culture media.
    2. Failure to grow the organism is usually related to sample handling.
    3. *Pythium* spp. are sensitive to temperature stress and dehydration.
      a. Freezing of samples results rapidly in organism death.
      b. Chilling samples for short periods does not seem to reduce the likelihood of successful culture.
IV. Serological findings
  A. Antibody titers via ELISA appear sensitive in diagnosing pythiosis and lagenidiosis.
  B. A polymerase chain reaction (PCR) assay has been developed for use on tissue and blood that is able to differentiate between *Pythium insidiosum* and *Lagenidium* spp.

Differential Diagnosis

I. With the GI form of disease, rule out neoplasia, such as lymphosarcoma or adenocarcinoma.
II. True Zygomycetes such as *Mucor* spp., *Absidia* spp., or *Rhizopus* spp. infections, as well as *Basidiobolus* spp. and *Conidiobolus* spp. infections, must be differentiated from pythiosis.
III. Differential considerations for the cutaneous form of disease are the same as for blastomycosis.

Treatment

I. Wide surgical excision is the preferred treatment.
II. Amphotericin B and ketoconazole have been unsuccessful in resolving the disease.
III. Itraconazole 10 mg/kg PO SID to BID and terbinafine 10 mg/kg PO SID are efficacious in approximately 10% to 20% of dogs
IV. Amphotericin B lipid complex 2 mg/kg IV QOD for 12 treatments has been successful in some cases.
V. The prognosis is generally poor if surgical resection is not possible.

Monitoring of Animal

I. Resolution of clinical signs and weight gain are the primary monitoring tools.
II. It may take a month or more before improvement occurs with itraconazole and terbinafine therapy.
III. Abdominal palpation or ultrasonography can be used to assess the size of the abdominal mass.
IV. Serological evaluation is an effective means of evaluating surgical success and for recurrence.

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CHAPTER 112

Viral Infections

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CANINE CORONAVIRUS

Definition

I. Canine coronavirus (CCV) causes contagious enteritis of variable severity (rarely fatal) in young dogs.
II. The true significance of this pathogen in juvenile diarrhea is not fully known, but it may contribute to the morbidity and mortality of other infectious enteropathies, such as canine parvovirus (CPV) (Pratelli et al., 2004).

Cause and Pathophysiology

I. CCV, a single-stranded (SS) ribonucleic acid (RNA) virus of the family Coronaviridae, is closely related to feline coronavirus and transmissible gastroenteritis virus of pigs.
II. CCV is highly contagious via fecal–oral transmission.
III. Fecal shedding results in environmental contamination, an important route of exposure.
IV. CCV infects any age group, but clinical disease is usually seen only in very young puppies.
V. After ingestion, the virus localizes in the villus tips of the small intestines, where it replicates and results in villous atrophy and crypt cell hyperplasia.

Clinical Signs

I. Adults
   A. Infected, seronegative adult dogs usually asymptomatic
   B. Possibly mild gastrointestinal (GI) signs
II. Puppies
   A. Acute onset of mild to severe, ± bloody diarrhea in neonatal and very young puppies
   B. Lethargy, anorexia, vomiting ± dehydration
   C. Typically self-limiting, but possibly life-threatening

Diagnosis

I. Suspicious signalment, history, and clinical presentation
II. Clinical pathology: findings nonspecific, leukopenia not recognized
III. CCV-specific testing
   A. Virus identification is rarely necessary or indicated.
   B. Fourfold rise in immunoglobulin (Ig) G titer on paired serum samples is supportive, but rarely performed.
   C. Direct viral detection may be performed on feces.
      1. Electron microscopy (EM)
      2. Enzyme-linked immunosorbent assay (ELISA)
      3. Intestinal tissue fluorescent antibody (FA) testing (Tuchiya et al., 1993)
   D. Viral detection may also be done with intestinal tissue immunohistochemistry (Evermann et al., 2005).
   E. CCV can also be detected in the feces of clinically healthy dogs (Tennant et al., 1993).

Differential Diagnosis

I. Canine parvovirus
II. Parasites, bacterial enteritis
III. Canine distemper virus (CDV), canine herpesvirus (CHV)
IV. Toxins, foreign bodies, intussusception, or metabolic diseases

Treatment

I. Supportive care may be instituted, although many dogs require no therapy.
II. See Box 112-1 for treatment of GI signs.

Monitoring and Prevention

I. The need for routine CCV vaccination is questionable, although inactivated and modified live virus (MLV) vaccines are available for at-risk populations.
II. Avoid exposure of young puppies to potentially contaminated environments.
III. CCV is inactivated by various disinfectants (Table 112-1).
IV. Viral shedding may occur for up to 6 months postinfection (Pratelli et al., 2004).

CANINE DISTEMPER VIRUS

Definition

I. CDV is a highly contagious virus with either focal or multisystemic manifestations, and variable morbidity and mortality.
II. Respiratory, GI, and neurological tissues are all targets.

Cause and Pathophysiology

I. CDV is a SS-RNA virus of the family Paramyxoviridae and is closely related to measles virus of primates and rinderpest in domestic livestock.
II. CDV is highly contagious.
   A. Large viral concentrations occur in respiratory secretions.
   B. It is commonly spread by aerosolization.

Box 112-1

Therapy for Gastrointestinal Manifestations of Viral Disease*

1. Animals with vomiting ± moderate to severe diarrhea are kept NPO.
2. Crystalloids (LRS, Plasmalyte, 0.9% NaCl) via parenteral routes (IV, intraosseous, SC) are indicated to rehydrate, replace ongoing losses, and maintain hydration.
   a. Maintenance: 55-66 mL/kg/day; rehydration and losses must be estimated and added to the maintenance fluid rate.
   b. SC fluids are not effective for moderate to severe dehydration.
   c. Potassium and dextrose supplementation are often required.
3. Colloid therapy is indicated for moderate to severe hypoalbuminemia and hypotension.
   a. Hydroxyethyl starch (Hetastarch): give 10 mL/kg in dogs, 5 mL/kg in cats IV bolus or 20-30 mL/kg/day CRI.
   b. Plasma provides minimal oncotic support.
4. Antiemetics may be useful if obstructive GI disease is ruled out, especially when risk of aspiration exists.
   a. Metoclopramide 0.2-0.4 mg/kg SC BID-TID or 1-2 mg/kg/day IV as CRI (dogs)
   b. Prochlorperazine 0.1-0.5 mg/kg IM, SC TID or chlorpromazine 0.2-0.4 mg/kg IM, SC TID (dogs)
      (1) Contraindicated in hypotensive or dehydrated animals
      (2) May cause sedation; contraindicated with seizure disorders
   c. Ondansetron 0.1-0.2 mg/kg SC, IV BID-QID for intractable vomiting
5. Antibiotics BID-QID are given for hemorrhagic diarrhea, neutropenia, or suspected bacterial infection.
   a. Ampicillin 10-20 mg/kg IV TID-QID; gram-negative coverage may be inadequate
   b. Enrofloxacin 2.5-5.0 mg/kg SC BID for dogs; relatively contraindicated in growing puppies and kittens owing to potential cartilage damage
   c. Gentamicin 6-6.6 mg/kg IV, IM, or SC SID or amikacin 15-30 mg/kg IV, IM, or SC SID
      (1) Contraindicated in dehydration, hypotension, or renal failure
      (2) May cause renal failure, ototoxicity
      (3) Covers gram-negative bacteria only
   d. Cefazolin 22 mg/kg IV TID with enrofloxacin or gentocin
   e. Cefoxitin 22 mg/kg IV TID
6. H_2-blocker therapy may decrease gastric acidity and its associated complications.
   a. Famotidine 0.5-1.0 mg/kg IV, SC, or IM SID-BID
   b. Cimetidine 5-10 mg/kg IV, SC, or IM TID
   c. Ranitidine 2 mg/kg IV BID
7. Adjunctive therapy includes the following:
   a. Animals on NPO restrictions for 3 days or longer require parenteral nutrition.
   b. Whole blood, packed RBCs, or blood substitute are indicated for anemia.
   c. Routine nursing care is critical to keep IV sites clean and prevent urine or fecal scald.
8. Recovery and realimentation are important.
   a. Small amounts of water are offered 12-24 hours after cessation of vomiting.
   b. If no vomiting occurs within 12-24 hours of water administration, small amounts of a bland diet are offered every 2-3 hours.
   c. Animals are gradually weaned onto maintenance requirements of a bland diet over 2-4 days.
   d. Bland diet is maintained for 1-3 weeks, followed by gradual reintroduction of a diet appropriate for age.

NPO, Nothing by mouth; *LRS*, lactated Ringer solution; *CRI*, constant rate infusion; *GI*, gastrointestinal; *H_2*, histamine$_2$; *RBCs*, red blood cells.
*Doses are recommended for both dogs and cats unless otherwise specified.

C. Infective virus is also present in urine and other bodily fluids.
D. Recovered dogs shed the virus for 60 to 90 days postinfection (Greene and Appel, 2006).

III. The virus is viable in cold and freezing environments, but susceptible to heat, drying, and ultraviolet light.
IV. Younger animals are most susceptible to infection.
V. Susceptibility is enhanced in older dogs not adequately vaccinated and with either concurrent stress or immunosuppressive conditions.
VI. During systemic infection, CDV contacts upper respiratory epithelium; replicates within respiratory lymphatics; eventually disseminates to other lymphatic tissues, intestines, and liver; and produces viremia.
   A. Host immunity may be suppressed by the virus.
   B. Several outcomes are possible, depending on immunity and antibody (Ab) response.
      1. Adequate immunity
         a. Virus cleared with no illness
         b. Central nervous system (CNS) invasion possible
      2. Partial immunity
         a. Virus spreads to epithelial tissues and CNS
         b. Mild or subclinical illness
         c. Virus partially cleared, CNS persistence possible
      3. No immunity
         a. Viremia, epithelial and CNS infection, and viral persistence
         b. Illness often severe and fatal
VII. CNS infection is common, but the exact mechanism of entry into the CNS is unknown.
   A. Direct viral injury in animals with poor immunity results in acute multifocal encephalitis of gray and white matter.
   B. White matter lesions of demyelination are possible, and this noncytolytic form does not induce inflammatory changes.
   C. Chronic CNS infection leads to progressive dysfunction or relapse months to years after subclinical

TABLE 112-1

Efficacy of Common Disinfectants against Viruses

DISINFECTANT CLASS	ENVELOPED VIRUS*	NONENVELOPED VIRUS†
Alcohols		
Ethyl alcohol	+	+
Isopropyl alcohol	+‡	–
Aldehydes (gluteraldehyde)	+	+
Bisguanide (chlorhexidine)	+‡	±
Halogens		
Hypochlorite (bleach)	+	+
Iodines (tinctures)	+	±
Iodophores (providone-iodine)	+	±
Peroxygens (hydrogen peroxide)	+	+
Phenolics *(Lysol)*	+	±
Quartenary ammonium	+	–

Data from Greene CE: Environmental factors in infectious disease. p. 673. In Greene CE (ed): Infectious Diseases of the Dog and Cat. 2nd Ed. WB Saunders, Philadelphia, 1998; Love BC, Hirsch DC: Disinfectant and antiseptic use in small animal practice. p. 258. In Bonagura JD (ed): Kirk's Current Veterinary Therapy XIII: Small Animal Practice. WB Saunders, Philadelphia, 2000.

+, Susceptible; ±, somewhat susceptible; –, not susceptible.

*Enveloped viruses include canine distemper, coronaviruses, herpesviruses, rabies virus, and feline leukemia and immunodeficiency viruses.

†Nonenveloped viruses include canine adenoviruses, parvoviruses, and feline calicivirus.

‡Rabies virus is not susceptible.

infection or apparent recovery (also called *old dog encephalitis*).

Clinical Signs

I. Mild or subclinical infection
   A. Mild lethargy, fever
   B. Cough, oculonasal discharge possible
   C. Often unnoticed
II. Systemic infection
   A. Most common in young puppies, unvaccinated adults, and immunosuppressed animals
   B. First clinical signs: fever and general malaise
   C. Respiratory signs common
      1. Serous or mucopurulent oculonasal discharge soon after onset of fever
      2. Dry cough that becomes productive, and/or dyspnea
   D. GI signs common
      1. Anorexia, vomiting, dehydration, diarrhea
      2. Shock from hypovolemia or secondary bacterial sepsis and/or endotoxemia
III. CNS infection
   A. Signs often occur 1 to 3 weeks after recovery from systemic signs, but may be delayed for months to years after infection (Greene and Appel, 2006).
   B. CNS manifestations may be the only signs of CDV infection.
   C. CNS signs vary from multifocal to localized, with variable progression.
   D. Neurological signs include seizures, vestibular disease, myoclonus, behavioral changes, hyperesthesia, tetraparesis, paraparesis, and cervical pain.
      1. Myoclonus (involuntary, repetitive muscle contraction of a specific area) is common, with or without other CNS signs.
      2. Classic focal facial seizures ("chewing gum seizures") may occur.
IV. Additional manifestations
   A. Dermatological: hard pad disease
   B. Ocular: keratoconjunctivitis sicca, chorioretinitis
   C. Dental enamel hypoplasia (pock marks)
   D. Transplacental infection possible

Diagnosis

I. Compatible signalment, history, and clinical presentation
II. General diagnostic tests
   A. Hematological evaluation: lymphopenia common with acute infections
   B. Rarely, pathognomonic cytoplasmic inclusions in blood cells or conjunctival scrapings
   C. Hyperglobulinemia and hypoalbuminemia, or hypoglobulinemia with transplacental or neonatal infection
   D. Cerebrospinal fluid (CSF) analysis
      1. Lymphocytic pleocytosis (>5 to 10 cells/μL) and increased protein (>25 mg/dL) common
      2. Inclusion bodies rare
      3. Possibly normal in noninflammatory demyelinating disease
   E. Radiography
      1. Thoracic radiographs normal, or possibly interstitial or alveolar patterns
      2. Intussusception ruled out with abdominal radiographs and/or ultrasonography
III. CDV-specific testing
   A. Elevated serum Ab titers as detected by virus neutralization or ELISA support the diagnosis.
      1. Increased IgG titer indicates vaccination or either prior or recent CDV infection.
      2. A fourfold rise in IgG titers from paired serum samples suggests recent infection.
      3. Increased IgM titers without recent vaccination suggest acute infection.
   B. CSF Ab titers, if uncontaminated by blood, provide direct evidence of CNS infection.
      1. Vaccination does not produce detectable antibodies within the CSF.
      2. To rule out the possibility that serum Ab has contaminated CSF, a ratio of serum to CSF titers is compared for CDV and another vaccine component, such as canine adenovirus-2.
   C. FA testing performed on conjunctival or other epithelial scrapings, CSF, buffy coat, or bone marrow often yields false-negative results.
   D. Histopathologic evaluation may demonstrate inclusion bodies.

Differential Diagnosis

I. Respiratory signs: infectious tracheobronchitis, aspiration, bacterial or parasitic pneumonia, rickettsial diseases, dysautonomia
II. GI signs: CPV or CCV, bacterial enteritis, toxin ingestion, foreign bodies, intussusception, metabolic disease
III. Neurological signs: hypoglycemia, toxins, hepatic encephalopathy, hypocalcemia, rabies, other causes of CNS disease (see Chapter 23).

Treatment

I. Maintain adequate hydration.
II. Administer antibiotics for secondary bacterial infections.
III. Provide good nursing care with physical therapy (chest coupage) as needed.
IV. Consider the use of bronchodilators.
V. CNS therapy may involve the following:
   A. Phenobarbital 2.5 mg/kg PO, IM, or IV BID to TID
   B. Diazepam 0.3 to 1.0 mg/kg IV to effect or 1 to 2 mg/kg per rectum during seizures
   C. Diazepam, pentobarbital, or propofol IV for refractory or recurrent seizures (see Chapter 22)
   D. Myoclonus often refractory to medication and usually persists for life
   E. Prednisone 0.5 to 1.0 mg/kg/day PO for 2 weeks, with gradual tapering, for progressive CNS signs, refractory seizures, and late-onset encephalitis

Monitoring and Prevention

I. Isolate sick dogs.
II. Maternal Ab is usually gone by 12 weeks of age, but may interfere with initial vaccination (Greene and Appel, 2006).
III. MLV vaccines are administered 3 to 4 weeks apart, with at least one vaccine given after maternal Ab has waned.
   A. Annual to triennial vaccines are currently recommended to booster protection (Table 112-2).
   B. Measles vaccine provides cross-protection against CDV and may be given as an initial puppy vaccination at 6 to 12 weeks, when maternal Ab interferes with CDV vaccine response.
   C. Inactivated (i.e., killed virus) vaccine is used in pregnant or immunosuppressed animals, but it confers a lower degree and duration of immunity than MLV vaccines.
   D. MLV vaccines are contraindicated in pregnant or immunosuppressed animals.
IV. Vaccination complications can occur.
   A. Encephalitis may develop in severely immunosuppressed puppies or in puppies whose dam received MLV vaccination while pregnant.
   B. CDV vaccine is inactivated by hyperthermia, and an attenuated response may occur with concurrent parvovirus infection or chemotherapy (Greene and Appel, 2006).
V. Recovery from natural infection provides prolonged immunity.
VI. CDV is inactivated by various disinfectants (see Table 112-1).

CANINE HERPESVIRUS

Definition and Cause

I. CHV is a relatively common infection, but an uncommon cause of disease.
II. When disease occurs, it causes abortions in pregnant bitches or a fatal hemorrhagic disease in puppies <3 weeks of age.
III. CHV, a double-stranded DNA virus of the family Herpesviridae, infects only Canidae.

TABLE 112-2

Viral Vaccination Recommendations for Adult Dogs*

VIRUS	ADMINISTRATION FREQUENCY	COMMENTS
Core vaccines†		
Canine distemper	1 year, then every 3 years for MLV or recombinant product	Annual booster vaccines are suggested by some manufacturers; distemper-measles vaccine should never be used in adult dogs
Canine adenovirus-2	1 year, then every 3 years	Parenteral MLV forms are generally preferred to killed or topical MLV vaccines
Canine parvovirus	1 year, then every 3 years for MLV vaccines	Efficacy may last >3 years
Rabies	1 year, then every 1 to 3 years	Local regulations impact frequency of booster vaccines
Noncore vaccines†		
Canine parainfluenza virus	1 year, then every 3 years	Intranasal or parenteral forms

Adapted from Canine Vaccine Task Force: 2006 AAHA canine vaccine guidelines. J Am Anim Hosp Assoc 42:80, 2006.

MLV, Modified live virus.

*Vaccination protocols must be tailored to the individual dog in a given environment. This table provides guidelines only and does not address vaccine recommendations for nonviral diseases (bordetellosis, leptospirosis, borreliosis).

†Core vaccines are recommended for all dogs; noncore vaccines are optional and recommended only in some dogs.

Pathophysiology

I. CHV requires close contact for transmission.
II. It spreads transplacentally at birth or through direct dog-to-dog contact (e.g., during breeding).
III. It is unstable in the environment, so it is rarely transmitted through fomites.

Clinical Signs

I. Consequences of rare, transplacental infection include abortions, stillbirths, weak puppies, and puppies that succumb to neonatal infection.
II. Neonatal infection occurs via exposure to the dam's vaginal secretions at birth or to infected littermates, and is most common during the first 3 weeks of life (Anvik, 1991).
III. Signs in puppies 3 to 5 weeks old may be less severe and include neurological signs, such as trigeminal neuropathy, ataxia, and blindness.
IV. Adults are usually asymptomatic.
    A. Females that appear healthy may experience infertility, abortion, or stillbirths.
    B. Genital lesions include papulovesicular lesions that regress and reappear in both males and females.
    C. CHV may play a minor role in canine respiratory infections.
    D. Latent infections recrudesce in some immunosuppressed dogs (Okuda et al., 1993).

Diagnosis

I. Clinical pathologic evaluation
    A. Limited usefulness in neonates because of sampling difficulty and lack of specificity
    B. Puppies: thrombocytopenia, evidence of disseminated intravascular coagulopathy and increased liver enzyme activity (particularly alanine aminotransferase)
II. CHV-specific testing
    A. Virus isolation from tissues of affected puppies is diagnostic.
    B. Serological testing indicates exposure, but does not diagnose active infection in adults.
    C. Multifocal hemorrhages and necrosis with inclusion bodies in epithelial tissues, or CHV identified in tissue via FA, EM, or polymerase chain reaction (PCR) assays are also conclusive.

Differential Diagnosis

I. Neonatal death
    A. Bacterial septicemia with *Salmonella* spp., *Streptococcus* spp.
    B. Other viral infections: CPV-1, CPV-2, CDV
    C. Protozoal diseases
II. Abortion and stillbirths: brucellosis, leptospirosis, bacterial metritis, CDV, protozoal diseases, endocrinopathies

Treatment

I. Supportive therapy is typically unsuccessful.
II. Provide parenteral fluids with oral or IV dextrose, nutritional support, nursing care, animal warming, and broad-spectrum antibiotics.
III. Hyperimmune serum from recovered dogs may protect other puppies (<5 weeks of age) in an affected litter; administer 1 to 2 mL intraperitoneally (Anvik, 1991; Greene and Carmichael, 2006).
IV. Rapid progression of neonatal disease makes the role of antiviral therapy questionable.
V. Infected adult dogs remain latently infected because there is no way to clear all virus from the body.

Monitoring and Prevention

I. Puppies that are kept warm (37° to 38° C [99° to 100° F]) have lower morbidity and mortality.
II. Although bitches that have recovered from infection usually raise subsequent litters without problems, it is recommended they not be bred again.
III. Isolate young puppies from dogs that might shed viral particles.
IV. A preventative vaccine is available only in Europe.
V. CHV is easily inactivated by most disinfectants (see Table 112-1).

CANINE PARVOVIRUS

Definition

I. CPV causes acute contagious enteritis with a high morbidity and mortality in immunologically naive dogs.
II. Rarely, myocardial disease results from perinatal infection.

Cause

I. Canine parvovirus-2
II. SS-DNA virus of the family Parvoviridae
III. CPV-2b: most common disease-causing strain in the United States
IV. CPV-2: distinct from CPV-1 (including disease manifestations)

Pathophysiology

I. Epidemiological findings
    A. This highly contagious virus is shed primarily in the feces of infected and recovering animals.
    B. Fomites are a more common source of exposure than direct contact with feces, and CPV-2 persists in the environment.
    C. Incidence is higher in summer and late fall (Houston et al., 1996).
    D. Immunologically naive animals (young puppies) are the most susceptible to CPV-2 infection; however, older, immunocompromised animals are also at risk.
    E. Reported breed predispositions include the rottweiler, American pit bull terrier, Doberman pinscher, and German shepherd dog (Houston et al., 1996).
II. Pathogenesis
    A. After oronasal exposure (primary route) initial replication occurs in local lymphoid tissues, with subsequent viremia in 2 to 5 days.
    B. Rapidly dividing tissues (e.g., intestinal crypt cells, bone marrow leukocyte precursors) are preferentially infected; dissemination to the lungs, kidneys, and myocardium is possible.

C. Infection of intestinal crypt cells and leukocyte precursors leads to classic manifestations of the disease.
   1. Crypt necrosis and villous blunting with secondary diarrhea
   2. Neutropenia with increased susceptibility to secondary bacterial infections and sepsis
D. In utero or perinatal infections cause myocardial disease (rare) if insufficient maternal antibody is present.

Clinical Signs

I. Enteritis
   A. Initially anorexia, depression, vomiting, ± fever (Cohn et al., 1999)
   B. Diarrhea, often hemorrhagic
   C. Dehydration with inadequate fluid intake and losses via the GI tract
   D. Hypovolemic or endotoxic shock in severely affected dogs or progressive disease
II. Myocarditis
   A. Entire litter affected (rare)
   B. Sudden death or congestive heart failure

Diagnosis

I. General diagnostic testing
   A. Hematological findings
      1. Neutropenia is a classic finding.
      2. Lymphopenia, anemia, and thrombocytopenia are also possible.
   B. Serum biochemistry: panhypoproteinemia and electrolyte imbalances possible
   C. Abdominal imaging
      1. Nonspecific findings suggestive of enteritis
      2. Used to rule out other intestinal diseases, especially intestinal intussusception
II. CPV-2–specific testing
   A. Fecal ELISA for viral antigen is the most commonly used test, but false positives (MLV vaccine 5 to 12 days previously) and false negatives (limited fecal shedding) occur (McCaw and Hoskins, 2006).
   B. Fecal or intestinal EM, fecal PCR, and virus isolation are rarely used clinically.
   C. Serological testing is rarely performed, but a fourfold rise in convalescent IgG titers is diagnostic.
   D. Histological findings include intestinal crypt necrosis or nonsuppurative myocarditis (rare).

Differential Diagnosis

I. GI signs: CCV, bacterial enteritis, parasites, CDV, CHV, toxins, foreign body, intussusception, metabolic diseases
II. Congestive heart failure: congenital heart disease, protozoal diseases, noncardiogenic pulmonary edema (e.g., electrocution, neurological disease, trauma)

Treatment

I. Antiviral therapy is not necessarily required.
   A. Interferon omega 2.5 million units/kg IV SID for 3 consecutive days (de Mari et al., 2003) may be tried.
   B. Oseltamivir phosphate *(Tamiflu)* is a neuraminidase inhibitor used for influenza virus, and may be given for parvoviral enteritis at 2 mg/kg PO BID for 5 days (anecdotal).
II. GI therapy is outlined in Box 112-1.
   A. Adjunctive therapy involves hyperimmune plasma transfusions (1.1 to 2.2 mL/kg IV) from recovered dogs (Cohn LA, unpublished data, 2006).
   B. Empirical deworming is used to eliminate concurrent intestinal parasites.
   C. Treatment with recombinant human granulocyte colony-stimulating factor (G-CSF) is not beneficial (Rewerts et al., 1998).
   D. CPV-2 infection may be fatal, but many animals fully recover.
III. Myocardial disease is extremely difficult to treat.
   A. Because the disease is rapidly progressive and fatal, therapeutic intervention is rarely attempted.
   B. Treat congestive heart failure in survivors.

Monitoring and Prevention

I. Quarantine unvaccinated animals.
II. Passive immunity is important in neonates.
   A. Maternal Ab titers >1:80 (hemagglutination-inhibition) are protective (McCaw et al., 1997).
   B. Maternal Ab typically protects for 6 to 12 weeks and may interfere with vaccination responses up to 18 weeks of age (Coyne, 2000).
III. Good acquired immunity is achieved through vaccination.
   A. High-titer potentiated MLV CPV-2 vaccines are preferred.
      1. They induce protective immunity in puppies when maternal Ab is present (Larson and Schultz, 1997).
      2. Annual (McCaw et al., 1997) to triennial booster vaccines (see Table 112-2) are recommended.
   B. Low-titer, MLV CPV-2 vaccines do not always protect puppies with high maternal Ab levels, even at 20 weeks of age, but the vaccines do provide adequate protection for older puppies and adults (Hoskins, 1998).
IV. Following natural infection, recovered animals have long-lasting immunity.
V. The virus is resistant to most disinfectants (see Table 112-1).

RABIES VIRUS

Definition and Cause

I. Rabies is an invariably fatal infection resulting in encephalitis in most mammals.
II. Although now rare in domestic animals, the zoonotic potential of this fatal disease makes it crucial that every veterinarian understand the disease.
III. Rabies virus (RV) is an SS-RNA virus if the family Rhabdoviridae.

Pathophysiology

I. Epidemiological findings
   A. RV is maintained in wildlife reservoirs worldwide (e.g., fox, skunk, bat, raccoon).

B. Different wildlife reservoirs predominate in certain geographic areas and carry different RV variants.
C. Cats have a higher incidence of RV infection than dogs in the United States.

II. Transmission
A. It occurs primarily through contact with infectious particles in saliva via bite wounds or contamination of mucous membranes or open wounds.
B. Other minor sources include other body fluids, particularly urine, airborne virus, or ingestion.
C. Rabies in dogs and cats is usually contagious only if a bite exposure occurs.

III. Pathogenesis
A. The virus replicates locally and then spreads along the peripheral nervous system axons to the CNS and back down the peripheral nervous system and cranial nerves to the salivary glands.
B. Inoculation at the head often leads to signs of encephalitis more rapidly than inoculation elsewhere on the body.
C. Viral shedding via saliva typically does not begin until 5 to 10 days before the onset of clinical signs.

Clinical Signs

I. The onset of CNS signs is usually with in 2 to 24 weeks, but depends on the viral load inoculated, the degree of innervation at the site, the proximity of the site to the CNS, and the strain of RV.
II. Classic clinical presentation is either "furious" or "paralytic," but not all cases fit these categories, and a combination of signs is possible.
III. With the furious form of rabies, the disease course lasts only days.
A. Behavioral changes, hyperexcitability, hyperesthesia, and aggression occur.
B. Ataxia and seizures develop and are followed by death.
IV. With the paralytic form, the disease course typically lasts about 1 week.
A. Progressive ascending lower motor neuron paralysis begins at the inoculation site and leads to dysphagia, masticatory muscle paralysis, and laryngeal and pharyngeal dysfunction, with classic signs of salivation.
B. Death is caused by respiratory paralysis.

Diagnosis

I. History of a recent bite wound and classic clinical presentation may be helpful.
II. Clinical pathologic findings are nonspecific.
III. Antemortem testing may confirm RV infection, but cannot adequately rule it out.
IV. Owing to the serious public health implications, euthanasia of animals suspected of RV infection is urgently recommended and often required by law.
V. Postmortem testing confirms or denies the diagnosis.
A. Submit the brain—chilled but not frozen—as soon as possible to a state diagnostic laboratory.
B. Direct FA testing of the brain is the diagnostic method of choice.
C. Additional tests on brain specimens include PCR for viral particles, histopathologic evaluation (intracellular inclusions or Negri bodies), and mouse inoculation (Kasempimolporn et al., 2000).
D. RV strains may be identified to help determine the source of exposure.

Differential Diagnosis

I. Dogs: CDV, acute polyradiculoneuritis, botulism, tick paralysis, pseudorabies, neoplasia, organophosphate intoxication, other intoxications, and other causes of meningitis and encephalitis
II. Cats: toxoplasmosis, feline infectious peritonitis (FIP), feline immunodeficiency virus (FIV), feline leukemia virus (FeLV), pseudorabies, thiamine deficiency, intoxications, and other causes of meningitis and encephalitis

Treatment

I. Treatment is unsuccessful and RV infection is invariably fatal.
II. Because of the public health risk, animals with suspected RV infection are euthanized.

Monitoring and Prevention

I. Vaccination provides excellent protection against the disease.
A. Vaccination in most states is initiated by a killed vaccine at 12 to 16 weeks of age, with a booster vaccination at 1 year of age followed by triennial boosters.
B. Some states require yearly vaccination; some vaccines are approved for yearly use only (e.g., canary pox-vectored vaccines).
C. The use of rabies vaccine has been associated with injection-site sarcomas in cats.
II. In most municipalities, rabies vaccination for dogs and cats is required by law.
III. Recommendations for preexposure vaccination and management and postexposure management are available yearly from the American Veterinary Medical Association (AVMA; www.avma.org/issues/policy/rabies_control.asp) and from the Centers for Disease Control and Prevention (CDC; www.cdc.gov/ncidod/dvrd/rabies; see Table 112-2).
IV. Use extreme care when handling an animal or its bodily fluids if RV infection is suspected.
V. RV is susceptible to most disinfectants and does not survive well in the environment (see Table 112-1).

FELINE CORONAVIRUS

Definition and Cause

I. Feline coronavirus (FCoV) causes either subclinical infection or mild, transient diarrhea in exposed cats.
II. Spontaneous mutation of enteric FCoV may lead to clinical FIP, which is associated with very high morbidity and mortality.
III. FCoV is an SS-RNA virus of the family Coronaviridae.

Pathophysiology

I. FCoV is highly contagious via fecal–oral transmission, but salivary, urinary, and transplacental sources of exposure are uncommon.
II. Most infected cats shed the virus intermittently and then stop shedding, although some shed persistently.
III. FCoV that has mutated to an FIP-causing form is seldom shed in feces, so epizootics are rare.
IV. Although inactivated by most disinfectants, FCoV may persist in the environment (see Table 112-1).
V. Enteric infection results in villous atrophy and mild, self-limiting diarrhea.
VI. With FIP, a history of recent stress or illness may precede the disease.
    A. Mutated FCoV invades intestinal epithelium and enters macrophages, resulting in disseminated spread of mutated viral particles.
    B. Immunological response is ineffective and pathologic changes occur.
    C. Two forms of FIP are recognized.
        1. Effusive (wet) form
            a. Immune complexes circulate and are deposited in endothelia.
            b. A vasculitis ensues with exudation of protein-rich fluid into body cavities.
            c. The wet form is usually more rapidly progressive than the dry form.
        2. Noneffusive (dry) form
            a. An ineffective cell-mediated immune response is mounted against the virus.
            b. Pyogranulomatous inflammation in a variety of tissues results in disease.
            c. The dry form may become effusive in its terminal stages.

Clinical Signs

I. Enteric FCoV: often subclinical or mild diarrhea
II. FIP
    A. Young (<2 years) and elderly cats more commonly affected
    B. Sexually intact and purebred cats more commonly affected
    C. Effusive FIP
        1. Common: fever, pale mucous membranes, dyspnea, abdominal distention
        2. Variable: abdominal masses, abdominal organomegaly, icterus
    D. Noneffusive FIP
        1. Development of clinical signs is often insidious.
        2. Signs reflect the body system affected.
            a. Hepatomegaly, icterus, abdominal masses, renomegaly
            b. Pathologic ocular findings: uveitis, chorioretinitis
            c. CNS signs, dyspnea
            d. Fever and weight loss common

Diagnosis

I. Enteric FCoV infection
    A. Definitive diagnosis is seldom necessary.
    B. Antibody titers suggest prior exposure, but do not reflect fecal shedding or active infection.
    C. Viral particles identified in fecal specimens by PCR or EM have few, if any, implications for the health of an individual cat.
II. FIP infection
    A. General diagnostics tests
        1. Hematological findings: nonregenerative anemia, neutrophilia ± left shift
        2. Supportive biochemical findings
            a. Hyperglobulinemia with a low albumin:globulin ratio
            b. Other potential findings: icterus, elevated liver enzymes, azotemia
        3. Serum electrophoresis: polyclonal gammopathy
        4. Fluid analysis
            a. Clear to straw-colored, viscous effusion with low to moderate cellularity, and high protein content
            b. Contains lymphocytes, macrophages, and non-degenerate neutrophils
        5. Radiography: body cavity effusions ± organomegaly, pulmonary infiltrates
        6. Ultrasonography: nodular lesions within organs, organomegaly, effusions (pleural, peritoneal, pericardial, retroperitoneal)
    B. Coronavirus-specific serological tests
        1. Detection of serum Ab identifies exposure to FCoV, but is not diagnostic of FIP.
        2. Titers cannot distinguish exposure to enteric FCoV from exposure to the mutated virus causing FIP.
        3. Titers cannot distinguish exposure to corona viruses of other species from exposure to FCoV.
        4. Most healthy cats with Abs to FCoV never develop FIP.
        5. Positive FCoV Ab titers do not suggest that the cat is shedding virus.
        6. Cats with FIP occasionally have negative titers, especially during terminal stages of disease.
        7. In cats with signs suggestive of FIP, high Ab titers support a diagnosis of FIP.
    C. PCR tests for coronavirus
        1. PCR may identify FCoV in cats with either FIP or enteric FCoV.
        2. It cannot distinguish between enteric FCoV and the FIP-causing mutated forms.
        3. The test result may be negative in a significant number of cats with confirmed FIP.
        4. Positive PCR results from body effusions support a diagnosis of FIP.
        5. A fecal PCR test identifies viral shedding; although persistent viral shedding does not increase the risk for development of FIP, it can be a source of exposure for other cats.
    D. Histopathologic findings
        1. Histopathologic evaluation remains the best method to diagnose FIP.
        2. Affected tissues exhibit pyogranulomatous inflammation with vasculitis and perivascular cuffing with

mononuclear cells, macrophages, lymphocytes, and neutrophils.
3. FA and immunohistochemical testing of tissue specimens from biopsy (ultrasound-guidance or surgically obtained hepatic or renal tissue) or necropsy may confirm FIP.

Differential Diagnosis

I. Enteric FCoV infection with diarrhea: feline panleukopenia, parasites, dietary indiscretion, protozoal infections, bacterial infections, foreign body, and inflammatory bowel disease
II. Effusive FIP: peritonitis, pyothorax, chylothorax, neoplasia, heart failure, cholangiohepatitis, and disseminated fungal or bacterial infections
III. Noneffusive FIP: toxoplasmosis, fungal infection, neoplasia, and cholangiohepatitis

Treatment

I. Enteric FCoV with diarrhea
   A. Because the disease is usually subclinical or self-limiting, specific therapy is not often necessary.
   B. No known therapy reduces the small chance that FCoV-infected cats will develop FIP.
II. Feline infectious peritonitis
   A. Treatment is unsuccessful because the disease is usually fatal.
   B. Spontaneous remissions occur rarely.
   C. Supportive care with nutritional supplementation, relief of effusions that impair respiration, blood transfusions, parenteral fluid therapy, and antibiotic therapy for secondary infections may help prolong life.
   D. Immunosuppressive or immunomodulatory therapy may benefit a small number of cats.
      1. Prednisone 2 to 4 mg/kg PO BID
      2. Cyclophosphamide 2.2 mg/kg PO 4 days/week or chlorambucil 20 mg/m^2 PO every 2 to 3 weeks
      3. Human-recombinant interferon-α 30 U PO SID on alternating weeks
      4. Pentoxifylline: suggested therapy but data insufficient
   E. Clinical studies of other proposed treatments (e.g., vitamins E, A, C) are not availble.

Monitoring and Prevention

I. Catteries and multicat households
   A. Control exposure to feces and disinfect fomites.
   B. Ab tests identify exposed cats but do not predict fecal shedding or propensity to develop FIP, so do not euthanize healthy cats based on positive Ab test results.
   C. Fecal PCR identifies chronic shedders; segregation may reduce exposures.
   D. Strategy to eradicate FCoV is as follows:
      1. Obtain negative (zero) titers on new cats.
      2. Segregate positive cats in the facility from negative cats.
      3. Keep all cats indoors.
      4. Remove kittens from seropositive queens at 5 to 6 weeks of age.
II. Vaccination
   A. The available intranasal vaccine appears safe when used as directed.
      1. Temperature-sensitive vaccine virus replicates only in respiratory epithelium, inducing mucosal immunity.
      2. Vaccine efficacy is 50% to 75% for previously unexposed cats (Pederson, 1995).
      3. It is not indicated in low-risk cats, such as adults or cats in single-cat households.
      4. At-risk kittens possibly benefit from vaccination, with two doses given 3 to 4 weeks apart and followed by yearly booster vaccinations.
      5. Currently, the vaccine is not recommended for routine use (Table 112-3).
   B. Vaccination does not prevent mutation of FCoV in an infected cat.

FELINE IMMUNODEFICIENCY VIRUS

Definition and Cause

I. FIV causes chronic infections with a long subclinical period, and eventual development of acquired immunodeficiency with associated clinical syndromes.
II. FIV, a lentivirus, is a SS-RNA virus of the family Retroviridae that only infects Felidae and is closely related to human immunodeficiency virus.

Pathophysiology

I. Epidemiological findings
   A. Horizontal and vertical transmission occur, but vertical spread is not epidemiologically important.
   B. Close contact is required for transmission, and fomites are involved only minimally.
   C. Horizontal transmission occurs primarily via bite wounds, and also occurs via blood transfusions, contaminated needles and instruments, or other contact with bodily fluids.
   D. Males, particularly intact, outdoor cats that fight, are more commonly infected than females.
   E. Adults (middle aged and older) are infected more often than kittens.
   F. A higher seroprevalence of FIV occurs in areas with large outdoor cat populations.
II. Pathogenesis
   A. FIV initially replicates in lymphoid (including thymic) and salivary tissue, with subsequent dissemination to many tissues.
   B. As the cat mounts a partially effective immune response, the number of circulating viral particles lessens and the cat appears healthy.
   C. During the subclinical period (possibly many years), gradual deterioration in immune function occurs (not a true latency).
   D. Secondary infections and associated illness eventually occur, resulting in the terminal phase of disease.

TABLE 112-3

Viral Vaccination Recommendations for Adult Cats*

VIRUS	ADMINISTRATION FREQUENCY	COMMENTS
Core vaccines†		
Panleukopenia	1 year, then every 3 years	Efficacy of MLV may last >3 years MLV should not be administered to pregnant queens
Herpesvirus-1	1 year, then every 3 years	Either parenteral or topical MLV product may be given Inactivated-virus vaccine with an adjuvant is an alternative
Calicivirus	1 year, then every 3 years	Either parenteral or topical MLV product may be given Inactivated-virus vaccine with an adjuvant is an alternative
Rabies	1 year, then every 1 to 3 years	Local regulations impact frequency of booster vaccines
Noncore vaccines†		
Feline leukemia virus	Annually	Test cats before vaccination Kittens and young cats are more susceptible to infection than adult cats Consider lifestyle risks
Feline immunodeficiency virus	Annually	Test cats before vaccination Vaccinated cats cannot be distinguished from infected cats Consider lifestyle risks
Feline infectious peritonitis	Annually	It is not recommended for most cats

Adapted from Richards JR, Elston TH, Ford RB et al: The 2006 American Association of Feline Practitioners Feline Vaccine Advisory Panel Report. J Am Vet Med Assoc 229:1405, 2006.

MLV, Modified live virus.

*Vaccination protocols must be tailored to the individual cat in a given environment. This table provides guidelines and does not address vaccine recommendations for nonviral diseases (chlamydophilosis, bordetellosis).

†Core vaccines are recommended for all cats; noncore vaccines are optional and recommended only in some cats.

Clinical Signs

I. Acute infection may be inapparent, but can cause self-limiting fever, neutropenia, and lymphadenopathy.
II. Lymphadenopathy is variably present during the subclinical period (months to years).
III. Clinical illness has a variety of manifestations.
  A. Recurrent fevers, anorexia, malaise, gingivitis, stomatitis (common)
  B. Secondary infections of the GI, respiratory, and urinary tracts
  C. Inflammatory diseases of the eye (Hartmann, 1998)
  D. A variety of malignancies (Hutson et al., 1991)
  E. Rare peripheral or central neurological dysfunction (Podell et al., 1993)
  F. Severe weight loss and cytopenia (terminally)

Diagnosis

I. Hematological findings
  A. Lymphopenia and neutropenia acutely, and during later stages of disease
  B. Anemia and thrombocytopenia
II. Serum biochemistry profile: hyperglobulinemia or findings related to secondary diseases
III. Cytological evaluation of fine-needle aspirates of enlarged lymph nodes: hyperplasia or mimic lymphoma
IV. FIV-specific diagnostic testing
  A. In-hospital ELISA tests identify Abs.
    1. FIV is not always detected during acute infection or during terminal stages.
    2. False positives can occur from maternal Ab, so retest positive kittens after 6 months of age (Sellon, 2006).
    3. False positives can occur in vaccinated cats.
  B. Although Western blot is used as a confirmatory test for a positive ELISA result, it cannot distinguish Ab formed in response to infection from maternal Ab or Ab formed in response to vaccination (Levy et al., 2004).
  C. PCR assays are available but vary greatly in reliability (Crawford et al., 2005).

Differential Diagnosis

I. Primary infections with any of the secondary pathogens
II. FeLV infection
III. Bone marrow infiltrative diseases
IV. Neoplasia
V. Chronic fungal infections

Treatment

I. Asymptomatic cats
  A. Keep the animal indoors and well vaccinated for other diseases to minimize risks of other infections.
  B. No specific treatment is available.
II. Symptomatic cats

A. Provide supportive care and prompt therapy for secondary infections.
B. Human recombinant G-CSF may be helpful for severe neutropenia (see Treatment under Feline Leukemia Virus).
C. The use of recombinant human granulocyte-macrophage colony stimulating factor may lead to increased FIV load (Arai et al., 2000).
D. Other immune modulators and antiviral therapy may be tried (see Treatment under Feline Leukemia Virus).

Monitoring and Prevention

I. A vaccine is available but does not confer perfect protection (Huang et al., 2004).
   A. Test cats for FIV before administering the vaccine.
   B. The vaccine is effective for at least 12 months.
   C. Vaccinated cats can test positive on ELISA and Western blot FIV Ab tests.
   D. Consider microchip identification for all vaccinated cats so that ownership and FIV vaccination status can be determined.
   E. Vaccine is not currently recommended for routine use (see Table 112-3).
II. Discourage fighting, and do not breed infected cats.
III. Ideally, separate FIV-positive cats from FIV-negative housemates; however, unless they fight, the risk of transmission with normal contact (e.g., sharing litter boxes, food bowls) is low.

FELINE LEUKEMIA VIRUS

Definition and Cause

I. FeLV causes a chronic infection that may induce neoplasia, immune deficiency, or bone marrow suppression.
II. FeLV is an SS-RNA virus of the family Retroviridae, subfamily Oncornavirinae.

Pathophysiology

I. Epidemiological findings
   A. Horizontal and vertical transmission occur.
   B. Close contact is required, and fomites are minimally involved.
   C. FeLV, though shed in all bodily secretions, is transmitted primarily via saliva (usually during grooming); bite wounds; and shared use of food bowls, water bowls, and litter boxes.
   D. Rarely, transmission occurs transplacentally via the milk during nursing and through blood transfusions, needles, or surgical instruments.
   E. Viral particles are shed from both ill and healthy infected cats.
   F. Kittens are far more susceptible to infection than adult cats.
II. Pathogenesis
   A. Many outcomes are possible after exposure, including recovery, latent infection, or persistent viremia.
   B. The outcome depends on the subgroup of FeLV, age of the cat, immune response, and other variables.
   C. If the initial immune response is ineffective, viremia occurs with replication in lymphoid tissue and bone marrow.
   D. With an effective immune response, viremia ceases, but virus may remain integrated in bone marrow cells.
      1. Latently infected cats are not viremic and not a source of exposure for other cats.
      2. Infections can remain latent for life or may reactivate during stress or immunosuppression.
   E. Many viremic cats remain persistently viremic, with viral particles in bone marrow, epithelial tissues, and salivary glands.
      1. Persistently viremic cats may be healthy for a period of time or develop one of several clinical diseases.
      2. Malignancy is thought to result from insertional mutagenesis during viral replication.
      3. Antibodies to feline oncornavirus cell-associated membrane antigen protect the cat from malignancy, but not from other disease manifestations.
      4. Direct viral invasion of stem cell precursors or stromal damage causes myelosuppression.
      5. Immunosuppression may arise from lymphopenia and alterations in lymphocyte function.
      6. Decreased T suppressor cells and antigen–Ab complexes contribute to immune-mediated disease.

Clinical Signs

I. Acute infection has a variety of manifestations.
   A. Often subclinical
   B. Fever, depression, diarrhea, lymphadenopathy, ± leukopenia
   C. Possible apparent recovery with no signs for months to years
II. Cats with latent infection may be asymptomatic.
III. Immunosuppression with secondary infections is the major cause of morbidity and mortality.
IV. Myelosuppression causes nonregenerative anemia, leukopenia, and thrombocytopenia.
V. Malignancy has several forms.
   A. Lymphoma is the most common neoplasia associated with FeLV infection.
   B. Clinical signs of lymphoma reflect the site involved, and include dyspnea (mediastinal); uremia (renal); and ataxia, paralysis, or seizures (CNS).
   C. Less commonly, hematopoietic malignancies (leukemias) develop and can involve any cell line, with clinical signs reflecting a reduction in normal hematopoietic cell numbers.
VI. Other signs include evidence of immune-mediated hemolytic anemia (IMHA), glomerulonephritis, infertility, abortion, and osteochondromatosis.

Diagnosis

I. Hematological findings
   A. Nonregenerative anemia, macrocytic anemia, nucleated red blood cells
   B. Possibly circulating blast cells, cytopenia, or leukemia

II. Serum biochemistries and urinalysis: nonspecific changes reflecting secondary conditions
III. Lymph node, bone marrow, or mass aspirates: confirm neoplasia or secondary infection
IV. Radiography and ultrasonography: useful to identify neoplasia
V. FeLV-specific diagnostic testing
   A. A very sensitive and specific ELISA test detects circulating FeLV p27 core antigen.
      1. No false positives occur with maternal Abs.
      2. In-hospital kits can be used on serum, plasma, whole blood, saliva, or tears; saliva and tears are less reliable than serum.
      3. ELISA tests are positive earlier in infection than FA tests.
      4. Test results may revert from positive to negative with latent or cleared infection, so confirm a positive ELISA result by FA testing or a second ELISA test in 1 to 3 months.
   B. FA tests are confirmatory.
      1. FA detects p27 core antigen in leukocytes and platelets from blood or bone marrow.
      2. Because a positive FA test means the virus has replicated in precursor cells in the bone marrow, positive cats are unlikely to revert to a negative status.
   C. Culture or FA of bone marrow samples can be done to diagnose latent FeLV infection.
   D. PCR has no advantage over ELISA on blood samples and is useful only to identify FeLV in preserved neoplastic tissues.
   E. Identification of FeLV does not confirm a particular illness is secondary to FeLV.

Differential Diagnosis

I. Acute illness: feline panleukopenia, FCoV, bacterial infections, FIP
II. Anemia: hemorrhage, hemotrophic *Mycoplasma* spp. (see Chapter 115), chronic disease, renal failure, IMHA, histoplasmosis, atypical tuberculosis, myelophthisis, toxin exposure, etc.
III. Neoplasia: non–viral-related leukemia and lymphoma, non-neoplastic causes of lymphadenopathy, pleural effusion, renomegaly, etc.

Treatment

I. No specific treatment is necessary in asymptomatic cats.
II. FeLV-induced neoplasia is treated similarly to non-FeLV neoplasia.
III. Myelosuppression is addressed as follows:
   A. Anemia
      1. Blood transfusion may be life saving.
      2. Although erythropoietin levels in anemic FeLV-positive cats are elevated, short-term use of exogenous erythropoietin is potentially beneficial at 100 U/kg SC 3 times per week (Arai et al., 2000).
      3. Address other causes of anemia, such as hemotrophic *Mycoplasma* spp. infection and IMHA.
   B. Neutropenia
      1. The use of human recombinant G-CSF (5 μg/kg/day SC for ≤2 weeks) in severe neutropenia is controversial (Obradovich et al., 1993; Hartmann, 2006; Arai et al., 2000), because at higher doses or for longer periods it may cause production of antibodies to feline colony stimulating factors.
      2. Consider prophylactic antibiotics.
IV. Secondary bacterial infections require prompt therapy with appropriate antibiotics.
V. Immune modulator and antiviral therapy may be tried, but evidence of efficacy is slim (McCaw et al., 2001).
   A. *Staphylococcus aureus* protein A 10 μg/kg IP twice weekly
   B. Human recombinant interferon-α 30 U PO SID on alternating weeks
   C. Feline recombinant interferon omega 1×10^6 U/kg/day SC for 5 consecutive days in 3 series, beginning on days 0, 14, and 60 (de Mari et al., 2004).

Monitoring and Prevention

I. Isolate cats with FeLV from noninfected cats; keep infected cats indoors, vaccinate them for other infectious diseases, and do not breed them.
II. Vaccination involves the following (see Table 112-3).
   A. Test before FeLV vaccination, because vaccination of positive cats provides no benefits.
   B. Vaccination is not indicated for low-risk cats (e.g., indoor cats, single-cat households, or households in which all cats test negative).
   C. Killed and subunit vaccines are equally efficacious.
   D. Vaccine efficacy is <100%, and estimates of true efficacy vary (Legendre et al., 1991; Jarret and Ganiere, 1996).
   E. Initially give two vaccines 3 to 4 weeks apart, with annual booster vaccinations.
   F. Use of FeLV vaccine has been associated with injection-site sarcomas in cats.

FELINE PARVOVIRUS

Definition and Cause

I. Feline panleukopenia is a highly contagious, acute enteric disease of young cats, typically accompanied by severe leukopenia and high morbidity and mortality.
II. In utero or early neonatal infection may cause cerebellar disease.
III. Feline parvovirus (FPV), an SS-DNA virus of the family Parvoviridae, is related to CPV-2, which is rarely isolated from cats with panleukopenia.

Pathophysiology

I. Epidemiology
   A. FPV is highly contagious to all domestic and wild members of the family Felidae.
   B. Virus is shed in all body secretions, with fecal shedding being the primary source of infection.
   C. Transmission is from contact with infected animals, contaminated environment, or fomites.

D. FPV is seldom encountered in vaccinated domestic cats, but is problematic in feral, shelter, and stray cats.
E. Disease is most common in 3- to 5-month-old kittens, because most cats >1 year old are immune from subclinical infection and younger kittens are protected by maternal Abs.

II. Pathogenesis
A. After oronasal exposure, the virus replicates in regional lymph nodes and causes viremia.
B. FPV preferentially infects rapidly dividing cells (e.g., intestinal epithelial cells, lymph tissue, hematopoietic cells of bone marrow).
C. Secondary GI bacterial infection, translocation of gut bacteria, and increased susceptibility to bacterial infection and sepsis all contribute to the clinical signs produced.

Clinical Signs

I. Adult cats: usually asymptomatic
II. Kittens
A. Initial signs: fever, lethargy, complete anorexia, vomiting, diarrhea (sometimes hemorrhagic), severe dehydration
B. Outcome: peracute death or spontaneous recovery, with milder disease in older kittens
III. Transplacental and early neonatal infection
A. Early gestational infection: fetal resorption, infertility in apparently healthy queens
B. Late gestational or neonatal infection
1. Abortion of mummified fetuses, stillbirths
2. CNS abnormalities: cerebellar hypoplasia with hypermetria and intention tremors
C. Other signs of in utero infection: hydrocephalus, hydranencephaly, retinal dysplasia

Diagnosis

I. Hematological findings
A. Severe leukopenia, neutropenia, variable lymphopenia (early)
B. Rebound leukocytosis (often pronounced) during the recovery phase
C. Anemia: rarely severe with intestinal blood loss
D. Thrombocytopenia
II. Serum biochemistry profile
A. Increased hepatic enzyme activity
B. Azotemia, electrolyte imbalances
III. Specific diagnostic testing
A. Canine parvoviral fecal ELISA kits can detect FPV antigen (imperfect sensitivity).
B. Virus isolation (fecal material and/or urine) is not routinely used.
C. A fourfold increase in paired serum Ab titers is diagnostic, but the test is not commercially available.
IV. Histopathologic findings are similar to those with CPV.

Differential Diagnosis

I. Bacterial enteric infection
II. Septicemia
III. Parasitism
IV. FeLV, FCoV
V. GI obstruction

Treatment

I. Provide supportive care as for CPV (see Box 112-1).
II. CNS signs are not treatable but are nonprogressive, and many affected kittens can be functional pets.

Monitoring and Prevention

I. Passive immunity
A. Colostral Ab prevents infection and interferes with vaccination up to 12 weeks of age.
B. Plasma provides passive immunity (up to 4 weeks) if the kitten is colostrum-deprived.
II. Active immunity
A. Inactive (killed virus) vaccine
1. Requires at least two administrations to be effective
2. Safe in pregnant queens or young kittens (<4 weeks of age)
B. MLV vaccines
1. They provide long-lasting immunity, although yearly booster vaccinations are still recommended by manufacturers.
2. They are not safe in pregnant queens and potentially cause neurological dysfunction in kittens.
3. Give kittens at least two vaccines, with at least 1 dose occurring after 12 weeks of age.
4. For current recommendations, see Table 112-3.
III. Natural infection produces lifelong immunity.
IV. FPV is resistant to environmental degradation and to many disinfectants (see Table 112-1).

MISCELLANEOUS VIRAL INFECTIONS

See Table 112-4.

TABLE 112-4

Other Viruses Affecting Dogs and Cats

VIRUS	SPECIES	PATHOPHYSIOLOGY	CLINICAL SIGNS	DIAGNOSIS	TREATMENT/PREVENTION
Feline sarcoma virus	Cat	Requires FeLV to replicate Induces multicentric fibrosarcoma in young cats Unrelated to injection-site sarcomas	Solitary or multiple cutaneous masses ± visceral metastases	FeLV positive with fibrosarcoma	Wide surgical excision
Feline syncytium-forming virus	Cat	Highly prevalent, but rarely produces disease Coinfection with FeLV results in immune complex deposition in joints	Most infections are asymptomatic Severe progressive polyarthritis may occur	Inflammatory joint tap, FA serology Diseased cats are FeLV positive	Treatment unrewarding Immunosuppressive therapy with prednisone or cyclophosphamide may provide some relief
Astrovirus	Cat	Unknown clinical significance Experimentally, fecal–oral transmission occurs	Diarrhea, anorexia ± vomiting, fever, dehydration	EM of feces	Supportive care Routine disinfection No vaccine is available
Poxvirus	Cat	Found in Europe and Asia Oronasal or skin inoculation Spreads via blood stream to distant skin	Single or multiple skin lesions with scabs ± draining cellulitis	Virus culture, EM of scab, FA test for serum Ab	Supportive care Vaccine not available Zoonotic potential
Borna disease virus	Cat	Found in Europe Believed to cause acute progressive nonsuppurative gray matter encephalomyelitis	Fever and anorexia followed by behavioral change, stiff legs, ataxia, ± seizures, salivation, constipation, altered vision	Histopathology, IHC	Supportive care Vaccine not available
Papillomavirus	Dog, cat	Species-specific virus infects basal cells Young and/or immunodeficient animals affected	Single or multiple oral, ocular, or cutaneous proliferative "wart-like" lesions Lesions often more plague-like in cats	Visual diagnosis ± histopathology and virus identification	Spontaneous regression typical May be excised if interfere with function
Pseudorabies virus	Dog, cat	Pigs are common reservoir, with virus ingested in raw pork Virus travels through nerves to brain, often to brainstem	Peracute illness Behavioral changes, GI signs, dyspnea, intense pruritus Cranial nerve deficits are common	Direct FA, PCR, VI, rabbit inoculation	Typically fatal despite supportive care Prevent exposure to pigs, raw pork No commercial vaccine available

FeLV, Feline leukemia virus; *FA*, fluorescent antibody; *EM*, electron microscopy; *Ab*, antibody; *IHC*, immunohistochemistry; *GI*, gastrointestinal; *PCR*, polymerase chain reaction; *VI*, virus isolation.

TABLE 112-4

Other Viruses Affecting Dogs and Cats—*cont'd*

VIRUS	SPECIES	PATHOPHYSIOLOGY	CLINICAL SIGNS	DIAGNOSIS	TREATMENT/PREVENTION
Rotavirus	Dog, cat	Infects epithelial cells of intestinal villi in dogs and cats Clinically affected dogs are usually young puppies High rate of infection but rare disease in cats	No signs or mild diarrhea for several days Severe, fatal diarrhea can occur in young puppies	ELISA, EM of feces, FA of tissue	Supportive care Vaccine not available
Canine adenovirus-1 (CAV-1; infectious canine hepatitis)	Dog	Highly contagious, shed in secretions Young, unvaccinated dogs most commonly affected Viremia leads to hepatocyte and endothelial damage causing hepatic necrosis, disseminated intravascular coagulation, ± neurological signs	Signs may be peracute, acute, or mild/subclinical Fever, abdominal pain, vomiting, diarrhea, icterus, lymphadenopathy may occur Milder signs with possible corneal edema and anterior uveitis may be noted	Paired Ab titers, virus culture, histopathology (inclusion bodies), FA testing of tissues	Passive (up to 7 wk of age) or acquired immunity is protective Modified live canine adenovirus-2 vaccine provides protection CAV-1 vaccines are avoided owing to risk of secondary corneal edema
Canine parvovirus-1	Dog	Affects puppies <3 wk; may cross placenta Infects lymphoid tissue and rapidly dividing cells	Sudden death or GI signs, dyspnea, crying ("fading puppy syndrome") ± Abortions	EM of feces, hemagglutination inhibition	Supportive care typically unrewarding Vaccine not available
Canine influenza virus	Dog	Highly contagious respiratory virus of high morbidity but low mortality Hemorrhagic pneumonia is rare but life-threatening. Secondary bacterial infections account for most mortality	Cough (often soft), fever, and nasal discharge are common	Paired antibody titers, PCR assay, viral isolation	No vaccine yet available Treatment is largely supportive and includes antibiotics for secondary bacterial infections

ELISA, Enzyme-linked immunosorbent assay.

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CHAPTER 113

Bacterial Infections

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SALMONELLOSIS

Definition

I. Salmonellosis is a bacterial disease of the gastrointestinal (GI) tract of dogs and cats, as well as many other mammals, birds, reptiles, and insects.
II. Under certain circumstances, the disease can become systemic.
III. Subclinical infections can also occur.

Causes

I. *Salmonella enterica* are motile, non–spore-forming, gram-negative bacilli, the majority of which show little or no specific host adaptation.
II. Serovariety *Salmonella typhimurium* is most commonly isolated from dogs and cats.

Pathophysiology

I. Organisms enter the body through the GI tract from contaminated food, water, and fomites.
II. Salmonellae attach preferentially to tips of intestinal mucosal villi, where they invade and multiply.
III. Localization and persistence in intestinal epithelium and lymph nodes account for shedding of organisms for 3 to 6 weeks, or intermittently, and for longer periods.
IV. Once infected, stress (e.g., overcrowding, hospitalization) increases the risk of clinical disease.

Clinical Signs

I. Clinical signs may vary with the number of infecting organisms, host immune status, complicating factors, and concurrent diseases.
II. Clinical syndromes are referable to the organ system affected (most likely in tissues damaged or devitalized by a previous disease), and include gastroenteritis, bacteremia, and endotoxemia.
III. Within 3 to 5 days of exposure, signs may include fever, malaise, anorexia, vomiting, abdominal pain, pale mucous membranes, diarrhea (from watery to mucoid with fresh blood present in severe cases), weight loss, dehydration, epistaxis, or coughing and dyspnea from pneumonia.
IV. Central nervous system (CNS) signs include hyperexcitability, incoordination, posterior paresis, blindness, and seizures.
V. Cardiovascular collapse, shock, disseminated intravascular coagulopathy, and icterus may precede death.
VI. Rarely, chronic or intermittent diarrhea of up to 8 weeks duration may occur.
VII. An asymptomatic carrier state may also develop.

Diagnosis

I. Hematological and serum biochemical findings are nonspecific and typical for infectious diarrhea or septicemia.
II. Isolation of the organism is most definitive.
  A. Isolation is especially significant if it is from normally sterile body fluids or tissues (e.g., blood, urine, synovial fluid, transtracheal washings, cerebrospinal fluid, bone marrow).
  B. Isolation rates are improved by use of selective media.
  C. Isolation only from the GI tract or its secretions does not confirm *Salmonella*-induced disease.
III. Histopathologic evaluation may show hemorrhagic ulcerative enteritis and suppurative lesions in lungs, liver, and brain (with disseminated infection).

Differential Diagnosis

I. Canine and feline enteric viral infections
II. Canine distemper
III. Feline panleukopenia
IV. Campylobacteriosis
V. Helicobacteriosis
VI. Giardiasis, coccidiosis, cryptosporidiosis

Treatment

I. Treatment varies with the type and severity of clinical illness.
II. For acute gastroenteritis without systemic signs, give parenteral isotonic fluids to replace losses.
III. Antibiotics are used only in animals with immunosuppression or signs of systemic illness and are chosen based on susceptibility testing.

Monitoring and Prevention

I. Surviving animals usually recover within 3 to 4 weeks of infection.
II. Surviving animals may shed organisms for ≥6 weeks.
III. Zoonotic potential exists, so isolate affected animals from other animals and people.

IV. Practice proper hygiene if contact is made with affected animals or their feces.
V. People may transmit infection as a reverse zoonosis.
VI. Organisms are susceptible to disinfection with phenolic compounds or household bleach (5.25% sodium hypochlorite diluted 1:32), but the presence of organic material interferes with disinfection.
VII. Handle food properly to avoid contamination.
VIII. Feed only fully cooked foods and treats.

CAMPYLOBACTERIOSIS

Definition and Causes

I. Campylobacteriosis is an enteric bacterial disease associated with diarrhea in dogs and cats that are housed in densely populated or unsanitary environments.
II. *Campylobacter jejuni* is a gram-negative, slender, curved or spiral-shaped rod associated with diarrhea in animals and people.
III. *Campylobacter upsaliensis* and *Campylobacter lari* are isolated from diarrheic and asymptomatic dogs and asymptomatic cats (Hald and Madsen, 1997; Koene et al., 2004).

Pathophysiology

I. Transmission is by the fecal–oral route, usually via contaminated food, such as poultry and milk, or from water supplies.
II. Most infected dogs and cats are asymptomatic carriers and may shed organisms for prolonged periods (Hald and Madsen, 1997).
III. Clinical disease usually occurs in animals <6 months old, and has a duration of 5 to 15 days.
IV. Severity is dependent on prior exposure, number and virulence of organisms ingested, development of protective antibodies, and presence of other enteric pathogens.
V. Disease severity is exacerbated by environmental and physiological stresses.

Clinical Signs

I. Acute diarrhea: soft feces to watery, bloody, or mucoid stool, possibly bile-streaked
II. Rare signs: partial anorexia, occasional vomiting, fever

Diagnosis

I. Microscopic examination of feces with darkfield or phase-contrast microscopy may reveal organisms.
II. Definitive diagnosis is by culture.
   A. Fresh feces or rectal swabs are streaked onto specific isolation media maintained in a reduced-oxygen atmosphere at 42° C for up to 96 hours.
   B. Multiple colonies must be evaluated, because coinfection with multiple *Campylobacter* spp. occurs (Koene et al., 2004.)
III. Gram stain of feces may show gram-negative "gull wing"–shaped organisms.

Differential Diagnosis

I. Canine and feline enteric viral infections
II. Canine distemper
III. Feline panleukopenia
IV. Salmonellosis, helicobacteriosis
V. Giardiasis, coccidiosis, cryptosporidiosis

Treatment

I. Efficacy of antibiotic treatment in animals is unknown; however, treatment may be instituted in animals with clinical signs to minimize exposure of other pets and people.
II. Erythromycin, chloramphenicol, and second generation cephalosporins may be effective.
III. Avoid routine use of enrofloxacin to limit development of resistant bacterial strains.
   A. Enrofloxacin is contraindicated in young animals.
   B. The dose in cats is restricted to 5 mg/kg/day to avoid retinal toxicity.

Monitoring and Prevention

I. Fecal culture should be repeated 1 to 4 weeks after therapy to confirm efficacy.
   A. Clinical improvement may occur despite continued fecal shedding.
   B. Antibiotic therapy has been associated with protracted shedding and antibiotic resistance, particularly to fluoroquinolones (Fox, 2006a).
II. Campylobacteriosis causes enteric disease in people, and pets may be a source of exposure.
III. Strict sanitation and hygiene are essential for control of this disease.
IV. Organisms are viable at room temperature for at least 3 days and for at least 1 week at refrigerated temperatures.

HELICOBACTERIOSIS

Definition and Causes

I. Several *Helicobacter* spp. are associated with gastritis in dogs, cats, and people, and prevalence of infection is high (Fox, 2006b).
II. Other *Helicobacter* spp. are associated with proctitis, colitis, and hepatitis, especially in immunocompromised hosts.
III. *Helicobacter* spp. are gram-negative microaerophilic bacteria similar to *Campylobacter* spp.

Pathophysiology

I. Transmission is via the direct fecal–oral or oral–oral route through contact with infected animals or from fomites.
II. Bacterial proliferation likely causes gastric inflammation and lymphoid proliferation.
III. The pathogenic nature of nongastric *Helicobacter* spp. is poorly defined.
IV. Many infected animals remain asymptomatic.

Clinical Signs

I. Gastric and intestinal infections: vomiting, weight loss, diarrhea

II. Hepatic infections: signs of hepatitis, generally in immunocompromised hosts

Diagnosis

I. *Helicobacter*-positive cultures are not always associated with clinical disease, so histological confirmation is needed.
II. Tests to detect urease activity in biopsy specimens help confirm the diagnosis.
III. Culture is difficult; therefore notify commercial laboratories in advance and use special transport broth to send the specimens.

Differential Diagnosis

I. Gastric infection: campylobacteriosis and other causes of gastritis (see Chapter 31)
II. Intestinal and hepatic infection: other causes of enteritis or hepatitis (see Chapters 33 and 37)

Treatment

I. Antibiotic therapy for gastric infection has not been thoroughly evaluated, and there is no clearly superior treatment (Simpson, 2005).
II. Treatment usually involves a regimen of three oral drugs given for 14 to 28 days:
    A. Gastrointestinal protectant
        1. Dogs: bismuth subsalicylate 0.5 to 2 mL/kg PO TID to QID
        2. Dogs or cats: famotidine 0.5 mg/kg PO SID to BID
    B. Metronidazole
        1. Dogs: 15 mg/kg PO SID to BID
        2. Cats: 62.5 mg PO SID
    C. Amoxicillin 22 mg/kg PO TID: dogs and cats
III. Treatment of nongastric infections is also poorly defined.

Monitoring and Prevention

I. Animals can asymptomatically harbor the infection.
II. Transmission to people is possible through oral contact.

MYCOBACTERIOSIS

Definition and Causes

I. Three forms are recognized, and involve tuberculous, lepromatous, and opportunistic organisms.
II. Tuberculosis is caused by *Mycobacterium tuberculosis, Mycobacterium bovis,* and *Mycobacterium avium*.
III. Feline leprosy is caused by *Mycobacterium lepraemurium*.
IV. *Mycobacterium fortuitum, Mycobacterium chelonei, Mycobacterium smegmatis,* and *Mycobacterium plei* are the most common causes of opportunistic infections in dogs and cats.
V. *Mycobacterium* spp. are environmentally resistant, non–spore-forming, acid-fast bacteria.

Pathophysiology

I. *Mycobacterium* spp. are ubiquitous in nature and not highly pathogenic under normal circumstances.
II. Tuberculous mycobacteria enter the body via the lungs, GI tract, or the skin.
    A. They induce granuloma formation at the site of entry.
    B. They sometimes disseminate systemically.
III. Lepromatous *Mycobacterium* spp. are transmitted from bites or contact with infected rats, and cause primarily cutaneous disease in cats.
IV. Opportunistic mycobacterial infections follow penetrating skin or soft-tissue injuries and cause pyogranulomas.

Clinical Signs

I. Infections are frequently subclinical in dogs and cats.
II. When clinical signs occur, they reflect the sites of granuloma formation.
    A. Bronchopneumonia, pulmonary nodule formation, and hilar lymphadenopathy are common in dogs and cause fever, weight loss, anorexia, and harsh nonproductive coughing.
    B. Cats with intestinal lesions have weight loss, anemia, vomiting, and diarrhea.
III. Feline leprosy manifests as soft, fleshy nodules in the skin and subcutis.
IV. Opportunistic mycobacterial infections occur as multiple, fistulous, draining tracts with purulent drainage into subcutaneous tissues.

Diagnosis

I. Tuberculosis
    A. Cytological evaluation of exudates with acid-fast staining allows a rapid, presumptive diagnosis.
    B. Intradermal skin testing of the inner side of the pinna with tuberculin may induce a delayed-type hypersensitivity reaction in dogs.
    C. Polymerase chain reaction (PCR) assays are available for some species.
    D. Definitive diagnosis requires demonstration of organisms within lesions.
II. Feline leprosy
    A. Large numbers of organisms in histological sections
    B. Identification of organisms in impression smears of affected tissues
III. Opportunistic infections
    A. Difficult to diagnose
    B. Require finding extensive granulomatous to pyogranulomatous inflammation of the dermis and panniculitis
    C. PCR assays at certified laboratories helpful

Differential Diagnosis

I. Consider other causes of respiratory problems, such as canine distemper, feline respiratory viruses, chlamydial and mycoplasmal infections (see Chapters 18 and 114).
II. Rule out feline lymphosarcoma (LSA), bacterial L-form infections, feline abscesses, and dermatophilosis.

Treatment

I. Tuberculous mycobacterial infections
    A. Treatment is not recommended for confirmed infections.
    B. Consider euthanasia, because of public health concerns, particularly for infections with *M. tuberculosis* and *M. bovis*.

C. For treating possible infections, use combination antibiotic therapy for ≥6 months (Greene and Gunn-Moore, 2006).

II. Feline leprosy is treated with aggressive surgical excision of all nodules and medical therapy for at least 2 months.
   A. Clofazimine 25 mg PO SID or 50 mg PO QOD
   B. Combined with clarithromycin 62.5 mg PO BID or rifampin 10 to 15 mg/kg PO SID (Malik et al., 2006).

III. Opportunistic mycobacterial infections are treated as follows:
   A. Administer antibiotics in accordance with susceptibility testing.
      1. While awaiting results, treat empirically with fluoroquinolones or clarithromycin.
      2. Treatment may be necessary for 6 to 12 months (Malik et al., 2006).
   B. Surgical resection of large granulomas may be more successful in dogs than in cats.

Monitoring and Prevention

I. If treatment is pursued, monitor tuberculous mycobacterial infections closely because of the zoonotic potential.
II. Lepromatous infections may be minimized by preventing contact with rodents.
III. Opportunistic mycobacteriosis has a guarded prognosis because lesions frequently recur and can spread.
IV. *Mycobacteria* spp. are killed by heat, phenolic compounds, and direct sunlight.

BRUCELLOSIS

Definition and Cause

I. Brucellosis is a zoonotic disease affecting reproductive organs and is associated with a persistent, insidious bacteremia.
II. *Brucella canis* is a small, gram-negative coccobacillary organism with a rough colonial morphology that distinguishes it from other *Brucella* spp.

Pathophysiology

I. Transmission usually occurs during breeding or birth, possibly via inhalation of aerosols associated with abortion or vaginal discharges.
II. Organisms penetrate mucous membranes, enter lymphatic and genital tissues, and persist intracellularly or spread to intervertebral disks, eyes, and kidneys.
III. Infected adult dogs are rarely seriously ill.

Clinical Signs

I. Reproductive problems
   A. Late gestational abortion of dead (partially autolyzed) puppies
   B. Stillborn or weak puppies
   C. Conception failures
   D. Epididymitis, scrotal enlargement, scrotal dermatitis
II. Nonreproductive abnormalities
   A. Spinal hyperesthesia, paresis, or paralysis with discospondylitis
   B. Anterior uveitis

Diagnosis

I. Hematological and serum biochemical tests results are usually normal or have nonspecific changes.
II. Hyperglobulinemia, ± concomitant hypoalbuminemia, occurs in chronic infections.
III. Semen abnormalities are seen and include immature sperm, deformed acrosomes, swollen midpieces, detached tails, and head-to-head agglutination.
IV. Serological testing is the primary method of diagnosis.
   A. Mercaptoethanol rapid slide agglutination test (ME-RSAT) is the preferred in-office screening test.
      1. It is quick and highly sensitive.
      2. False-positive results are common.
      3. Results are confirmed by additional tests.
   B. Tube agglutination test is used by some laboratories to confirm ME-RSAT and quantitate titers, but it lacks specificity.
   C. Agar-gel immunodiffusion test is the most sensitive test and is used by commercial laboratories to confirm infection.
V. Bacterial culture, especially of the blood, is valuable.
   A. It is the only definitive way to resolve serological differences.
   B. Negative results may occur owing to intermittent bacteremia.
VI. Histopathologic findings may show diffuse lymphoreticular hyperplasia or necrotizing vasculitis of reproductive tissue.

Differential Diagnosis

I. Infectious diseases: canine herpesvirus and canine parvovirus-1 infections, ehrlichiosis, anaplasmosis, Rocky Mountain spotted fever (RMSF), neonatal streptococcal infections, neosporosis
II. Other diseases with similar clinical signs: intervertebral disk disease, LSA, testicular inflammation or tumors, any cause of recurrent uveitis

Treatment

I. Treatment may not be advisable.
   A. Uncertain eradication from tissues
   B. Zoonotic potential
II. Neutering of all infected animals is highly recommended.
III. Combination therapy with a tetracycline and an aminoglycoside may be tried (Mateu de Antonio and Martin, 1995).
   A. Resolving the infection is difficult because *B. canis* is intracellular.
   B. Relapses are common once therapy is stopped.
IV. Multiple courses of therapy, separated by 1 to 2 months, may be necessary.
   A. Doxycycline or minocycline 12.5 mg/kg PO BID for 4 weeks *with*
   B. Gentamicin 5 mg/kg IM, SC SID during weeks 1 and 4
   C. Rifampin 10 mg/kg PO BID to TID in combination with doxycycline 5 mg/kg PO SID for 4 weeks
V. Male dogs may be sterile if they recover, and recovery with return to successful breeding is rare in bitches.

Monitoring and Prevention

I. Measure serological titers every 3 to 6 months to monitor treatment efficacy.
II. Test all breeding animals before breeding.
III. Test blood donors.
IV. Because people are susceptible, consider euthanasia of infected dogs, although neutering and treatment are possibly an option.

ACTINOMYCOSIS AND NOCARDIOSIS

Definition

I. Actinomycosis is a pyogranulomatous disease that produces abscesses, chronic draining fistulas, or infections of bones or body cavities.
II. Nocardiosis causes similar lesions; however, a disseminated form originating in the respiratory tract also occurs.

Causes

I. *Actinomyces* spp. are branching, filamentous, gram-positive, fastidious, microaerophilic bacteria of the family Actinomycetaceae.
II. *Nocardia* spp. are acid-fast staining, aerobic members of the family Nocardiaceae.

Pathophysiology

I. Epidemiological findings and transmission
  A. *Actinomyces* spp.
    1. Commensal organisms, found in oral cavities of animals and people
    2. Inoculation via bite, puncture wounds, or tissue trauma
    3. More commonly infects outdoor dogs and cats
  B. *Nocardia* spp.: inoculation of soil saprophytes via wound contamination or inhalation
  C. Entry and spread influenced by host immunocompetence
II. Actinomycosis
  A. Usually involves the cervicofacial region, thorax, abdomen, retroperitoneal space, bone, and subcutaneous tissues
  B. Spreads to adjacent tissues by direct extension via normal tissue planes
III. Nocardiosis
  A. Usually develops in alveolar spaces
  B. Erodes blood vessels and spreads systemically (e.g., thoracic cavity, CNS, retroperitoneal space)
  C. Cutaneous-subcutaneous disease in cats (Malik et al., 2006)

Clinical Signs

I. Actinomycosis
  A. Localized swellings or fluid accumulation in body cavities with serosanguineous drainage often containing small yellow granules
  B. Persistently draining, fistulous tracts
II. Nocardiosis
  A. Localized lesions similar to actinomycosis
  B. Chronic respiratory signs
    1. Mucopurulent oculonasal discharge
    2. Anorexia, weight loss
    3. Cough, dyspnea
    4. Diarrhea, hyperthermia
  C. Disseminated nocardiosis
    1. Rare without obvious pulmonary disease
    2. Signs referable to organ systems involved

Diagnosis

I. Hematological and serum biochemistry changes are nonspecific and typical of any pyogenic inflammation.
II. Cytological examination of lesion exudates is most specific when granules are present.
  A. Gram-positive branching filamentous rods and cocci
  B. Acid-fast staining for *Nocardia* spp. identification
III. Histopathologic examination of tissue with Gram stain and acid-fast stains may reveal organisms.
IV. Definitive diagnosis is via bacterial culture.
  A. Notify the laboratory that these organisms are suspected.
  B. Obtain samples anaerobically to aid the isolation of *Actinomyces* spp.

Differential Diagnosis

I. Other causes of draining skin lesions
II. Other causes of pyothorax (see Chapter 19)
III. Systemic fungal diseases

Treatment and Monitoring

I. For both disorders, surgical drainage and debridement of focal affected areas is undertaken.
II. Antibiotic therapy is administered for several weeks to months.
  A. Actinomycosis: penicillin V or G 40 mg/kg PO TID
  B. Nocardiosis: trimethoprim/sulfonamide (TMS) 15 to 30 mg/kg PO BID
    1. Some *Nocardia* spp. require alternative therapies.
    2. *Nocardia farcinia* may respond to amikacin or imipenem in addition to TMS.
    3. *Nocardia farci* may respond to TMS followed by amoxicillin (20 mg/kg PO BID) plus clarithromycin (62.5 to 125 mg PO BID) or doxycycline (5 mg/kg PO BID) (Malik et al., 2006).
III. Monitor closely for potential relapse, especially following completion of antibiotic therapy.

BORRELIOSIS

Definition and Cause

I. Borreliosis is one of a large group of tick-borne diseases caused by spirochetes that affect people and animals worldwide.
II. These diseases are divided into the Lyme disease group (transmitted by ixodid ticks) and the relapsing fever group (transmitted by soft ticks).

III. Lyme borreliosis is caused by *Borrelia burgdorferi sensu lato,* which is transmitted by nymph or adult *Ixodes ricinus* ticks.

Pathophysiology

I. Following tick attachment, organisms enter the host and spread to connective tissues, joints, and other tissues.
II. Clinical syndromes are produced by the host's inflammatory reaction to the organism (documented in naturally infected dogs but not in cats).

Clinical Signs

I. Fever, inappetence, lethargy, lymphadenomegaly, and episodic, shifting lameness develop 60 to 90 days after infection.
II. Skin lesions (expanding erythema around tick bite) and neurological signs (meningitis or encephalitis) are not well documented in dogs.

Diagnosis

I. Diagnosis is based on clinical signs, a history of recent tick exposure, serological testing, and response to treatment.
II. No specific hematological or serum biochemical changes occur.
   A. Dogs with renal involvement may be azotemic.
   B. Proteinuria, hematuria, pyuria, and tubular casts can be found on urinalysis.
III. Serological testing is used as a screening tool.
   A. A fourfold rise in titer over 2 to 4 weeks is significant.
   B. Rule out nonspecific or vaccine-induced positive titers with use of a quantitative antibody assay (e.g., C6 enzyme-linked immunosorbent assay [ELISA]) or immunoblotting procedures.
IV. Bacterial isolation is the most definitive means of confirmation of disease, but is difficult owing to low numbers of organisms.
V. PCR assays of infected skin or connective tissue biopsies offer a specific means of confirmation.

Differential Diagnosis

I. Consider other tick-borne diseases (e.g. ehrlichiosis, anaplasmosis, RMSF).
II. Geographic location and regional tick populations are also important considerations.

Treatment

I. Antibiotic treatment is usually begun before infection is confirmed.
   A. Doxycycline is the drug of choice (10 mg/kg PO BID for 30 days).
   B. Amoxicillin 20 mg/kg PO TID for 30 days is used.
II. Nonsteroidal antiinflammatory drugs (NSAIDs) can relieve pain during episodes of recurrent synovitis.

Monitoring and Prevention

I. Relapse and recrudescence of infection is possible even if treatment is continued for months.
II. Vaccines available in the United States must be given before exposure to ticks.
III. Tick control in endemic areas requires use of residual acaricides and environmental management (Stafford, 2004).

LEPTOSPIROSIS

Definition and Causes

I. Leptospirosis is a multisystemic disease in dogs, livestock, people, and many other animals, with worldwide significance; it is rare in cats.
II. Serovars of the spirochete *Leptospira interrogans sensu lato* are the causative agents.
   A. Serovars *grippotyphosa, pomona, bratislava,* and *autumnalis* are currently the most common serovars detected in clinically ill dogs.
   B. *Leptospira icterohemorrhagiae* and *Leptospira canicola* are now less commonly associated with clinical illness.

Pathophysiology

I. Epidemiological findings
   A. Leptospires persist in stagnant or slow-moving water.
   B. Various mammals serve as reservoirs (e.g., fox, mouse, rat, raccoon, opossum, deer).
II. Pathogenesis
   A. Leptospires are shed in the urine of infected animals.
   B. They penetrate mucous membranes or abraded skin and enter blood vascular spaces, where they replicate and produce inflammation.
   C. Damage to kidneys, liver, and other tissues ensues.

Clinical Signs

I. Mild or inapparent in cats
II. Signs in dogs
   A. Dependent on age, immunity, environment, and virulence factors of the serovar
   B. Chronic or subclinical infections common
   C. Peracute infections: massive leptospiremia, shock, death
   D. Other infections: fever, anorexia, vomiting, dehydration, increased thirst, reluctance to move
   E. Progressive deterioration in renal and hepatic function: oliguria or anuria, icterus possible

Diagnosis

I. Hematological findings: leukocytosis, thrombocytopenia
II. Serum biochemistry and urine tests
   A. Increased serum urea nitrogen and creatinine concentrations with isosthenuria reflect renal involvement.
   B. Electrolyte alterations parallel the degree of renal and GI tract dysfunction.
   C. High serum hepatic transaminase activity and bilirubinemia indicate liver damage.
III. Serological testing
   A. Microscopic agglutination test is the standard serological test.
   B. A fourfold rise in titer over 2 to 4 weeks is required to confirm infection.

C. Single high (>800) titers are often indicative of recent or active infection or prior vaccination.

IV. PCR assays and culture of urine for leptospires may also be used.

Differential Diagnosis

Rule out other causes of kidney and liver disease (see Chapters 37 and 48).

Treatment

I. Penicillins for 2 weeks are the drug of choice for initial treatment of leptospiremia.
   A. Ampicillin 22 mg/kg PO, SC, IV TID
   B. Amoxicillin 22 mg/kg PO BID
   C. Penicillin G 25,000 to 40,000 U/kg IM, SC, IV BID

II. Use doxycycline to minimize or eradicate the carrier state.
   A. Started after penicillin treatment is completed
   B. Dosage: 5 mg/kg PO, IV BID for 2 weeks

Monitoring and Prevention

I. Vaccination is available for serovars canicola, icterohaemorrhagiae, pomona and grippotyphosa.

II. Leptospires are killed by heat and most disinfectants; removal of organic debris before disinfection is essential.

TETANUS

Definition and Cause

I. Tetanus is a disease of warm-blooded animals that results from a potent bacterial neurotoxin formed in the host by *Clostridium tetani*.

II. Spores of *C. tetani*—a motile, gram-positive anaerobic bacillus—are introduced into wounds, vegetate, and then produce tetanospasmin.

Pathophysiology

I. Dogs and cats are relatively resistant to the effects of the toxin.

II. Toxin produces either a localized progressive illness or a generalized syndrome, depending on how it is spread throughout the body.

III. Visceral and motor neuron disturbances also occur.

Clinical Signs

I. Usually occur within 5 to 21 days of exposure

II. Localized signs common
   A. Increased stiffness in a muscle or an entire limb (Malik et al., 1989)
   B. Gradual progression to involve the entire nervous system

III. Generalized signs
   A. Facial muscle spasms (risus sardonicus)
   B. Protrusion of the third eyelid
   C. Trismus (lockjaw)
   D. Increased salivation
   E. Laryngeal spasms, dysphagia
   F. Extreme muscle rigidity
   G. Elevated body temperature from excessive muscular activity
   H. Altered heart and respiratory rates

Diagnosis

I. Usually based on the clinical signs and history.

II. History of a bite wound or surgical wound is variable.

III. Isolation of the organism is very difficult.

Differential Diagnosis

I. Strychnine intoxication

II. Meningitis

III. Other causes of seizures or muscle rigidity (see Chapters 22 and 82)

Treatment

I. Mildly affected animals may recover with wound management only.

II. Severely affected animals require labor-intensive supportive therapy and prolonged hospitalization; complications are possible.

III. Supportive care may include the following (Bandt et al., 2007):
   A. Intravenous fluids
   B. Tracheostomy with assisted ventilation
   C. Indwelling feeding tube, partial or total parenteral nutrition

IV. Antitoxin is used to neutralize toxin that is unbound or as yet unformed.
   A. Initial dose is 0.1 to 0.2 mL SC, ID; observe for 30 minutes for signs of anaphylaxis.
   B. Equine antitoxin (100 to 1000 U/kg) may be administered once IV, IM, SC near or proximal to the wound site for localized tetanus (Bandt et al., 2007).

V. Metronidazole (15 mg/kg PO, IV BID) or penicillin G (20,000 U/kg IV QID or 20,000 to 100,000 U/kg IV, SC, IM BID to TID) for 10 days is used to kill vegetative organisms.

Monitoring and Prevention

I. Supportive care is essential to maximize recovery of animals with severe clinical signs.

II. Avoid exposure to the bacteria by thorough cleansing and treatment of wounds.

BOTULISM

Definition and Cause

I. Botulism is a bacterial disease that produces neuromuscular paralysis.

II. *Clostridium botulinum* is a gram-positive, anaerobic, spore-forming soil saprophyte that produces neurotoxins.

Pathophysiology

I. Botulism is usually caused by ingestion of a preformed toxin in food.

II. Toxin absorbed from the stomach and upper small intestine circulates to neuromuscular junctions or cholinergic nerves.

III. Toxin prevents presynaptic release of acetylcholine, resulting in generalized lower motor neuron disease and parasympathetic dysfunction.

Clinical Signs

I. Symmetrical ascending weakness from rear to forelimbs
II. Depressed limb reflexes
III. Mydriasis and other signs (see Chapter 25)
IV. Decreased jaw tone, gag reflexes, and excessive salivation

Diagnosis

I. Electromyography shows conduction defects at the neuromuscular junction.
II. Finding toxin in the serum, feces, vomitus, or food sample by using specific assays for the most common toxin (type C) confirms the diagnosis, but assays are not always readily available.

Differential Diagnosis

I. Polyradiculoneuritis
II. Myasthenia gravis
III. Tick paralysis
IV. Organophosphate toxicity (nicotinic receptor paralysis)

Treatment

I. Supportive treatment (see Chapter 25) is most important; spontaneous recovery can occur in moderately affected animals.
II. Metronidazole or penicillins have been used to reduce potential intestinal growth of the clostridial agents, but are not recommended because they may not alter the course of disease and may cause further toxin release upon death of the bacteria (Barsanti, 2006).

Monitoring and Prevention

I. Monitor for aspiration pneumonia and urinary tract infections in recumbent, paralyzed animals.
II. Preventing access to carrion and thorough cooking of food reduces the prevalence of the disease.
III. Toxin is destroyed by heating to 100° C for 10 minutes.

BARTONELLOSIS

Definition and Causes

I. Bartonellosis is a group of arthropod-borne bacterial diseases of people and animals caused by members of the genus *Bartonella*.
II. *Bartonella* spp. are fastidious gram-negative bacteria.
III. Multiple *Bartonella* spp. infect cats and dogs.
   A. Cats: *B. henselae, B. clarridgeiae, B. koehlerae, B. bovis, B. quintana*
   B. Dogs: *B. vinsonii* subsp. *berkhoffii, B. henselae*, *B. clarridgeiae, B. elizabethae, B. quintana*

Pathophysiology

I. *B. henselae* is transmitted to cats by fleas (Chomel et al., 1996).
II. Cats are reservoirs and vectors for human *B. henselae* infections.
III. *B. vinsonii* subsp. *berkhoffii* and other species are probably transmitted among dogs by ticks.
IV. Coyotes are likely reservoirs for canine and human *B. vinsonii* subsp. *berkhoffii* infections (Chang and Kasten, 2000).
V. Cats develop relapsing *B. henselae* bacteremia that persists for months to years.
VI. *Bartonella* spp. are presumed to be intracellular bacteria.

Clinical Signs

I. Cats infected with *B. henselae* may have a self-limiting, febrile illness for days to weeks; most infections appear to be subclinical.
II. Transient fever, lymphadenomegaly, CNS signs, and reproductive failure are reported in experimentally infected cats, especially with more virulent strains (Guptill, 2003).
III. Evidence is lacking to confirm a causal association between natural *Bartonella* spp. infection and stomatitis, uveitis, and CNS signs in cats (Brunt et al., 2006).
IV. Dogs infected with *B. vinsonii* subsp. *berkhoffii* may have inapparent signs or severe signs from endocarditis and bacteremia.
V. It was recently proposed that *B. henselae* and other *Bartonella* spp. may cause multiple clinical syndromes in dogs alone (opportunistic pathogens) or in combination with other vector-transmitted pathogens (Breitschwerdt et al., 2004; Goodman and Breitschwerdt, 2005).

Diagnosis

I. Cultivation and identification of the organism is as follows:
   A. Blood culture: negative results possible from relapsing bacteremia in cats; rarely useful for dogs
   B. Identification in tissues via PCR
II. Positive serological tests (immunofluorescent assay, ELISA) indicate exposure, and are not indicative of active infection (approximately 50% positive predictive value for cats).

Differential Diagnosis

I. Other causes of fever
II. Other causes of endocarditis
III. Other causes of lymphadenomegaly

Treatment

I. Antibiotic treatment is not proven to be effective at clearing infections in cats or dogs.
II. Doxycycline, enrofloxacin, or azithromycin treatment (2 to 6 weeks) may decrease bacteremia in cats.
   A. Whether any treatment eradicates infection is not known (Brunt et al., 2006).
   B. Use caution when administering doxycycline tablets to cats; to avoid esophagitis and subsequent strictures, follow tablets with water and do not crush or use partial tablets.
III. Bacteremia in cats may recur after treatment is discontinued (Greene et al., 1996).

Monitoring and Prevention

I. Bacteremia relapses, so follow-up cultures may not reveal the true efficacy of treatment.
II. *Bartonella henselae* is transmitted from cats to people by scratches and possibly bites; the role of fleas in this transmission has not been determined.
III. *Bartonella vinsonii* subsp. *berkhoffii* is possibly transmitted from dogs to people by bites (Chang and Kasten, 2000).
IV. Vector control is essential to decrease transmission among cats and dogs, and possibly from animals to people.
V. Cats may be reinfected or coinfected with multiple *Bartonella* spp. or subtypes (Guptill, 2003).

OTHER BACTERIAL INFECTIONS

See Table 113-1.

TABLE 113-1

Other Bacterial Diseases in Dogs and Cats

DISEASE	ORGANISM	SPECIES	CLINICAL SIGNIFICANCE	DIAGNOSIS	TREATMENT
Shigellosis	*Shigella* spp.	Dogs, cats	Asymptomatic to diarrhea	Culture	Ampicillin, sulfonamides, tetracycline
Yersiniosis	*Yersinia enterolytica*	Dogs, cats	Asymptomatic to diarrhea, increased stool frequency, tenesmus	Culture	Chloramphenicol, gentamicin Avoid raw foods
Clostridium perfringens infection	*Clostridium perfringens*	Dogs, cats	Diarrhea, tenesmus, inflamed anal tissues	Clinical signs plus culture	Metronidazole
Staphylococcal infections	*Staphylococcus* spp.	Dogs	Opportunistic pathogens Abscesses of the skin, eyes, ears, respiratory and urinary tracts, skeleton, and joints	Culture, Gram stain of clinical specimens	β-Lactamase–resistant penicillins, first-generation cephalosporins
	MRSA	Dogs, cats	Same as for other *Staphylococcus* spp. Possible zoonosis or reverse zoonosis	Oxacillin resistance is a marker PCR test required to confirm	Based on susceptibility tests, but multiple drug resistance possible Avoid clindamycin, as resistance may develop quickly
Melioidosis	*Burkholderia (Pseudomonas) pseudomallei*	Dogs, cats	Chronic nodular or purulent inflammatory disease of the skin	Isolation and identification from blood or lesion	Surgical drainage Antimicrobial therapy for months
Glanders	*Pseudomonas mallei*	Dogs, cats	Wound contamination with bacteremia Nodular lesions resembling tuberculosis	Culture and identification	Sulfonamides, tetracycline
Plague	*Yersinia pestis*	Dogs, cats Fleas involved in transmission	Buboes, pneumonia, septicemia Zoonosis	Epidemiological evidence, clinical signs, isolate from clinical samples Contact state veterinarian or public health officials	Gentamicin and streptomycin are drugs of choice Exercise caution and use appropriate PPE Flea control
Tularemia	*Francisella tularensis*	Dogs, cats Rabbits and ticks involved in transmission	Fever, anorexia, listlessness Zoonosis	Serological testing	Gentamicin may be best choice Possibly doxycycline or chloramphicol, but relapse possible Use appropriate PPE

MRSA, Methicillin-resistant *Staphylococcus aureus; PCR,* polymerase chain reaction; *PPE,* personal protective equipment.

TABLE 113-1

Other Bacterial Diseases in Dogs and Cats—*cont'd*

DISEASE	ORGANISM	SPECIES	CLINICAL SIGNIFICANCE	DIAGNOSIS	TREATMENT
Dermatophilosis	*Dermatophilus congolensis*	Dogs, cats	Dermatological lesions in dogs; deeper abscesses in cats	Culture, cytological examination	Wound management Penicillins most practical
Rhodococcosis	*Rhodococcus equi*	Dogs, cats	Abscess, pyogranuloma Possible zoonosis	Culture	Wound management, surgical drainage Lincomycin and gentamicin most effective
Feline abscesses	Bacterial flora of the oral cavity and claws	Cats	Abscess	Culture, physical examination	Wound management, surgical drainage Penicillin derivatives
L-form infections	Cell wall–deficient bacteria	Cats	Fever; lymphadenomegaly; persistently draining, spreading cellulitis and synovitis often involving the extremities	History, clinical signs Culture rarely positive	Tetracyclines
Tyzzer's disease	*Clostridium piliforme*	Dogs, cats	Multifocal hepatic necrosis, rapid-onset lethargy, anorexia, abdominal discomfort, hepatomegaly Affected animals often stressed or immunosuppressed	Rapidly fatal (with 24-48 hours) Usually diagnosed at necropsy	Unsuccessful Prevented by avoiding contact with infected rodent urine
Streptococcosis	*Streptococcus* spp.	Dogs, cats	Depends on affected tissue or organ: skin lesions, metritis, pyelonephritis, necrotizing fasciitis, toxic shock–line syndrome	Culture	Based on susceptibility testing

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CHAPTER 114

Mixed Respiratory Infections

Leah A. Cohn | Paige Langdon

CANINE INFECTIOUS TRACHEOBRONCHITIS

Definition

I. Canine infectious tracheobronchitis (ITB) is a highly contagious syndrome resulting from acute respiratory infections caused by viral and/or bacterial pathogens.
II. The term *kennel cough* is often used synonymously with ITB.

Causes

I. Multiple pathogens have been incriminated in the ITB disease complex (Box 114-1).
II. ITB may be caused by a single pathogen or mixed infections including secondary bacterial pathogens.
III. ITB is most commonly encountered when dogs are housed close together.
IV. Viral pathogens and *Bordetella bronchiseptica* spread quickly by aerosolization.
V. Dogs of any age, sex, or breed are susceptible.

Pathophysiology

I. The common viral pathogens replicate in the respiratory epithelium, where damage facilitates secondary infection.
II. Most viruses are cleared in 1 to 2 weeks, but clinical signs may persist longer.
III. *Bordetella bronchiseptica* elaborates toxic substances that inhibit ciliary movement and impair phagocytic function, thereby facilitating primary infection.
IV. *Mycoplasma* spp. colonize the upper airways; although they seldom cause disease, they may worsen clinical signs of other respiratory infections.
V. Secondary infections with opportunistic pathogens worsen clinical signs.

Clinical Signs

I. Signs depend on the type of pathogens, host immunity, and presence of opportunistic infection.
II. Paroxysmal coughing is the most consistent clinical sign.
  A. The cough may be dry, hacking, or productive.
  B. Owners may mistake productive coughing for retching or vomiting.
III. Uncomplicated cases are not associated with systemic illness.
IV. Secondary infection, or infection in young or unvaccinated dogs, produces more severe disease.
  A. Productive cough, mucopurulent nasal discharge
  B. Fever, anorexia, depression
  C. Less common: dyspnea, pneumonia, respiratory failure, or sepsis
  D. Canine influenza
    1. It is often associated with fever and mild systemic illness (Joly, 2005; Crawford et al., 2005).
    2. Mortality ranges from 1% to 8%.
    3. Mortality may be associated with hemorrhagic viral pneumonia or secondary bacterial pneumonia.
V. Prior vaccination alleviates the severity of signs.

Box 114-1

Pathogens Incriminated in the Canine Infectious Tracheobronchitis Disease Complex

Viruses	
Canine parainfluenza virus (CPiV)	Most common isolate from dogs with ITB
Canine adenovirus-2 (CAV-2)	Frequent isolate; related CAV-1 causes infectious canine hepatitis and may be isolated during ITB
Other viruses	
Canine reoviruses and herpesvirus	May contribute to ITB
Canine distemper virus	*Not* considered agent of ITB despite frequent respiratory signs
Canine influenza virus	Associated with cough, fever, and nasal discharge
Bacteria	
Bordetella bronchiseptica	Most common bacterial isolate in ITB; may be a primary or secondary pathogen
Streptococcus spp., *Pasteurella* spp., *Pseudomonas* spp., coliforms	May be isolated; often opportunistic; cause morbidity and mortality
Mycoplasma spp.	Fastidious microbes lacking cell wall; may be a primary or secondary pathogen

ITB, Infections tracheobronchitis; *CAV-1,* canine adenovirus-1.

Diagnosis

I. History and clinical presentation
  A. Recent exposure to other dogs
  B. Acute onset of cough several days after exposure
II. Routine laboratory tests
  A. No abnormalities or nonspecific changes
  B. Neutrophilia ± left shift with some complicated infections or pneumonia
III. Thoracic radiography
  A. Indication depends on severity of clinical signs
  B. Moderate to severe disease
    1. Possibly abnormal lung patterns: interstitial, bronchointerstitial, or alveolar infiltrates
    2. Lung consolidation (rare)
  C. Helps rule out other causes of cough and dyspnea
IV. Other diagnostic aids
  A. In complicated cases, transtracheal wash or bronchoalveolar lavage may show neutrophilic exudate.
  B. Culture and sensitivity testing helps with choosing antibiotic therapy.
  C. Viral isolation and antibody titers are rarely indicated for mildly affected dogs.
  D. Acute phase and convalescent titers can distinguish canine influenza from other causes of infectious tracheobronchitis.
    1. Titers may be useful as an epidemiological tool.
    2. Paired titers are generally preferred over polymerase chain reaction (PCR) assays for influenza.

Differential Diagnosis

I. Other infections causing a cough: canine distemper; rickettsial, fungal, bacterial, or parasitic infections
II. Aspiration pneumonia
III. Collapsing trachea or bronchi
IV. Airway foreign body
V. Allergic tracheobronchitis
VI. Pulmonary edema: cardiogenic, noncardiogenic
VII. Pulmonary hemorrhage: trauma, coagulopathy

Treatment

I. Uncomplicated ITB
  A. Although it is typically a self-limiting disease, owners often request therapy.
  B. Paroxysmal coughing is treated with cough suppressants.
    1. Hydrocodone 0.25 mg/kg PO BID to QID
    2. Butorphanol 0.5 to 1.0 mg/kg PO BID to QID
    3. Contraindicated if pneumonia present
  C. Antibiotics, although not necessary, possibly prevent opportunistic infection.
    1. Doxycycline 10 mg/kg PO SID
    2. Chloramphenicol 40 to 50 mg/kg PO TID
    3. Amoxicillin/clavulanic acid 13.75 mg/kg PO BID
    4. Trimethoprim/sulfonamide 15 mg/kg PO BID
  D. Nebulized antibiotics (gentamicin 6 to 8 mg/kg diluted 1:5 to 1:10 in 0.9% saline) delivered by face mask SID may be useful for *B. bronchiseptica* infection.
  E. Rest the animal and isolate it from other dogs for at least 2 to 3 weeks.
II. Complicated ITB
  A. Intensive care may be required in an isolation ward.
  B. Antibiotic therapy, with bactericidal antibiotics, is started based on culture and sensitivity testing.
    1. Trimethoprim/sulfonamide 15 to 30 mg/kg IV/PO BID
    2. Amoxicillin/clavulanic acid 13.75 mg/kg PO BID
    3. Cefoxitin 22 mg/kg IV TID
    4. Ampicillin 10 to 20 mg/kg IV TID to QID or amoxicillin 20 mg/kg SC, PO plus enrofloxacin 2.5 to 10 mg/kg IM, PO BID
  C. Hydration with parenteral crystalloid solutions facilitates loosening of respiratory secretions.
  D. Consider inhalation therapy with saline, bronchodilator, and/or antibiotic nebulization.
  E. Supplemental oxygen may be indicated.

Monitoring and Prevention

I. Isolate animals until all clinical signs resolve.
II. Thoroughly clean and disinfect kennel facilities with dilute (1:32) bleach solution.
III. Adequate immunity prevents or lessens severity of the disease.
  A. Passive immunity
    1. Currently, all dogs are considered susceptible to canine influenza virus.
    2. Maternal immunity to other pathogens is variable.
    3. Unvaccinated puppies are at high risk for severe infections.
  B. Acquired immunity from natural infection
    1. Duration of immunity to viruses after exposure is unknown.
    2. At least 6 months of immunity occurs after *B. bronchiseptica* exposure (Bemis, 1992).
  C. Acquired immunity from vaccination
    1. Vaccination is available and suggested for canine parainfluenza virus (CPiV) and canine adenovirus-2 (CAV-2).
      a. They provide protection from clinical disease, although infection is still possible.
      b. Administer routine parenteral combination canine vaccines (CPiV and CAV-2) 2 to 3 times to puppies (3 weeks apart).
      c. CPiV and CAV-2 vaccines are administered again at 1 year and every 3 years thereafter.
    2. Vaccine is not yet available for canine influenza virus infection.
    3. Vaccination for *B. bronchiseptica* is considered optional.
      a. Many boarding facilities and canine competitions require current *B. bronchiseptica* vaccination.
      b. Both parenteral and intranasal vaccines can be effective.
      c. Duration of immunity is generally ≤1 year.
    4. Intranasal vaccines for CPiV and *B. bronchiseptica* are available.
      a. Quicker onset of local and systemic immunity with intranasal forms

b. No maternal antibody interference with intranasal vaccination
c. Mild upper respiratory signs possible after intranasal vaccination

IV. *B. bronchiseptica* is potentially a zoonotic risk for immunocompromised people.
V. There is no evidence of zoonosis associated with canine influenza virus infection.

FELINE UPPER RESPIRATORY INFECTION COMPLEX

Definition

I. Feline upper respiratory infection (URI) complex results from infection with one or more of a number of viral and bacterial pathogens.
II. URI is highly contagious and results in high morbidity and low mortality in infected cats.
III. A virulent variant of one cause of feline URI, feline calicivirus (FCV), results in systemic illness with high mortality (Hurley et al., 2004).

Causes

I. Multiple pathogens have been incriminated in the URI complex (Box 114-2).
II. URI develops from any of several single agents or may be a mixed infection, with most cases arising from feline herpesvirus 1 (FHV-1; feline rhinotracheitis) or FCV infection.
III. URI is most prevalent in group-housed or outdoor cats.
IV. Viral pathogens and *B. bronchiseptica* are spread by aerosolization, close contact, and/or fomites.
A. *Chlamydophila felis* is rarely spread by aerosolization.
B. Direct contact with infected secretions is most important for spread of all URI pathogens.
C. Virulent FCV is readily transmitted via fomites.
V. Many URI pathogens cause acute disease followed by latency with occasional recrudescence.
VI. Kittens and young cats are more often affected, but cats of any age are susceptible.
A. Respiratory disease severity is worse in kittens.
B. Systemic illness from virulent FCV is worse in adult cats.
C. Except for virulent FCV, vaccinations limit severity of signs.

Pathophysiology

I. Viral replication occurs primarily in oral, respiratory, and ocular epithelial tissues, causing direct damage and providing opportunity for secondary pathogens to colonize.
II. Each pathogen has particular propensities for certain tissue damage, thereby producing certain clinical signs (Gaskell et al., 2006).
III. Secondary infection with bacterial pathogens, including *Mycoplasma* spp., worsens tissue damage.
IV. Carrier states are common in cats infected with FHV-1, FCV, *B. bronchiseptica*, and *C. felis* (Helps et al., 2005).
A. The majority of cats infected with FHV-1 maintain latent infections.
1. Active infection may recrudesce years after initial infection.
2. Damage or inflammation in intranasal tissues may predispose to chronic rhinosinusitis.
3. Viral shedding of FHV-1 is intermittent in carrier cats.
B. Cats with FCV may either remain carriers or clear the infection after weeks to months
1. As many as 24% of healthy cats may be FCV carriers (Wardley et al., 1974).
2. Viral shedding of FCV is nearly continuous in carrier cats.

Box 114-2

Pathogens Incriminated in the Feline Upper Respiratory Infection Complex

Viruses	
Feline herpesvirus (FHV-1)	Causes inapparent carrier state with intermittent shedding; kittens typically infected by asymptomatic carrier queen
Feline calicivirus (FCV; formerly feline picornavirus)	Causes inapparent carrier state with continual shedding
Other Viruses	
Feline reoviruses	May contribute in some cases
Poxviruses	May cause mild upper respiratory signs in cats; rare virulent form possibly fatal
Bacteria	
Bordetella bronchiseptica	May be a primary or secondary pathogen; can be found in normal cats
Chlamydophila felis (formerly *Chlamydia psittaci* var. *felis)*	Obligate intracellular bacteria, associated with more ocular than respiratory symptoms
Staphylococcus spp., *Streptococcus* spp., *Pasteurella* spp., *Escherichia coli*	May be isolated primary cause but are most likely secondary, opportunistic pathogens
Mycoplasma spp.	Fastidious microbes lacking cell wall; a primary or secondary pathogen; can be found in normal cats

Clinical Signs

I. Signs depend on the pathogens involved, host immunity, and any opportunistic infections present.
II. The most common signs of uncomplicated URI are oculonasal discharge, conjunctivitis, lethargy, and anorexia with variable sneezing and fever.

A. FHV-1 infection is more likely to cause salivation and corneal disease (see Chapter 98).
B. FCV infection is most likely to cause oral ulcers; sneezing is a less prominent feature.
C. *Chlamydophila felis* infection is likely to cause severe conjunctivitis, sometimes as the only clinical sign.
D. *B. bronchiseptica* infection is more likely to cause coughing.

III. Complicated infections lead to pneumonia and other systemic signs.
A. Young cats and unvaccinated cats are particularly susceptible to complications of URI.
B. Secondary bacterial infections worsen disease severity.
C. *B. bronchiseptica* or secondary bacterial infections may lead to bronchopneumonia.
D. Infection with *Mycoplasma* spp. and FCV is sometimes associated with lameness.
E. Virulent FCV is rare, but it causes systemic and respiratory signs.
1. Clinical signs include the following:
a. Fever
b. Facial, limb, and ventral edema
c. Ulcers, sores, and crusting of the skin and mucus membranes
2. Mortality associated with virulent FCV is approximately 50% (Hurley and Sykes, 2003).
3. Mortality from virulent FCV is higher in adult cats than kittens.

Diagnosis

I. History and clinical signs are usually highly suggestive of URI.
A. Cats often have a history of recent exposure to other cats, recent stress, or concurrent immunosuppressive therapy or disease.
B. Clinical signs may suggest the specific agents involved.

II. Routine laboratory tests are generally inconclusive; however, a neutrophilia ± a left shift occurs with complicated infections and pneumonia.

III. Thoracic radiography is not indicated unless clinical signs of pneumonia are present.

IV. Pathogen-specific diagnostic tools are employed on occasion, particularly in cattery situations.
A. Conjunctival scrapings, oropharyngeal swabs, and transtracheal washes provide diagnostic specimens, with separate swabs and different transport media required for viral versus bacterial culture.
B. Various tests exist for FHV-1 and FCV.
1. The viruses may be isolated in cell culture or detected by fluorescent antibody techniques; however, false negatives occur, especially with chronic FHV-1 infection.
2. PCR assay is a more sensitive way to detect infection, but test results may be positive in healthy cats.
3. Serological testing is generally not useful because of the presence of antibody owing to vaccination or natural exposure.
4. Virulent FCV infection is confirmed by genetic sequencing from multiple infected cats.
C. *B. bronchiseptica* and *Mycoplasma* spp. may be cultured from both infected and healthy cats.
D. *C. felis* is identified by enzyme-linked immunosorbent assay (ELISA), cell culture isolation, or intracellular inclusion bodies identified on cytological examination.

Differential Diagnosis

I. Uncomplicated disease
A. Exposure to irritant or caustic substances
B. Allergic bronchitis
C. Nasopharyngeal, tracheal foreign body
D. Cryptococcal infection

II. Complicated disease
A. Other infectious pneumonias: hematogenous bacterial, fungal, protozoal, parasitic
B. Aspiration pneumonia
C. Heartworm disease
D. Neoplasia
E. Systemic vasculitis

Treatment

I. Uncomplicated URI
A. Mainly supportive with routine nursing care
1. Isolate symptomatic cats and disinfect food bowls and all potential fomites.
2. Ensure adequate water and food intake.
a. Entice cats to eat by heating food or offering pungent foods like tuna.
b. Force-feed or tube feed if necessary.
3. Provide adequate airway hydration to facilitate loosening of respiratory secretions.
a. Parenteral fluids are sometimes required—usually subcutaneously.
b. Environmental humidification eases breathing and loosens secretions.
B. Antibiotics to prevent or treat secondary infections
1. Amoxicillin 10 to 20 mg/kg PO TID or amoxicillin/clavulanic acid 13.75 mg/kg PO BID
2. Doxycycline 5 mg/kg PO BID
a. Treatment of choice for *C. felis* and *Mycoplasma* spp.
b. Followed with water to avoid esophageal erosions and stricture
C. Ocular therapy (see Chapter 98)
1. Clean away eye secretions TID to QID.
2. Consider idoxuridine (1 drop OU 4 to 6 times daily) for severe or chronic FHV-1 corneal disease.
3. Oxytetracycline ointment is applied TID for conjunctivitis associated with *C. felis* or *Mycoplasma* spp.
D. Adjunctive therapy for chronic FHV-1
1. L-Lysine 250 mg PO BID
2. Human interferon-α 30 U PO SID on alternative weeks

II. Complicated URI

A. Cats with pneumonia may require intensive care, isolation, intravenous crystalloid fluid therapy, and supplemental oxygen.
B. Bacteriocidal antibiotics are chosen based on culture and sensitivity testing.
   1. Trimethoprim/sulfonamide 15 to 30 mg/kg IV, PO BID
   2. Amoxicillin/clavulanic acid 13.75 mg/kg PO BID
   3. Cefoxitin 22 mg/kg IV TID
   4. Ampicillin 10 to 20 mg/kg IV TID to QID or amoxicillin 20 mg/kg SC, PO BID plus enrofloxacin 2.5 mg/kg PO SID to BID
C. Consider doxycycline 5 mg/kg PO, IV BID for *Mycoplasma* spp.
D. Consider inhalation therapy with saline, a bronchodilator, or antibiotic nebulization.
   1. Plain saline nebulization TID to QID may loosen secretions.
   2. Gentamicin (diluted 1:5 to 1:10 in 0.9% saline) can be nebulized by face mask at 6 to 8 mg/kg SID.
   3. Albuterol may be given SID to QID by metered dose inhaler (90 μg/actuation at 1 to 2 actuations) or by nebulization through a face mask (0.5 mL of a 2.5-mg/3-mL solution in 3.5 mL saline).

Monitoring and Prevention

I. Husbandry is important in preventing the spread of URI.
   A. Isolate cats with URI while they are clinically ill, but realize that shedding may persist or recur intermittently.
   B. Isolate recovered cats from unvaccinated or immunocompromised cats and kittens.
   C. If virulent FCV is suspected, facilities must be closed to unexposed cats.
      1. Virulent FCV is readily transmitted by fomites; therefore the feline pets of exposed clinic personnel are at risk.
      2. Isolation of cats and disinfection of premises must be stringent.
   D. Thoroughly clean and disinfect cattery facilities.
      1. Most agents, including virulent FCV, are effectively inactivated by dilute (1:32) bleach solutions.
      2. *C. felis* is inactivated by quaternary ammonium compounds.
II. Adequate immunity may prevent disease or reduce its severity.
III. Passive immunity with maternal antibodies has a variable duration (Wills et al., 1988; Jacobs et al., 1993; Coutts et al., 1996).
   A. FHV: 2 to 10 weeks
   B. FCV: 10 to 14 weeks
   C. *C. felis:* 9 to 12 weeks
   D. *B. bronchiseptica:* 2 to 6 weeks
   E. Protection unpredictable: unvaccinated kittens probably at risk
IV. Acquired immunity is achieved following natural infection or vaccination.
   A. Natural infection
      1. FHV-1 and FCV result in carrier states with possible periods of disease recrudescence; immunity after natural infection is not considered protective.
      2. Some short-term immunity to *C. felis* infection exists, but it is unknown whether effective immunity develops to *B. bronchiseptica* and *Mycoplasma* spp.
   B. Vaccination
      1. Vaccines are available for FHV-1, FCV, *C. felis*, and *B. bronchiseptica*.
      2. FHV and FCV vaccines are available as a modified live virus (MLV) form for parenteral use, intranasal use, or as killed vaccines for parenteral use (see Table 112-3).
         a. Initially 2 to 3 vaccinations are given 2 to 3 weeks apart in kittens, repeated at 1 year of age, and then given every 3 years.
         b. Vaccines are better suited to limiting disease than preventing all infections.
         c. Parenteral MLV vaccines may produce a brief period of mild respiratory signs.
         d. Intranasal MLV vaccines induce rapid immunity and often induce mild clinical signs.
         e. Killed vaccines are used in pregnant queens or retrovirus-positive cats.
         f. Current FCV vaccines do not offer protection from virulent FCV.
      3. Vaccination for *C. felis* protects against disease for 1 year, but vaccination is not routinely recommended or necessary.
      4. Intranasal vaccination for *B. bronchiseptica* is available, but not routinely recommended or necessary.
V. The zoonotic potential exists for development of *C. felis* and *B. bronchiseptica* in immunocompromised people.

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CHAPTER 115

Rickettsial Infections

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EHRLICHIOSIS, ANAPLASMOSIS AND NEORICKETTSIOSIS

Feline Ehrlichiosis

Laia Solano-Gallego

Definition and Causes

Ehrlichiosis, anaplasmosis and neorickettsiosis are clinical syndromes induced by *Ehrlichia canis*, *Anaplasma phagocytophilum,* and *Neorickettsia risticii*, respectively.

Pathophysiology

I. Epidemiology
   A. Most affected cats are >2 years of age and are domestic shorthair cats.
   B. Intracytoplasmic morulae in leukocytes are detected in cats in multiple countries.
   C. DNA consistent with *E. canis* and *A. phagocytophilum* has been sequenced or amplified from tissues of naturally infected cats.
   D. Antibodies (Ab) against *N. risticii, E. canis* and *A. phagocytophilum* occur in sera of healthy and ill cats in multiple countries.

II. Transmission
   A. The method of transmission is currently unknown.
   B. *Haemophysalis leachi* and *Ixodes ricinus* ticks are identified on some infected cats.

III. Pathogenesis
   A. The pathogenesis is currently unknown.
   B. Owing to clinical similarities in cats and dogs with ehrlichiosis, anaplasmosis, and neorickettsiosis, the pathogenesis is likely similar.
   C. Experimental infections have certain characteristics:
      1. Morulae of *N. risticii* develop in mononuclear cells (Dawson et al., 1988).
      2. Morulae of *A. phagocytophilum* develop in neutrophils and eosinophils (Lewis et al., 1975).
      3. No *E. canis* DNA or Abs have been detected in experimentally inoculated cats (Lappin and Breitschwerdt, 2006).

Clinical Signs

I. Common signs include fever, inappetence, lethargy, weight loss, hyperesthesia, joint pain and/or polyarthritis, pale mucous membranes, splenomegaly, dyspnea, and lymphadenomegaly.

II. Concurrent diseases may include *Mycoplasma haemofelis, Candidatus* Mycoplasma haemominutum, *Cryptococcus neoformans*, feline leukemia virus (FeLV), feline immunodeficiency virus (FIV), and lymphosarcoma.

III. An epidemiological comparison of cats that are seropositive and seronegative for *Ehrlichia* spp. (Stubbs et al., 2000) revealed the following:
   A. Cats with *E. canis* Abs were more likely to have ocular discharge, monoclonal gammopathy, or polyarthritis.
   B. Cats with *N. risticii* Abs had more vomiting than seronegative cats.
   C. Cats with *N. risticii* and/or *E. canis* Abs were more likely to have ocular discharge with uveitis than seronegative cats.

IV. Cats experimentally infected with *N. risticii* occasionally developed fever, lethargy, lymphadenopathy, anorexia, and diarrhea (Dawson et al., 1988).

Diagnosis

I. Clinical pathologic abnormalities vary.
   A. Regenerative or nonregenerative anemia
   B. Leukocytosis (neutrophilia, lymphocytosis, monocytosis) or leukopenia
   C. Intermittent thrombocytopenia, hyperglobulinemia
   D. Rarely, polyclonal or monoclonal gammopathy (Stubbs et al., 2000)

II. Antibodies may be detected, but do not necessarily correlate to presence of clinical disease.

III. Some cats with positive polymerase chain reaction (PCR) assays are seronegative.

IV. Tentative diagnosis is based on a combination of serological results, compatible clinical signs, exclusion of other causes of the clinical signs, and response to treatment.

V. Definitive diagnosis is based on culture of the agent from blood or positive PCR assay.

Differential Diagnosis

I. Other infectious causes of fever, anemia, or splenomegaly
   A. FeLV-associated diseases
   B. Mycoplasmosis, bartonellosis
   C. Babesiosis, hepatozoonosis
   D. Plague, tularemia

II. Other causes of polyarthritis (see Chapter 80)

A. Feline calicivirus
B. Septic arthritis
C. Immune-mediated arthritis
D. L-form disease

III. Neoplasia, especially lymphosarcoma

Treatment

I. Doxycycline 5 to 10 mg/kg PO SID to BID is given as liquid or intact tablet for ≥28 days, with tablets followed by water to avoid esophagitis.
II. Tetracycline 15 mg/kg PO TID is given for 21 days, with monitoring for fever and anorexia.

Monitoring and Prevention

I. A positive therapeutic response is usually noted within 3 days.
II. Although it is unknown whether infection of cats is arthropod-borne, vector control is highly recommended.
III. Cats may be potential reservoirs for infection of vectors, but direct zoonotic transfer is unlikely.

Canine Ehrlichiosis

Laia Solano-Gallego

Definition and Causes

I. Ehrlichiosis, anaplasmosis and neorickettsiosis are clinical syndromes induced by *Ehrlichia* spp., *Anaplasma* spp., and *Neorickettsia* spp., respectively.
II. Geographical distribution and vector transmission are summarized in Table 115-1.

Pathophysiology

I. These species are obligate intracellular parasites that replicate in host cells, forming clusters of organisms called *morulae.*
II. They induce leukocyte and platelet abnormalities, plasma cell infiltration of parenchymal organs, and antigen–Ab complex formation.
III. Clinical course is variable, depending on the infecting species.
  A. In acute *E. canis* infection, clinical signs are possible, but asymptomatic infections also occur.
  B. Because of serological cross-reactivity (see Table 115-1), it is difficult to determine whether clinical conditions previously attributed to *E. canis* were actually *E. canis, E. ewingii*, or *E. chaffeensis* infections.
  C. Clinical signs attributed to *A. phagocytophilum* occur with acute or chronic infections.
  D. It is not known whether signs attributed to *N. risticii* occur during acute or chronic infection.
  E. Spontaneous resolution, resolution with treatment, or persistent subclinical infection may occur.
  F. Subclinical infections have a variable duration and may last for years.
    1. Organisms persist (primarily in spleen) and Abs are produced.
    2. Spontaneous clearance of organisms is possible.
IV. *Anaplasma platys* infection has a more predictable course.
  A. Initial thrombocytopenia occurs from platelet injury by replicating organisms.
  B. Platelet counts return to normal within 3 to 4 days after parasitemia resolves.
  C. Cyclic thrombocytopenia can occur every 1 to 2 weeks and immune-mediated mechanisms may cause subsequent thrombocytopenic episodes.
  D. Infection often resolves spontaneously.
  E. More virulent forms reportedly occur outside of the United States, causing clinical signs similar to those from the other species.
  F. Coinfection with other vector-transmitted diseases may result in more severe clinical signs.

Clinical Signs

I. *E. canis* infections (not *A. platys* infections)
  A. Coinfection with other tick-borne agents may alter the clinical presentation.
  B. Signs vary with the phase of disease.
    1. Fever, lethargy, anorexia, weight loss
    2. Lymphadenomegaly, splenomegaly, peripheral edema
    3. Petechiae, ecchymoses, epistaxis
    4. Ocular signs: anterior uveitis, chorioretinitis, retinal hemorrhages, papilledema, bullous retinal detachments, possible acute blindness
    5. Neurological signs from inflammation or bleeding: seizures, ataxia, paresis, vestibular disease, anisocoria, intention tremors, hyperesthesia
    6. Musculoskeletal signs: lameness, myalgia, muscle atrophy, joint swelling, myositis
II. Factors affecting severity
  A. Host age, breed (German shepherd dogs predisposed), immune status (Shaw et al., 2001)
  B. *Ehrlichia* spp., *Anaplasma* spp., and *Neorickettsia* spp. and strain involved
  C. Coinfection with other pathogens
III. Classification
  A. Originally divided into monocytic and granulocytic forms, the diseases are now classified by genogroup (see Table 115-1).
  B. It is difficult to attribute one set of clinical signs to any genogroup or forms.
  C. Natural *E. canis* and *E. chaffeensis* infections may cause more severe disease than other species.
  D. Experimental *E. chaffeensis* infections produce only mild clinical signs (Dawson and Ewing, 1992; Breitschwerdt et al., 1998b).
  E. *E. ewingii* and *A. phagocytophilum* may be more likely to cause mild clinical signs.
  F. *E. ewingii* and *A. phagocytophilum* may be more likely to cause polyarthritis (Goodman et al., 2003).
  G. *N. risticii* var. *atypicalis* may cause severe disease (Kakoma et al., 1994).
  H. Coinfection occurs and may result in more severe clinical signs.

TABLE 115-1

Classification of *Ehrlichia* spp., *Anaplasma* spp., and *Neorickettsia* spp. by Genogroup

ORGANISM	GEOGRAPHIC DISTRIBUTION	VECTORS	CELLS INFECTED	HOSTS	CROSS-REACTIVITY WITH *EHRLICHIA CANIS*
Monocytotropic, Genogroup/Serogroup I					
Ehrlichia canis	Worldwide	*Rhipicephalus sanguineus, Dermacentor variabilis*	Mononuclear cells	Dogs, wild canids, cats, humans (Venezuela)	NA
Ehrlichia chaffeensis	United States, Asia	*Amblyomma americanum, Amblyomma testudinarium, Dermacentor variabilis, Ixodes ovatus, Haemophysalis* spp.	Mononuclear cells, neutrophils	Dogs, humans, goats	3
Ehrlichia ruminatum	Sub-Saharan Africa	*Amblyomma hebraeum*	Mononuclear cells, endothelial cells, neutrophils	Cattle, sheep, goats, dogs	2
Monocytotropic, Genogroup/Serogroup III					
Neorickettsia risticii	United States, Canada	Trematode larvae	Mononuclear cells, enterocytes, mast cells	Snails (reservoir), dogs (subsp. *atypicalis*), horses, cats	0 to 1
Neorickettsia helminthoeca	Northwestern United States, southwestern Canada	Trematode	Mononuclear cells	Fish (reservoir), dogs	2
Granulocytotropic, Genogroup/Serogroup I					
Ehrlichia ewingii	United States, Africa	*Amblyomma americanum,* possibly *Dermacentor variabilis, Rhipicephalus sanguineus*	Neutrophils, eosinophils deer	Dogs, humans, white-tailed	3
Granulocytotropic, Genogroup/Serogroup II					
Anaplasma phagocytophilum	United States, Europe, Africa, Asia	*Ixodes scapularis, Ixodes ricinus, Ixodes pacificus, Ixodes persulcatus, Rhipicephalus sanguineus*	Neutrophils, eosinophils	Humans, dogs, cats, horses, sheep, goats	0 to 1
Thrombocytotropic, Genogroup/Serogroup II					
Anaplasma platys	Unites States, Australia, southern Europe, South America, Asia, Middle East, Africa	Possibly *Rhipicephalus sanguineus*	Platelets	Dogs	0

NA, Not applicable; *0,* no cross-reactivity; *1,* weak cross-reactivity; *2,* low cross-reactivity; *3,* high cross-reactivity.

Diagnosis

I. Hematological and coagulation abnormalities
  A. Thrombocytopenia common
  B. Nonregenerative (most common) or regenerative anemia
  C. Leukopenia, especially neutropenia
  D. Pancytopenia: usually in severe disease
  E. Possible large granular lymphocytosis
  F. Prolonged activated clotted time
  G. Prolonged bleeding time, especially with platelet dysfunction
  H. Prolonged prothrombin and partial thromboplastin times uncommon
II. Serum biochemistry changes
  A. Hyperproteinemia: monoclonal or polyclonal gammopathy with hypoalbuminemia, hyperviscosity
  B. Increased alanine transaminase, alkaline phosphatase (ALP) activities
  C. Possible azotemia
III. Urinalysis results
  A. Proteinuria
  B. Decreased urine specific gravity
  C. Possible bacteriuria: secondary infections in immunocompromised dogs
IV. Cerebrospinal fluid (CSF) analysis: increased protein; mononuclear, lymphocytic, neutrophilic pleocytosis
V. Bone marrow cytological findings: hyperplastic or hypoplastic cell lines, plasma cell infiltration
VI. Arthrocentesis: neutrophilic inflammation
VII. Organism identification
  A. Blood buffy coat and bone marrow smears or tissue aspirates (e.g., lymph node, spleen)
    1. Morulae are occasionally seen in monocytes, neutrophils, eosinophils, and platelets (see Table 115-1).
    2. False-negatives occur owing to a low number of organisms.
  B. Morulae rarely seen in joint fluid, CSF
  C. PCR assays using genus- or species-specific primers: spleen more sensitive than blood with *E. canis*
VIII. Serological testing
  A. Indirect immunofluorescent antibody (IFA) testing is the most common and best assay.
  B. Other techniques exist, including enzyme-linked immunosorbent assay (ELISA) and Western immunoblotting.
  C. Antibodies are detected 2 to 7 days postinfection, peak at 2 to 5 months, and may persist for long periods.
  D. No serological test exists for *E. ewingii,* but infected animals show cross-reactivity with *E. canis* antigens.
  E. Positive titers occur in some clinically healthy dogs in endemic areas.
  F. Serological cross-reactivity among different *Ehrlichia* spp., *Anaplasma* spp., and *Neorickettsia* spp. pose problems in interpretation (see Table 115-1).
  G. Perform acute and convalescent tests (2 to 4 weeks after initial presentation); a fourfold increase in titers indicates acute infection.

Differential Diagnosis

I. Rocky mountain spotted fever (RMSF)
II. *Leishmania infantum*
III. *Bartonella* spp.
IV. Other causes of thrombocytopenia (see Chapter 67) and pancytopenia
V. Other causes of lymphadenopathy and splenomegaly (see Chapters 69 and 70)

Treatment

I. Standard treatment: doxycycline 10 mg/kg PO, IV SID to BID for 4 to 6 weeks
  A. Shorter treatment with doxycycline or tetracycline (10 to 21 days) may be used for *E. ewingii* and *A. phagocytophilum* infections.
  B. If not certain of infecting species, treat for 4 to 6 weeks
II. Tetracycline 22 mg/kg PO TID for 28 days
III. Oxytetracycline 25 mg/kg PO, IV TID for 28 days
IV. Minocycline 10 mg/kg PO, IV BID for 28 days
V. Chloramphenicol 15 to 25 mg/kg PO, SC, IV TID for 28 days
VI. Imidocarb dipropionate 5 mg/kg IM once; repeat in 2 to 3 weeks, with cholinergic side effects treated with atropine
VII. Supportive care: IV fluids, blood transfusions

Monitoring and Prevention

I. Dogs treated in the acute phase usually respond within 72 hours.
II. Resolution of thrombocytopenia usually indicates a good response to therapy.
III. Platelet counts begin to increase within 48 hours and are commonly normal within 14 days.
IV. Chronically infected dogs often need long-term therapy and their response may be poor or incomplete.
V. Complete immunity does not occur in recovered animals and cross-protection probably does not occur.
VI. Titers often decline after treatment.
VII. Vector control is very important.
VIII. Prophylactic treatment with doxycycline at 3 mg/kg PO SID may reduce infections but can also result in antimicrobial resistance (Davoust et al., 2005).

ROCKY MOUNTAIN SPOTTED FEVER

Nolie K. Parnell

Definition and Cause

I. RMSF is a tick-borne disease of dogs that occurs throughout the United States.
II. The etiologic agent is *Rickettsia rickettsi,* an obligate intracellular organism in the family Rickettsiaceae.

Pathophysiology

I. Epidemiological findings
  A. Reported in all lower continental states except Maine

B. Predominantly seen in the southeastern states
C. Also reported in Canada, Mexico, Central America, and South America

II. Transmission
A. Ticks are the natural hosts, reservoirs, and vectors, and are infected by horizontal transmission either transtadially or transovarially.
B. *Dermacentor variabilis* (American dog tick) is the primary vector in the eastern United States, and *Dermacentor andersoni* (wood tick) is important in the western United States.
C. *Rhipicephalus sanguineus* (brown dog tick) was recently implicated as a vector for *R. rickettsii* (Demma et al., 2005).

III. Pathogenesis
A. *R. rickettsii* replicates in endothelial cells of small vessels, causing vasculitis and activation of the complement and coagulation systems.
B. Increased vascular permeability ensues, with plasma loss; hypotension; and subcutaneous, pulmonary, and sometimes cerebral edema.
C. Shock, multiple organ failure, and disseminated intravascular coagulopathy occur in the terminal stages.

Clinical Signs

I. Subclinical infections can occur.
II. Common signs include fever, lethargy, and anorexia.
III. Cutaneous edema, vesicles, macules, dermal necrosis, petechiae, and ecchymoses may occur.
IV. Neurological signs include central vestibular deficits (most common), seizures, and spinal hyperesthesia.
V. Other signs include the following:
A. Arthralgia
B. Ocular and nasal discharge: serous to serosanguineous
C. Retinal hemorrhages
D. Cough, dyspnea
E. Orchitis (Ober et al., 2004)

Diagnosis

I. Early diagnosis is important to reduce mortality.
II. Known tick exposure can be as low as 17% (Gasser et al., 2001).
III. Occurrence is highest from April through September.
IV. Hematological and clotting abnormalities are common.
A. Thrombocytopenia, anemia
B. Leukopenia early: predominately neutropenia
C. Leukocytosis as illness progresses: neutrophilia with a left shift
D. Prolonged clotting times, increased fibrin degradation products
V. Serum biochemistry findings are nonspecific.
A. Possibly no abnormalities
B. Increased liver and muscle enzyme activities
C. Electrolyte abnormalities
D. Hypoalbuminemia, hypercholesterolemia
E. Possibly azotemia
VI. Urinalysis may show proteinuria, hematuria, and bilirubinuria.
VII. CSF analysis may show normal to slightly increased protein, and neutrophilic pleocytosis.
VIII. Synovial fluid analysis often shows an increased leukocyte count (nondegenerate neutrophils).
IX. A mild interstitial pattern is common on thoracic radiographs.
X. Several diagnostic tests are available.
A. Indirect IFA, microimmunofluorescence, latex agglutination, ELISA tests
1. Immunoglobulin (Ig) M is detectable in the first 2 weeks, diminishes after 1 month, and becomes undetectable after 80 days.
2. IgG is detectable in 2 to 3 weeks, peaks at 1 to 2 months, and usually decreases by 4 to 5 months.
a. A single, very high IgG titer (>1:1024) supports the diagnosis.
b. Measurement of acute and convalescent IgG titers with a fourfold increase is diagnostic.
3. Cross-reaction with other nonpathogenic spotted fever group rickettsiae can occur.
B. Direct fluorescent antibody testing of biopsies of mucosal or skin lesions
C. Possible increased antiplatelet antibody titers
D. PCR of blood or tissues

Differential Diagnosis

I. Ehrlichiosis, anaplasmosis, borreliosis
II. Other causes of vasculitis and fever
III. Other causes of anterior and posterior uveitis (see Chapters 99 and 102)
IV. Other causes of seizures and neurologic signs (see Chapters 22 and 23)

Treatment

I. Antibiotics are given for 10 to 14 days.
A. Doxycycline 5 to 10 mg/kg PO, IV BID
B. Tetracycline 22 to 30 mg/kg PO, IV TID
C. Chloramphenicol 25 to 30 mg/kg PO, SC, IM, IV TID
D. Enrofloxacin 3 mg/kg PO, IM BID
II. Supportive care is also provided.
A. Intravenous colloid or cautious use of crystalloid solutions as needed
B. Transfusions as indicated
C. Judicious use of prednisone for immune-mediated complications (Breitschwerdt et al., 1997)

Monitoring and Prevention

I. A rapid response (24 to 48 hours) to therapy is common.
II. Delayed diagnosis and presence of severe disease delays the response.
III. Delayed recovery is more common with organ failure or central nervous system damage.
IV. Immunity to RMSF probably occurs for at least 3 years after recovery.
V. Tick control is important.

HEMOTROPIC MYCOPLASMOSIS

Laia Solano-Gallego

Feline Hemoplasmosis

Definition and Causes

I. The disease is caused by three variants of gram-negative, epicellular parasites of feline erythrocytes (red blood cell [RBC]).
   A. *Mycoplasma haemofelis (Mhf):* previously *Haemobartonella felis* large variant (Ohio strain)
   B. *Candidatus* Mycoplasma haemominutum *(Mhm):* previously *H. felis* small variant (California strain)
   C. *Candidatus* Mycoplasma turicensis *(Mht):* novel hemoplasma recently discovered in Swiss cats

II. All organisms are considered species-specific, do not survive outside the host, and culture attempts have been unsuccessful.

Pathophysiology

I. Epidemiology
   A. *Mhf* and *Mhm* are reported in clinically healthy and ill cats in North America, Europe, Japan, and Australia.
   B. A higher prevalence of *Mhf* infection occurs in anemic cats from North America and Spain, whereas prevalence of *Mhm* infection is similar between anemic and nonanemic cats (Jensen et al., 2000; Criado-Fornelio et al., 2003).
   C. Prevalence of coinfection with *Mhf* and *Mhm* is low.
   D. *Mht* has been detected by PCR in 1% of ill cats, and healthy cats have been PCR-negative in Switzerland (Willi et al., 2005, 2006).
   E. Natural hemoplasma infections are more likely in male, outdoor, older, and mixed-breed cats (Tasker et al., 2003, 2004; Willi et al., 2006).

II. Transmission
   A. *Mhf* is experimentally transmitted by IV, intraperitoneal, and oral inoculation of blood.
   B. *Mhm* and *Mht* are experimentally transmitted by IV inoculation of blood.
   C. *Ctenocephalides felis* transmission of *Mhf,* but not *Mhm,* via hematophagous activity is documented.
   D. Cat-to-cat transmission may occur by biting.
   E. Transmission from clinically ill queens to kittens may occur in utero, during parturition, or via nursing.

III. Pathogenesis
   A. RBC destruction via immune-mediated extravascular erythrophagocytosis
   B. Minimal direct RBC injury
   C. *Mhf* more pathogenic than *Mhm* or *Mht*
      1. One third of *Mhf*-infected cats die if not treated.
      2. Cats that recover from acute illness remain infected for months to years, if not for life.

Clinical Signs

I. Subclinical infection, mild anemia, or severe hemolytic anemia may occur (Messick, 2004).

II. Concomitant diseases or infections (e.g., neoplasia, FeLV) that modify the immune system, and stressful conditions can activate subclinical hemoplasma, resulting in clinical disease.

III. With *Mhf,* clinical disease occurs in immunocompetent and immunosuppressed naturally-infected cats.
   A. Hemolytic anemia: pale mucous membranes, tachypnea, lethargy, inappetence, weakness, icterus, dehydration, occasional splenomegaly
   B. Weight loss
   C. Intermittent fever: chronically infected cats

IV. With *Mhm,* subclinical infections or mild clinical signs occur in experimentally infected cats (Foley and Pedersen, 2000).
   A. Mild fever may occur.
   B. It is more often common in sick cats, but it is unclear whether signs are related to *Mhm* infection or to concomitant diseases.

V. With *Mht,* mild to severe hemolytic anemia occurs in ill or immunosuppressed cats (Willi et al., 2005, 2006).

Diagnosis

I. Hematological findings
   A. Regenerative anemia (normochromic or hypochromic) with polychromasia, macrocytosis, aggregate reticulocytosis
   B. Nonregenerative anemia: unusual
   C. Positive Coombs' test: common
   D. Possible neutrophilia or monocytosis

II. Serum biochemistry: possible hyperbilirubinemia, increased alanine aminotransferase (ALT) or ALP activity

III. Urinalysis: possible bilirubinuria

IV. Demonstration of organisms on RBCs
   A. Blood film examination result is falsely negative about half the time, especially with chronic infections.
   B. If the cat is cytologically negative, make a blood smear without ethylenediamine tetraacetic acid (EDTA) anticoagulant and consider PCR testing.
   C. Acridine orange labeling is more sensitive, but requires a fluorescence microscope.

V. PCR assay
   A. Test of choice because of its higher sensitivity
   B. Able to determine the infecting species

VI. Interpretation of test results
   A. Positive test results document infection, not clinical illness.
   B. Demonstration of organisms or a positive PCR test in a clinically ill cat indicate the need for treatment.

Differential Diagnosis

I. Other causes of hemolytic anemia
   A. *Cytauxzoon felis, Babesia* spp., bacterial septicemia
   B. Primary immune-mediated hemolytic anemia (IMHA)
   C. Secondary IMHA

II. Other infectious, neoplastic, and immune-mediated causes of fever and icterus

III. FeLV, FIV infections

Treatment

I. Because mycoplasmosis and primary IMHA are difficult to differentiate, treat cats with severe, regenerative anemia with antibiotics followed by glucocorticoids.
   A. Oxytetracycline 22 mg/kg PO TID for 21 days
   B. Doxycycline 2.5 to 5 mg/kg PO BID to SID for 14 to 21 days
      1. Preferred, fewer side effects
      2. Given as liquid or pills, followed with water to avoid esophagitis
   C. Enrofloxacin 5 mg/kg PO SID for 14 days; efficacy equals doxycycline, but blindness possible (Dowers et al., 2002)
II. Treatment does not eliminate *Mhf* or *Mhm* infections, but doxycycline may eliminate *Mht* infection.
III. If autoagglutination is evident, cautiously use prednisolone 1 to 2 mg/kg PO BID for the first 7 days or until autoagglutination is no longer evident.
IV. Administer supportive care, including IV fluids and blood transfusions as indicated.
V. Treatment of healthy cats infected with *Mhf* and *Mhm* may not be indicated as no drug has been shown to clear the organisms.
VI. Consider treating healthy *Mht* infected cats because clearance of the organism is reported after therapy, and immunosuppression or stress in infected cats may lead to severe, acute hemolysis.

Monitoring and Prevention

I. Monitor blood count SID to QOD until microagglutination resolves and hematocrit is normal.
II. Warn the owner that the disease can recur from recrudescence or reinfection.
III. The prognosis is generally good for immunocompetent cats.
IV. Control potential arthropod vectors such as fleas.
V. Keep cats indoors to avoid vectors and fighting.
VI. Use PCR assays to screen cats used as blood donors.

Canine Hemoplasmosis

Laia Solano-Gallego

Definition and Causes

I. *Mycoplasma haemocanis (Mhc)* is a rare cause of anemia in dogs.
II. Clinical relevance of a novel hemotropic *Mycoplasma (Candidatus* M. haemoparvum *[Mhp]),* recently detected in dogs and molecularly similar to *Mhm* is not known (Sykes et al., 2005; Kenny et al., 2004).

Pathophysiology

I. Epidemiological findings
   A. Dogs worldwide are likely infected.
   B. *Mhp* and/or *Mhc* have been detected in dogs in France.
   C. *Mhc, Mhp,* and *Mhm* have been detected by PCR in dogs in the United States (Sykes et al., 2006).
II. Transmission of *Mhc*
   A. *Rhipicephalus sanguineus*
   B. Blood transfusion, contaminated equipment
   C. Ingestion of infected blood
III. Pathogenesis of *Mhc*
   A. Organism attaches to RBC surface, distorting its shape.
   B. Lysis of the RBC may result.

Clinical Signs

I. Splenectomized or immunocompromised dogs are more likely to develop clinical signs of *Mhc.*
II. Possible signs include the following:
   A. Pale mucous membranes
   B. Lethargy, anorexia, icterus
   C. Death in severe infections

Diagnosis

I. Hematological findings with *Mhc* infection
   A. A regenerative anemia occurs within 1 to 2 days with constant parasitemia.
   B. A slow onset (2 to 3 weeks) regenerative anemia occurs with relapsing parasitemia.
   C. Severity of the anemia varies.
II. Urinalysis: possible bilirubinuria
III. Organism identification
   A. Chains of organisms on RBC surfaces
   B. PCR assay

Treatment

I. Antiparasiticidal treatment (when necessary) includes the following:
   A. Doxycycline 5 mg/kg PO BID for 21 days
   B. Tetracycline 20 mg/kg PO TID for 21 days
   C. Oxytetracycline 20 mg/kg PO TID for 21 days
II. Blood transfusions and other supportive care are administered as needed.

Monitoring and Prevention

I. Dogs that have recovered from clinical disease are persistently infected.
II. Clinical signs may recur with subsequent stress or other illnesses.
III. Tick control is important.
IV. Screen dogs used as blood donors via PCR assays.

SALMON POISONING DISEASE

Nolie K. Parnell

Definition and Cause

I. Salmon poisoning is a mild to severe (fatal) gastrointestinal (GI) or systemic disease of wild (e.g., coyote, fox) and domestic canids.
II. Elokomin fluke fever is nearly identical but associated with less mortality.
III. The etiologic agent is *Neorickettsia helminthoeca.*

Pathophysiology

I. Epidemiological findings
  A. It occurs primarily from northern California to central Washington and is also reported in British Columbia (Vancouver Island).
  B. The trematode vector *Nanophyetus salmincola* harbors the rickettsia throughout its life cycle and infects salmonid fish.
II. Life cycle
  A. Dogs ingest *N. helminthoeca*–infected metacercariae in raw fish, and the metacercariae mature in 5 to 6 days.
  B. The adult stage attaches to intestinal mucosa, and *N. helminthoeca* are released via unknown mechanisms.
  C. The agent enters monocytes and macrophages; migrates to the lymph nodes, spleen, brain, liver, and lungs; and causes severe inflammation and edema of the intestines.
  D. Although mild intestinal epithelial inflammation is possible without systemic signs, severe signs and death may occur.

Clinical Signs

I. Acute, transient fever (40° to 42° C) followed by hypothermia within 1 week
II. Moderate to marked anorexia, lethargy, vomiting, diarrhea (watery, yellowish, blood tinged), weight loss
III. Serous ocular and nasal discharge
IV. Lymphadenomegaly

Diagnosis

I. Exposure to endemic area
II. Hematological findings: thrombocytopenia, lymphopenia, eosinophilia, leukopenia followed by leukocytosis
III. Serum biochemistry results: increased ALP activity, hypoalbuminemia
IV. Lymph node aspirate cytology: organisms seen with Romanowsky or Giemsa stains
V. Discovery of trematode eggs in feces supportive but not definitive
VI. Serological testing with IFA and Western immunoblot analysis
  A. Antibodies are not detected until 2 weeks after infection.
  B. Do not delay treatment while waiting for serological test results.

Differential Diagnosis

I. Canine distemper
II. Parvovirus
III. Other causes of hemorrhagic diarrhea

Treatment and Monitoring

I. Parenteral antibiotic administration is preferred because of the severe GI involvement.
  A. Doxycycline 10 mg/kg PO, IV BID for 7 days
  B. Oxytetracycline 7 mg/kg PO, IV TID for 3 to 5 days
  C. Tetracycline 22 mg/kg PO, IV TID for 3 to 5 days
  D. Chloramphenicol 30 mg/kg PO, SC, IM, IV TID for 7 days
  E. Praziquantel 10 to 30 mg/kg PO, SC once to eradicate the fluke infestation
II. Supportive care includes IV fluids and maintaining body temperature.
III. Early treatment minimizes morbidity and helps prevent mortality.
IV. Prevent dogs from eating raw salmonid fish.
V. Freeze (–20° C for at least 24 hours) or cook fish completely to destroy organisms.
VI. Protective immunity occurs with recovery; however, immunity is not cross-protective for Elokomin fluke fever.

Q FEVER

Michael Lappin

Definition and Cause

Q fever is a systemic disease caused by *Coxiella burnetii,* a rickettsial agent found throughout the world, including North America.

Pathophysiology

I. Epidemiological findings
  A. Multiple arthropods, including *R. sanguineus*, are naturally infected with *C. burnetii*.
  B. Cats, dogs, cattle, sheep, and goats are subclinically infected and pass the organism into the environment in urine, feces, milk, and parturient discharges.
  C. The precise incidence of disease in cats and dogs has not been determined, but serological tests suggest exposure is common (Higgins and Marrie, 1988; Boni et al, 1998; Komiya et al, 2003a).
  D. The organism has been grown from vaginal cultures of normal cats in Japan (Nagoaka et al., 1998).
II. Transmission
  A. Infection may follow tick exposure, ingestion of contaminated carcasses, or aerosolization from a contaminated environment.
  B. Infection of people by exposure to cats or dogs most commonly occurs by inhalation of the organism in secretions from parturient or aborting animals.

Clinical Signs

I. Fever, anorexia, and lethargy develop in experimentally infected cats.
II. Natural infection is associated with abortion, but the role the organism plays in other clinical syndromes is unknown.

Diagnosis

I. Definitive diagnosis is based on culture or PCR (Greene and Breitschwerdt, 2006).
II. Positive serological tests confirm exposure to *C. burnetii.*

Differential Diagnosis

I. Other causes of abortion or fever must be ruled out.
II. Most cats and dogs are subclinically infected.

Treatment and Monitoring

I. Because infection is difficult to confirm and most cats and dogs are subclinically infected, successful treatment has not often been reported.
II. Minocycline 5 mg/kg PO SID for 4 weeks has converted a few dogs and cats from PCR-positive to PCR-negative status (Komiya et al., 2003b).
III. Because Q fever is an occupational hazard for veterinary health care providers, gloves and masks should be worn when attending to parturient or aborting cats and dogs.
IV. Medical attention is recommended for people with signs of severe respiratory disease who have recently been exposed to cats or dogs.

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CHAPTER 116

Protozoal Infections

Nolie K. Parnell | Lynn Guptill | Laia Solano-Gallego

ENTERIC INFECTIONS

Nolie K. Parnell

Giardiasis

Definition and Cause

I. Giardiasis is an acute or chronic gastrointestinal (GI) tract disease characterized by diarrhea and weight loss in both cats and dogs.
II. *Giardia duodenalis,* a flagellate protozoan, has many morphologically identical isolates.
III. There are at least seven described genetic groups; four (Groups A, B, C, D) infect dogs, and two (Groups A and F) infect cats.

Pathophysiology

I. Epidemiological findings
  A. Worldwide distribution
  B. Prevalence
    1. Dogs: 4.7% to 10%, up to 50% in puppies and 100% in kennels (Barr et al., 1994; Nolan and Smith, 1995)
    2. Cats
      a. 1.3% to 13.64% in general population (Vasilopulos et al., 2006)
      b. 3.9% to 35% in cats with diarrhea, from shelters, or from catteries (Hill et al., 2000; Gookin et al., 2004)
      c. Possibly higher in general population (McGlade et al., 2003)
  C. Risk factors
    1. High housing density, presence of nonfeline species (Gookin et al., 2004)
    2. Coinfection with *Cryptosporidium* spp. (Vasilopulos et al., 2006)
II. Transmission: direct fecal–oral
III. Life cycle
  A. Cysts are ingested from contaminated water, feces, or other items.
  B. Trophozoites exist in the small intestines, and then mature and attach to the enterocyte brush border.
  C. Cysts and trophozoites are passed in feces and are infective for the next host.
IV. Pathogenesis
  A. Attachment to epithelium may cause villous atrophy, malabsorption, and increased enterocyte turnover.
  B. Host immune responses (humoral and cellular) are important in clearing infection.
  C. Host immune response, nutritional status, concurrent GI disease, coinfection with multiple enteric protozoa, and virulence of *Giardia* strain all affect severity of clinical disease (Gookin et al., 2004; Lappin, 2005).

Clinical Signs

I. Most infections asymptomatic
II. Common: acute, often self-limiting small-bowel diarrhea
III. Less common: intermittent or chronic diarrhea, weight loss, inappetence, vomiting in cats
IV. Rare: acute or chronic large-bowel diarrhea

Diagnosis

I. Clinical pathological tests: nonspecific results
II. Parasite identification in feces
  A. Direct smear of fresh feces
    1. Some infected dogs (40%) are identified by direct fecal smears done on 3 separate days (Leib et al., 1999).
    2. Trophozoites have a "smiling face" appearance owing to two nuclei, erratic tumbling motion, and a concave ventral disk.
    3. Identification is made easier with one drop of Lugol's iodine.
  B. Zinc sulfate concentration technique (specific gravity 1.18)
    1. Approximately 70% of infected dogs are identified with a single assay, and up to 93% with three examinations on 3 consecutive days (Leib et al., 1999).
    2. Cysts are distorted by sucrose and other fecal analysis solutions.
  C. Enzyme-linked immunosorbent assay (ELISA) for fecal antigens: false-positives and false-negatives possible
  D. Polymerase chain reaction (PCR) assays: more sensitive (McGlade et al., 2003)
  E. Immunofluorescent antibody (IFA) (Lappin, 2005)
    1. Assays for human isolates, so false-negatives possible
    2. Can be performed on refrigerated or frozen stored samples
III. Parasite identification in duodenal aspirates possible

Differential Diagnosis

I. Rule out other causes of small-bowel diarrhea.
   A. Dietary indiscretion
   B. Viral enteritis
   C. Other intestinal parasites
   D. Drug reactions, toxicosis
   E. Food allergy
   F. Pancreatic exocrine insufficiency
   G. Inflammatory bowel disease, small intestinal bacterial overgrowth
   H. Feline hyperthyroidism
   I. Neoplasia
II. Rule out other causes of large-bowel diarrhea.
   A. Other intestinal parasites
   B. Bacterial or fungal enterocolitis
   C. Dietary indiscretion
   D. Inflammatory bowel disease
   E. Neoplasia

Treatment

I. Metronidazole 15 to 25 mg/kg PO BID for 5 to 7 days
   A. Used in dogs and cats
   B. Neurological side effects possible with prolonged treatment or higher dosages
II. Fenbendazole 50 mg/kg PO SID for 5 days in dogs and cats
III. Albendazole 25 mg/kg PO BID for 2 days in dogs
   A. Use it with caution, because it can cause bone marrow suppression.
   B. Do not use it in cats.
IV. Praziquantel, pyrantel pamoate, febantel combination *(Drontal-Plus)* at recommended label dose PO for 3 to 5 days

Monitoring and Prevention

I. Bathing animals during treatment is essential to remove parasites from the hair coat.
II. Treatment failures and relapses are possible, because drug-resistant *Giardia* spp. exist and reexposure occurs in contaminated environments.
III. Environmental management is essential and involves removal of feces and all organic material followed by disinfection with 1 part household bleach (5.25% sodium hypochlorite) in 32 parts water.
IV. A killed vaccine for dogs and cats is sometimes used in conjunction with other methods for high-risk populations or resistant infections, but efficacy is uncertain (Stein et al., 2003; Olson et al., 2001; Anderson et al., 2004).
V. Some *Giardia* spp. genogroups are known to infect dogs (A1 and B) and humans or cats (A1); therefore some forms of giardiasis are likely zoonotic.

Trichomoniasis

Definition and Cause

I. *Tritrichomonas foetus* is a single-celled, flagellated protozoa that causes diarrhea in cats (Gookin et al., 2004).
II. Trichomonad infections are documented in dogs with diarrhea, but their pathogenicity is unproven.

Pathophysiology

I. Epidemiological findings
   A. Young cats and cats from multiple-cat environments more susceptible
   B. Some breeds possibly more susceptible: Pixie-Bob cat, Abyssinian, Bengal (Romatowski, 2000)
II. Transmission: fecal–oral
III. Pathogenicity
   A. Debated and not completely understood
   B. Concurrent mild-to-moderate lymphoplasmacytic and neutrophilic colitis with crypt epithelial cell hypertrophy, hyperplasia, loss of goblet cells, and microabscesses (Yaeger and Gookin, 2005)

Clinical Signs

I. Asymptomatic infections occur.
II. Chronic large-bowel diarrhea is the primary clinical sign.
III. Diarrhea waxes and wanes and is not associated with systemic illness (Gookin et al., 2004)

Diagnosis

I. Diagnosis is by identification of the organism.
II. Test feces within 1 hour of defecation; do not refrigerate the sample.
   A. Direct smear to identify motile trophozoites
   B. Protozoal culture with modified Diamond medium or commercially available system (In Pouch) (Gookin et al., 2003)
   C. PCR more sensitive than culture (Gookin et al., 2002; Houser et al., 2006)
III. *T. foetus* is easily confused with *Giardia* spp. and *Pentatrichomonas* spp. on fecal examination.

Differential Diagnosis

I. Bacterial enterocolitis
II. Giardiasis
III. Inflammatory bowel disease
IV. Large-bowel neoplasia

Treatment

I. Ronidazole may be given at 30 to 50 mg/kg PO BID for 14 days (Gookin et al., 2006).
   A. Only used in a small number of animals to date
   B. May be difficult to acquire in the United States
   C. Neurological side effects possible
II. Metronidazole at 25 mg/kg PO BID for 5 to 7 days may improve clinical signs, but relapses are common and organisms may persist.

Monitoring and Prevention

I. Many cats have spontaneous resolution of clinical signs within 2 years (Foster et al., 2004).
II. Some cats remain infected for life.
III. Relapses occur following treatment.

IV. Zoonotic potential is unproven, but immunocompromised people should avoid contact with infected cats.

Cryptosporidiosis

Definition and Causes

I. *Cryptosporidium parvum,* a ubiquitous protozoan, has a wide mammalian host range and causes diarrhea in dogs and cats.
II. Other species may infect animals and are morphologically identical to *C. parvum* (Sargent et al., 1998).
  A. *Cryptosporidium felis* is primarily found in cats.
  B. *Cryptosporidium canis* is primarily found in dogs.

Pathophysiology

I. Transmission occurs via the fecal–oral route.
II. All stages of the life cycle take place in one host.
  A. Sporulated oocysts are ingested, and sporozoites infect enterocytes.
  B. Trophozoites form in parasitophorous vacuoles.
  C. Thick-walled oocysts are released into feces.
  D. Thin-walled oocysts may reinfect the host.
III. Pathogenesis is uncertain.
  A. It may cause morphological and functional changes in enterocytes.
  B. Host immune response influences pathogenesis.
  C. Clinical disease is more common in young or immunocompromised animals.

Clinical Signs

I. Asymptomatic infections possible
II. Common: small-bowel diarrhea
III. Less common
  A. Dogs and cats: large-bowel diarrhea (chronic)
  B. Cats: anorexia, weight loss

Diagnosis

I. Parasite identification
  A. Feces
    1. Direct smear using crystal violet or acid-fast stain: false-negatives possible
    2. Sugar solution centrifugation and zinc sulfate concentrations combined with staining
    3. Formalin–ether or formalin–ethyl acetate fecal sedimentation
    4. IFA assay
  B. Intestinal biopsy
    1. Giemsa stain is best; hematoxylin/eosin is acceptable.
    2. False-negatives occur.
    3. Organisms are most easily found in the ileum.
II. Ancillary testing
  A. IFA labeling of tissues is available.
  B. ELISA test for serum antibodies indicates exposure, but does not predict oocyst shedding.
  C. ELISAs to detect antigen in feces are being evaluated.
    1. Greater sensitivity in kitten feces than IFA (Marks et al., 2004)
    2. Not yet evaluated in dogs
  D. PCR is more sensitive than IFA (Scorza et al., 2003).

Differential Diagnosis

I. Other endoparasites
II. Inflammatory bowel disease
III. Viral and bacterial enteritis
IV. Dietary indiscretion
V. Neoplasia

Treatment

I. Treatment may not be necessary in immunocompetent animals because infections are often self-limiting.
II. Azithromycin 5 to 10 mg/kg (dogs) or 7 to 15 mg/kg (cats) PO BID may be given for 5 to 7 days (Barr, 2006b).
III. Tylosin 11 mg/kg PO BID in food for 28 days may improve diarrhea in cats (Lappin et al., 1997).
IV. Paromomycin 150 mg/kg PO SID to BID for 5 days must be used with extreme caution because it is nephrotoxic.
V. Supportive care with IV fluids and nutritional support as needed.

Monitoring and Prevention

I. Treatment failure is common and necessitates evaluation for concurrent immunosuppressive conditions or environmental contamination.
II. Clean the environment, then disinfect with steam followed by thorough drying, or apply 50% ammonia solution for 30 minutes using appropriate protective equipment.
III. Cryptosporidiosis can be zoonotic.
  A. Immunocompromised people should avoid infected animals.
  B. Use caution when handling feces and tissues to prevent accidental infection.

Enteric Coccidiosis

Definition and Causes

I. Coccidia cause GI disease that is characterized by diarrhea, weight loss, and possibly vomiting.
II. Multiple genera infect dogs and cats, including *Isospora (Cystoisospora), Hammondia*, *Besnoitia, Sarcocystis, Toxoplasma, Neospora*, and *Cryptosporidium*.
III. *Isospora (Cystoisospora)* is the most common genus, and multiple species are incriminated.
  A. Dogs: *I. canis, I. ohioensis, I. burrowsi, I. neorivolta*
  B. Cats: *I. felis, I. rivolta*
IV. *Eimeria* spp. oocysts appear in the feces of cats and dogs that ingest *Eimeria*-infected prey or feces, but are not considered pathogenic.

Pathophysiology

I. Oocysts in feces sporulate in 6 hours to 3 days.
  A. Sporozoites excyst from ingested oocysts and invade intestinal mucosa.
  B. Asexual reproduction produces meronts and schizonts with multiple cycles of merogony.

C. Sexual cycle (microgamonts and macrogamonts) produces oocysts.
II. Prepatent period is 5 to 11 days.
III. Transmission also occurs via ingestion of infected paratenic hosts (e.g., mice, insects).
IV. Sporozoites may invade extraintestinal tissues (e.g., mesenteric lymph nodes), form monozoic cysts, and persist for life.
V. Pathogenicity is possibly linked to oocyst dose, age of animal, and host immune status.

Clinical Signs

I. Animals <6 months of age or immunocompromised animals are more likely to develop clinical signs.
II. Subclinical carriers are common.
III. Small- and large-bowel diarrhea of varying severity is the major clinical abnormality.
IV. Rarely, abdominal pain, vomiting, dehydration, anorexia, anemia, and death occur.

Diagnosis

I. Diagnosis is easier when diarrheic feces are used for testing.
II. Diagnosis is by demonstration of oocysts in feces, preferably using Sheather's sugar centrifugation method.
III. Oocyst size aids in determining the genus and species.

Differential Diagnosis

I. Viral enteritis
II. Dietary indiscretion
III. Other endoparasites

Treatment

I. Sulfonamides
  A. Dogs and cats: trimethoprim-sulfonamide 15 mg/kg PO SID to BID for 5 days
  B. Dogs and cats: sulfadimethoxine 50 mg/kg PO SID for 10 days
  C. Dogs: ormetoprim-sulfadimethoxine 66 mg/kg PO (55 mg/kg sulfadimethoxine and 11 mg/kg ormetoprim) SID for 7 to 23 days
II. Amprolium 60 to 100 mg (total) PO SID for 5 days (Lappin, 2005)
III. Nitrofurazone 8 to 20 mg/kg PO SID to BID for 5 days in dogs and cats; decrease dose by 50% when used with sulfonamides.
IV. Supportive care as needed

Monitoring and Prevention

I. Most infections are self-limiting, but it is important to eliminate any underlying predisposing condition.
II. Bathe animals during treatment to remove fecal material and oocysts.
III. Environmental sanitation is important to prevent infection and facilitate treatment.
  A. Avoid contamination of food and water bowls by infected feces.
  B. Remove feces daily, wash and treat premises with 10% ammonia solutions, or use steam.
  C. Control insects (paratenic host) in the environment (e.g., flies).

GENERALIZED INFECTIONS

Babesiosis

Laia Solano-Gallego

Definition and Causes

I. Babesiosis is a worldwide, tick-borne disease caused by hemoprotozoa of the genus *Babesia.*
II. It is characterized by erythrocyte (red blood cell [RBC]) destruction and mild to severe systemic signs.
III. Canine babesiosis is usually caused by *B. canis* or *B. gibsoni* (Table 116-1).
IV. Two newly described species are associated with hemolytic anemia in dogs in the United States.
V. Feline babesiosis is not reported in the United States.

Pathophysiology

I. Epidemiology, transmission, life cycle
  A. For the geographic distribution, see Table 116-1.
  B. Transmission is mainly by ticks, but is also possible via blood transfusion, contaminated equipment, and transplacentally (Fukumoto et al., 2005).
  C. *Babesia gibsoni* is possibly transmitted via bite wounds, saliva, and ingested blood.
  D. *Babesia canis* sporozoites are transferred to the dog as ticks feed (over 48 to 72 hours), then they invade RBCs, reproduce by binary fission, and form merozoites.
II. Pathogenesis
  A. As parasites replicate in RBCs, osmotic fragility increases, hemolysis occurs, and results in anemia.
  B. Severe hypoxia and the inflammatory response from hemolysis lead to tissue damage, multiple organ dysfunction, and potentially death.

Clinical Signs

I. Canine babesiosis: severity varies with species and host
  A. Hyperacute infection with *B. canis rossi*: hypothermia, shock, coma, disseminated intravascular coagulopathy (DIC), metabolic acidosis, death
  B. Acute infections with *B. canis rossi*, *B. canis canis*, *B. gibsoni, B. conradae, B. microti-like*:
    1. Fever, anorexia, lethargy, weakness, icterus, pale or congested mucous membranes, vomiting, splenomegaly, lymphadenopathy
    2. Atypical signs mainly from *B. canis rossi*: rhabdomyolysis, myalgia, vomiting, diarrhea, ascites, edema, upper respiratory signs, pancreatitis, acute renal failure, neurological signs
  C. Chronic and subclinical infections with *B. canis vogeli, B. gibsoni*

TABLE 116-1

Distribution, Vectors, and Cytological Characteristics of Selected *Babesia* spp.

SPECIES APPEARANCE*	GEOGRAPHIC DISTRIBUTION	HOST	VECTORS	SIZE (μm)	CYTOLOGICAL CHARACTERISTICS
B. canis rossi	South Africa	Dog	*Haemaphysalis leachi*	2 × 5	Usually paired
B. canis canis	Europe, Asia	Dog	*Dermacentor reticulatus*	2 × 5	Usually paired
B. canis vogeli	Africa, Asia, Europe, North America, Central America, South America, Australia	Dog	*Rhipicephalus sanguineus*	2.5 × 4.5	Single or paired
B. gibsoni	Asia, United States,† Australia, Europe?	Dog	*Haemaphysalis bispinous?* *Rhipicephalus sanguineus?*	1 × 3	Usually singular
B. conradae	California	Dog	*Rhipicephalus sanguineus?*	0.3 to 3	Ring, tetrad, ameboid
B. microti-like (Theileria annae)	Spain (Galicia)	Dog	*Ixodes hexagonus?*	1 × 2.5	Usually singular
B. felis	Africa, Europe?, Asia?	Cat	Unknown	0.9 × 0.7	Single or in pairs
B. canis presentii	Israel	Cat	Unknown	2.5 × 1.5	Round to oval

?,Distribution suggested but unproven.

*Organisms possibly more concentrated in capillary blood (e.g. ear tip).

†Sporadic infections, mostly in American Staffordshire and pit bull terriers.

1. *B. gibsoni:* intermittent pyrexia, decreased appetite, weight loss, lymphadenopathy, splenomegaly, hepatomegaly
2. *B. canis vogeli*
   a. Usually subclinical
   b. Possible severe to fatal hemolytic anemia in puppies
   c. Clinically healthy seroreactive greyhounds in the United States

II. Feline babesiosis (chronic): lethargy, anorexia, weakness, pale mucous membranes, diarrhea

Diagnosis

I. Hematological findings
   A. Variable anemia: normocytic normochromic to macrocytic, hypochromic, or regenerative
   B. Thrombocytopenia: common in dogs, inconsistent in cats
   C. Variable leukocyte changes: neutropenia, neutrophilia, lymphocytosis

II. Serum biochemistry tests
   A. May be normal
   B. Azotemia, metabolic acidosis
   C. Elevated liver enzymes, hyperbilirubinemia
   D. Increased positive acute phase proteins: α_1-glycoprotein, C-reactive protein, ceruloplasmin (Ulutas et al., 2005)

III. Variable urinalysis results
   A. Bilirubinuria, hemoglobinuria
   B. Proteinuria casts

IV. Organism identification
   A. Wright's, Giemsa, or Diff-Quik stain of blood smears (see Table 116-1)
   B. PCR assay of blood: sensitive, determines infecting species

V. Serologic testing
   A. IFA is more specific.
   B. ELISA is more sensitive, but cross-reactions occur.
   C. False-negative results are possible in peracute or acute infection, so use convalescent titers.

Differential Diagnosis

I. Septicemia
II. Ehrlichiosis, anaplasmosis, rickettsiosis, hemoplasmosis
III. Other causes of hemolytic anemia: immune-mediated diseases, drug, zinc, onion toxicity
IV. Other causes of thrombocytopenia (see Chapters 67 and 68)

Treatment

I. Repeated therapy possibly needed

II. *B. canis*
   A. Imidocarb dipropionate 5 to 6.6 mg/kg IM once; may repeat in 14 days
   B. Diminazene aceturate 3.5 to 5 mg/kg IM once; not available in United States
   C. Phenamidine isethionate 15 to 20 mg/kg SC SID for 2 days; not available in United States
   D. Trypan blue (1% solution) 10 mg/kg IV once
      1. Does not eliminate infection
      2. For severe cases or relapses
      3. Followed by imidocarb if possible
      4. Induces blue discoloration of mucosae and urine

III. *B. gibson*
   A. Azithromycin 10 mg/kg PO SID for 10 days
   B. Atovaquone 13.3 mg/Kg PO TID for 10 days (Birkenheuer et al., 2004)

IV. *B. felis*
   A. Primaquine phosphate 0.5 mg/kg PO SID for 3 days or 1 mg per cat IM every 36 hours for 6 days
   B. NOTE: 1 mg/kg lethal to cats

V. Supportive care
   A. Blood and plasma transfusions, IV fluids
   B. Glucocorticoids controversial

Monitoring and Prevention

I. Institute tick control.
II. Species-specific immunity only lasts a few months.
III. Transmission to people may occur from laceration with blood-contaminated sharp equipment.
IV. Screen animals used as blood donors via PCR.
V. A vaccine for *B. canis* is available in some European countries and appears to limit clinical signs (Schetters et al., 2005).

Toxoplasmosis

Lynn Guptill

Definition and Cause

I. *Toxoplasma gondii*, an obligate intracellular protozoan with worldwide distribution, causes many clinical syndromes.
II. Enteroepithelial infection occurs only in the cat (definitive host).
III. Systemic infection develops in cats and many other intermediate hosts.

Pathophysiology

I. Life cycle
   A. Cats ingest tissue cysts, which undergo enteroepithelial replication.
   B. Oocysts are shed in feces for 1 to 3 weeks.
   C. Oocysts sporulate in the environment (>24 hours outside of body).
   D. Cats or other intermediate hosts ingest sporulated oocysts, then the sporozoites penetrate intestinal cells and divide into tachyzoites.
   E. Tachyzoites multiply intracellularly and are disseminated when cells rupture.
   F. Tissue cysts (bradyzoites) form and persist indefinitely.
II. Transmission in cats and dogs
   A. Common: ingestion of tissue cysts in small rodents, uncooked beef or pork, other sources
   B. Less common: ingestion of sporulated oocysts
   C. Transplacental or transmammary transmission
   D. Tissue cysts possibly reactivated, followed by dissemination of zoites
      1. It may occur during another illness or with immunosuppression.
      2. Cyclosporine therapy may reactivate or increase the susceptibility to disseminated toxoplasmosis in both dogs and cats (Barrs et al., 2006; Webb et al., 2005).
III. Pathogenesis
   A. Extent of replication and tissue damage vary with host age and immunity, number of parasites ingested, and strain of *T. gondii.*
   B. For example, cats with feline immunodeficiency virus (FIV) may have more severe disease.
   C. All tissues are susceptible, and the type of illness depends on tissues affected.

Clinical Signs

I. Signs are not observed in all infected animals.
II. Signs develop most commonly in animals that are young, immunosuppressed, or coinfected with another pathogen.
   A. Enteroepithelial infection: rare, self-limiting diarrhea
   B. Neurological signs: ataxia, weakness, cranial nerve deficits, abnormal mentation
   C. Respiratory signs: dyspnea, tachypnea, cough (see Chapter 18)
   D. Ocular signs (more common in cats): optic neuritis, chorioretinitis, anterior uveitis
   E. Liver disease and pancreatitis: fever, anorexia, vomiting, weight loss, icterus
   F. Disseminated disease: multisystemic signs
   G. Canine toxoplasmosis: similar signs to neosporosis

Diagnosis

I. Tentative diagnosis of clinical toxoplasmosis is based on a combination of the following (Lappin, 2000):
   A. Serum antibodies: high immunoglobulin (Ig) M titer, ≥fourfold increase in IgG titer
   B. Clinical signs consistent with *T. gondii* infection
   C. Exclusion of other common causes of clinical signs
   D. Positive response to treatment for *T. gondii*
II. Hematological and serum biochemistry results reflect the organ systems affected.
III. Cerebrospinal fluid (CSF) analysis often shows increased protein levels, and mixed pleocytosis.
   A. Organisms rarely seen
   B. May be submitted for immunological testing and PCR
IV. Diagnostic imaging results are variable and depend on the organ systems affected.
V. Immunological testing via IFA and ELISA for IgM and IgG antibodies (Abs) can be performed on serum, CSF, or aqueous humor.
   A. Serum Abs document exposure to *T. gondii,* but do not diagnose disease because clinically normal animals may have positive Ab titers.
   B. IgM Abs correlate best with clinical disease, but failure to detect IgM does not exclude toxoplasmosis.
   C. IgG Abs persist for years, because the host rarely clears the infection completely.
      1. A fourfold rise in titer suggests recent infection (Lappin, 2000).
      2. Failure to detect a fourfold rise does not exclude toxoplasmosis.
   D. Testing of CSF or aqueous humor complements serum testing.
      1. Compare *T. gondii*–specific IgM or IgG in these fluids to serum *T. gondii*–specific IgM or IgG to try to determine whether local antibody formation may reflect active disease.
      2. *T. gondii*–specific IgM plus detection of *T. gondii* DNA by PCR in CSF or aqueous humor correlates well with clinical disease (Lappin, 2000).

3. Circulating antigens of *T. gondii* may be detected in CSF and aqueous humor via ELISA tests.

VI. Fecal flotation with Sheather's sugar solution occasionally detects oocysts, but cats usually shed oocysts only in the first 2 weeks after infection.

VII. Organism identification in tissues or fluid helps confirm the diagnosis.
   A. Perform cytological examinations on tissue aspirates, CSF, tracheal wash or bronchoalveolar lavage fluid, and aqueous humor.
   B. Immunohistochemistry is required to differentiate *T. gondii* from *Neospora caninum* and other related protozoa.
   C. PCR can be performed on tissues, CSF, and aqueous humor.

Differential Diagnosis

I. Cats
   A. Other causes of anterior uveitis, chorioretinitis (see Chapters 99 and 102)
   B. Other infectious causes of systemic disease
      1. Feline infectious peritonitis, feline leukemia virus, FIV
      2. Systemic mycoses
      3. Neoplasia

II. Dogs
   A. Neosporosis
   B. Other causes of central nervous system (CNS) and ocular disease
      1. Canine distemper
      2. Systemic mycoses
      3. Protothecosis
      4. Lymphosarcoma
   C. Other causes of myositis (see Chapter 82)

Treatment

I. No drug clears all *T. gondii* from the body.

II. Choices of available drugs include the following:
   A. Best: clindamycin 12.5 mg/kg PO BID for 4 weeks
   B. Cats: trimethoprim/sulfonamide 15 mg/kg PO BID for 4 weeks
   C. Dogs: pyrimethamine 0.25 to 0.5 mg/kg PO SID for 4 weeks with sulfonamides at 30 mg/kg PO SID

III. Institute additional supportive care as needed.

Monitoring and Prevention

I. Prognosis for animals with disseminated disease is guarded to poor.

II. Ocular and CNS signs are slow to respond to treatment.

III. Vision is often diminished or lost with severe uveitis.

IV. Prevent exposure to oocysts and tissue cysts.
   A. Feed only fully cooked foods.
   B. Prevent hunting and coprophagy.

V. Toxoplasmosis is a zoonotic disease.
   A. Usually transmitted by ingestion of undercooked meat, contaminated water
   B. Rarely transmitted by direct contact with cats
   C. Possible exposure by contact with sporulated oocysts from litter boxes, or while gardening
   D. Prevention of exposure to people
      1. Practice good hygiene in food preparation, and cook meats thoroughly.
      2. Clean litter boxes daily so oocysts do not sporulate; do not aerosolize contents while cleaning litterbox.
      3. Wear gloves when gardening and cleaning the litter box, and cover children's sandboxes.

Neosporosis

Lynn Guptill

Definition and Cause

I. *Neospora caninum* causes multifocal neurological disease, myositis, and reproductive failure in dogs.

II. It has a worldwide distribution in dogs and many other species (Dubey, 1999).

Pathophysiology

I. Life cycle
   A. Dogs (definitive host) ingest tissue cysts, which undergo enteroepithelial replication.
   B. Cats have been infected experimentally, but clinical disease in naturally infected cats is not documented.
   C. Some cats are serologically positive, suggesting exposure to *N. caninum* (Ferroglio et al., 2005).
   D. Oocysts are shed in dog feces for 1 to 3 weeks, possibly more than once, and puppies may shed more oocysts than adult dogs (McGarry et al., 2003; Gondim et al., 2005).
   E. Oocysts sporulate in the environment (24 to 72 hours outside of body).
   F. Dogs or other intermediate hosts ingest sporulated oocysts; sporozoites penetrate intestinal cells and divide into tachyzoites.
   G. Tachyzoites multiply intracellularly and are disseminated when cells rupture.

II. Transmission
   A. Dogs and coyotes are definitive and intermediate hosts.
   B. Cattle, deer, and other herbivores are intermediate hosts.
   C. Congenital infection can occur (Barber and Trees, 1998).

III. Pathogenesis
   A. Tachyzoites proliferate in muscle (including myocardium) and neural tissue.
   B. The cells are destroyed, and an inflammatory response ensues with mononuclear cell infiltrates, central areas of necrosis, and granuloma formation.
   C. Other affected tissues include skin, eyes, liver, lungs, spleen, heart, lymph nodes, and adrenal glands.
   D. Tissue cysts containing bradyzoites induce minimal or no host reaction.
   E. Immunosuppression probably induces activation of tissue cysts and clinical neosporosis (La Perle et al., 2001).

Clinical Signs

I. Young dogs
  A. Congenital infection usually fatal
    1. Ascending paralysis, hyperextension and ataxia; pelvic limbs most severely affected
    2. Polymyositis: multiple affected areas
  B. Other possible clinical signs
    1. Multifocal CNS signs, cervical weakness, head tilt
    2. Dysphagia, muscle atrophy
  C. Rarely, myocarditis and sudden death (Odin and Dubey, 1993)
II. Adult dogs
  A. Possibly same signs as for young dogs
  B. Also ulcerative dermatitis, pneumonia

Diagnosis

I. Compatible signalment, history, clinical signs
II. Rare hematological abnormalities
III. Possible elevated liver and muscle enzymes
IV. CSF analysis
  A. Possible increased protein and mixed pleocytosis (non-suppurative meningoencephalitis)
  B. Abs to *N. caninum* in CSF supportive of diagnosis
V. Electromyographic findings consistent with lower motor neuron disease
VI. Organism identification
  A. Tachyzoites in CSF, tracheal wash or bronchoalveolar lavage fluid, lung aspirates, tissue biopsies, or impressions of dermal lesions are indistinguishable from *T. gondii* on light microscopy.
  B. Immunocytochemistry or electron microscopy is needed for definitive diagnosis.
  C. PCR is useful to distinguish *N. caninum* from other species.
VII. IFA test on CSF or serum not definitive
  A. Titers as high as 1:12,800 reportedly persist at least 4 years in clinically normal dogs (Barber and Trees, 1998).
  B. Histologically confirmed neosporosis is reported with titers <1:50 (Dubey and Lappin, 2006).

Differential Diagnosis

I. *Toxoplasma gondii* infection
II. Other causes of polymyositis (see Chapter 82), multifocal CNS disorders (see Chapters 23 and 24), necrotizing dermatitis, or pneumonia

Treatment

I. Early diagnosis and treatment may improve survival.
II. Potential effective treatments are as follows:
  A. Trimethoprim/sulfonamide 15 to 20 mg/kg PO BID *or*
  B. Sulfonamide 15 to 20 mg/kg PO BID with pyrimethamine 1 mg/kg PO SID for 2 to 4 weeks (Dubey and Lappin, 2006)
  C. Clindamycin 7.5 to 15 mg/kg PO TID for 4 to 8 weeks

Monitoring and Prevention

I. Pay particular attention to progression of neurological signs, and the animal's ability to prehend food, swallow, and breathe.
II. Pelvic limb rigidity may persist in treated dogs (Barber and Trees, 1996).
III. Gait abnormalities may require physical therapy.
IV. Puppies do not usually respond, particularly if diagnosis and treatment are delayed.
V. No treatment inhibits transplacental transmission, so do not breed animals with previously affected litters.
VI. The zoonotic potential of *N. caninum* is unknown.
VII. Avoid feeding uncooked meat or offal.

Hepatozoonosis

Lynn Guptill

Definition and Causes

I. Hepatozoonosis is a multisystemic disease of dogs, and occurs rarely in cats.
II. *Hepatozoon americanum* is the primary agent in North America.
III. *Hepatozoon canis* occurs in Japan, Africa, the Middle East, southern Europe, Asia, South America and other regions.

Pathophysiology

I. Infected ticks are ingested.
  A. *Rhipicephalus sanguineus* for *H. canis*
  B. *Amblyomma maculatum* for *H. americanum*
II. Vertical transmission of *H. canis* has been reported (Murata et al., 1993).
III. Life cycle is as follows:
  A. Ticks ingest gametocytes from leukocytes in dog peripheral blood.
  B. Oocysts with multiple sporozoites form within ticks and dogs ingest the ticks.
  C. Sporozoites penetrate intestines, with eventual formation of schizonts, cysts, and gametocytes in dogs.
IV. *Hepatozoon americanum* forms tissue cysts in striated muscle, and rarely other tissues (Panciera et al., 1998).
  A. Muscle cysts form by 5 weeks (Panciera et al., 1998).
  B. Intact cysts produce no inflammation.
  C. Ruptured cysts induce pyogranulomatous myositis (Vincent-Johnson et al., 1997).
  D. Marked periosteal proliferation occurs primarily in long bone diaphyses (Panciera et al., 2000).
  E. The disease is usually severe and often fatal without treatment.
V. *H. canis* localizes in liver, spleen, lymph nodes, lungs, kidneys, and bone marrow (Baneth et al., 1998b).
  A. Infection is often subclinical.
  B. Organisms occur in multiple tissues.
  C. Cysts resembling those of *H. americanum* are uncommon.
  D. Heavy parasite burdens can be life-threatening (Baneth and Weigler, 1997).

Clinical Signs

I. *Hepatozoon americanum*
  A. Subclinical infections rare
  B. Natural infections (Macintire et al., 2001)
    1. Fever, muscle pain, stiffness, gait abnormalities

2. Lethargy, mucopurulent ocular discharge
3. Possible glossitis, pharyngitis
4. Pelvic limb paresis and ataxia, with upper motor neuron signs
5. Generalized lymphadenopathy
6. Cachexia, vasculitis, and renal failure in late stages

II. *Hepatozoon canis*
   A. Subclinical infections common
   B. Dogs, often with severe parasitemia: lethargy, fever, weight loss, other signs (Baneth and Weigler, 1997)

III. Cats
   A. *H. canis* infection is possible.
   B. Other *Hepatozoon* spp. infections of cats are reported.
   C. Clinical signs may vary (Baneth, 2006).

Diagnosis

I. History of tick infestation with compatible clinical signs
II. Clinical pathologic findings
   A. Leukocytosis (commonly marked with *H. americanum*), nonregenerative anemia
   B. Increased serum alkaline phosphatase activity
   C. Hypoalbuminemia common with *H. americanum*
III. Radiological findings: periosteal reaction, especially long bones (*H. americanum*)
IV. Test of choice for identifying the organism
   A. *H. canis:* gametocytes in peripheral leukocytes
   B. *H. americanum:* schizonts or merozoites in tissues, histopathology of muscle biopsy
V. Serological testing with IFA and ELISA (Baneth et al., 1998b; Mathew et al., 2001)

Differential Diagnosis

I. Rule out other causes of fever, neutrophilia, myositis, and periosteal bone reaction.
II. Rule out other infectious, immune-mediated or metabolic diseases, and neoplasia with similar clinical signs.

Treatment

I. Dogs with advanced disease respond poorly.
II. No treatment eliminates tissue cysts.
III. *H. canis* is treated with imidocarb dipropionate 5 mg/kg IM in 2 doses, 14 days apart.
   A. Consider repeating treatment every 14 days until no gametocytes are seen on blood smears.
   B. Cholinergic signs are possible side effects; treat with atropine as necessary.
   C. Doxycycline 10 mg/kg PO SID for 14 days may be added to imidocarb.
IV. *H. americanum* is treated with a combination of four drugs for 14 days.
   A. Trimethoprim/sulfa 15 mg/kg PO BID
   B. Clindamycin 10 mg/kg PO TID
   C. Pyrimethamine 0.25 mg/kg PO SID
   D. These drugs followed with decoquinate *(Deccox)* 10 to 20 mg/kg PO BID in food indefinitely or at least for 2 years (Macintire et al., 2001)

Monitoring and Prevention

I. Monitor animals closely; relapses are common.
II. Prolonged treatment (years) tends to decrease relapses.
III. Tick control is the most important preventative measure.
IV. Test and/or monitor for co-infection with other tick-transmitted pathogens.
V. Zoonotic potential is unknown, but is thought to be low (Baneth, 2006; Macintire et al., 2006).

Leishmaniasis

Laia Solano-Gallego

Definition and Causes

I. Leishmaniasis is a group of infectious diseases affecting humans, and domestic and wild animals worldwide.
II. Canine visceral leishmaniasis (CVL) is caused by *Leishmania infantum.*
III. Dogs are also infected with *Leishmania mexicana* and *Leishmania braziliensis* (cutaneous leishmaniasis).
IV. Feline leishmaniasis is rare.
   A. It is usually caused by *L. infantum*, and has subclinical, cutaneous or visceral (immunosuppressed cats) manifestations.
   B. Cats may also be infected with *L. mexicana* or *L. braziliensis* (cutaneous form).

Pathophysiology

I. Epidemiology and transmission
   A. Dogs are a reservoir host for *L. infantum*.
   B. CVL is endemic in the Mediterranean basin and South America and is reported in foxhounds in North America.
   C. Female sand flies (*Phlebotomus* spp., *Lutzomyia* spp.) are the principal agents of transmission to dogs.
   D. Unusual routes of transmission (congenital, blood transfusion, direct contact, ingestion, laboratory inoculation) are also reported in dogs.
II. Life cycle
   A. Sandflies regurgitate promastigotes into skin where they become coated by complement and are phagocytized by macrophages.
   B. A parasitophorous vacuole develops and promastigotes become amastigotes that are resistant to enzymes and low pH.
   C. Amastigotes multiply until host cells burst and then enter other phagocytes to continue the cycle.
III. Host immune response
   A. Protective immunity is mediated by T-helper cells.
   B. Dogs that develop specific cell-mediated immunity restrict the infection and have no clinicopathological abnormalities.
   C. Susceptible or sick dogs develop an exaggerated, humoral immune response with a reduced or absent cell-mediated response, and progressive immunosuppression.
   D. In these dogs circulating immune complexes may cause uveitis, glomerulonephritis, meningitis, polyarthritis and vasculitis.

E. CVL is a chronic disease and clinical signs may develop up to 7 years after infection.

Clinical Signs

I. Clinical features vary widely (subclinical to fatal).
II. The main clinical findings (listed from most to least frequent) in dogs are skin lesions, local or generalized lymphadenopathy, weight loss, apathy, lameness, diarrhea, ocular lesions, vomiting, pale mucous membranes, fever and epistaxis.
   A. Cutaneous lesions: symmetrical dry, exfoliative; ulcerative; or nodular, proliferative, papular dermatitis
   B. Ocular signs: anterior uveitis, keratoconjunctivitis, blepharitis
III. Other signs: splenomegaly, hepatomegaly, polyuria, polydipsia

Diagnosis

I. Laboratory findings
   A. Complete blood count: nonregenerative anemia, thrombocytopenia, leukocytosis or leukopenia
   B. Serum biochemistry tests: increased total protein (hyperglobulinemia [polyclonal gammopathy]), hypoalbuminemia, renal azotemia, elevated liver enzymes
   C. Urinalysis: mild to severe proteinuria
II. Specific diagnostic tests
   A. Organism identification
      1. Parasite recovery methods (not routinely used)
         a. Culture: Novy-MacNeal-Nicolle or Schneider's *Drosophila* medium
         b. Hamsters inoculated with suspect tissue
      2. Direct visualization of amastigotes (2.5 to 5 μm 1.5 to 2 μm)
         a. Cytological or histological evaluation of cutaneous lesions, lymph nodes, bone marrow, etc.
         b. Improved detection with immunoperoxidase labeling
      3. Molecular testing: specific and sensitive
         a. PCR: conventional (qualitative) or real-time (quantitative)
         b. Tissue selection: lymph node, bone marrow, skin, blood
   B. Serological testing
      1. IFA, ELISA, direct agglutination (Dog-DAT), and Western blot assay have high sensitivity and specificity.
      2. Antibody quantification (IFA or ELISA) is recommended.
      3. Cross reaction can occur with *Trypanosoma* spp. and *Babesia* spp.
      4. Some clinically healthy, infected dogs are seropositive.
      5. Interpret test results in light of clinical signs, laboratory abnormalities, and test results.
III. Positive diagnosis: suspicious laboratory abnormalities and at least two positive specific tests (e.g., serology, organism identification)

Differential Diagnosis

I. Ehrlichiosis caused by *Ehrlichia canis*
II. Systemic lupus erythematosus
III. Neoplasia: lymphoma, multiple myeloma, leukemia

Treatment

I. Relapses are common and long-term therapy is necessary.
II. Preferred treatment is a combination of antimonials and allopurinol.
   A. Antimonials
      1. Meglumine antimonate *(Glucantime)* 75 mg/kg SC BID for 30 to 40 days
      2. Sodium stibogluconate *(Pentostam)* 30 to 50 mg/kg SC SID for 3 to 4 weeks
   B. Allopurinol 10 to 20 mg/kg PO BID for ≥6 months (duration depending on individual)

Monitoring and Prevention

I. Monitor for improvement of clinicopathological abnormalities.
II. Monitor for decrease in antibody levels and parasite load (via real-time PCR).
III. Stop treatment when serological evaluation is almost negative.
IV. Monitor dogs after treatment termination at least every 6 months, with routine laboratory tests, serological evaluation ± PCR.
V. Use insecticidal collars, and confine animals indoors during dawn and dusk to prevent infection.
VI. A new vaccine for CVL may reduce clinical disease and *L. infantum* infection in dogs.
VII. Most *Leishmania* spp. infecting humans are zoonotic.

OTHER PROTOZOAL INFECTIONS

See Table 116-2.

TABLE 116-2

Other Protozoal Infections

DISORDER	AGENT	AFFECTED SPECIES	TRANSMISSION	CLINICAL SIGNS	DIAGNOSIS	TREATMENT	PUBLIC HEALTH CONSIDERATIONS
Acanthamebiasis	*Acanthamoeba castellani* *A. culbertsoni*	Dog	Unknown	Fever, oculonasal discharge, anorexia, lethargy Later: respiratory distress, neurologic signs	Rarely diagnosed antemortem Clinical pathologic data usually nonspecific: leukopenia (marked lymphopenia), possibly pancytopenia Culture, histopathology	Poor efficacy of drugs attempted in dogs TMS 30 mg/kg PO BID attempted Sulfonamides effective in mice	No known zoonotic potential Dogs possibly sentinels
Cytauxzoonosis	*Cytauxzoon felis*	Cat	Ticks *(Dermacentor variabilis)*	Fulminating systemic disease (fever, disease anorexia, lethargy, dyspnea, dehydration) leads to death (probably more virulent strains) Recovery possible	Parasite identification in erythrocytes (possibly also in phagocytes) on blood smears or in aspirates of spleen, bone marrow, lymph nodes, liver, lungs	Imidocarb dipropionate 2-5 mg/kg IM once or repeated in 14 days Diminazene aceturate 2 mg/kg IM once Treatment may not affect course of disease	None known
Cyclosporiasis	*Cyclospora cayetanensis*	Possible in Brazilian dogs	Ingestion of contaminated water or food	Possibly causes small-bowel diarrhea, weight loss, vomiting	Direct fecal examination with Ziehl-Neelsen staining (8- to 10-μm oocysts) Do not confuse with smaller *Cryptosporidium* spp.	TMS 15 mg/kg PO BID for 7 days	Dogs possibly carry the organism and contaminate the environment
Encephalitozoonosis	*Encephalitozoon cuniculi*	Dog, cat	Ingestion or transplacental	Fulminating in puppies Renal failure, CNS signs Adults possibly same or asymptomatic	Identifing organism in urine or tissues Serological testing not commercially available	No successful treatment reported Provide supportive care	Possible zoonosis via contact with infected tissues or urine Immunocompromised people should use caution

TMS, Trimethoprim–sulfonamide; *CNS*, central nervous system.

TABLE 116-2

Other Protozoal Infections—*cont'd*

DISORDER	AGENT	AFFECTED SPECIES	TRANSMISSION	CLINICAL SIGNS	DIAGNOSIS	TREATMENT	PUBLIC HEALTH CONSIDERATIONS
Pneumocystosis	*Pneumocystis carinii*	Dog, cat	Aerosol	Rare Usually subclinical unless immunosuppressed Signs: weight loss, cough, dyspnea, possible vomiting, diarrhea	No commercial serological tests for dog and cat Thoracic radiographs: diffuse interstitial to aveolar pattern Detection of organism in TTW fluid, other secretions, and aspirates; biopsy specimens: PCR, immunofluorescence	TMS 15 mg/kg PO BID for 2 weeks Other agents less effective Supportive care: oxygen therapy, nebulization, coupage Glucocorticoids possibly improve survival in people	Minor zoonotic potential Caution if immuno-compromised
Trypanosomiasis	*Trypanosoma cruzi*	Dog, people	*Triatoma* spp. (reduviid bug), blood transfusion, across mucous membrane or open wounds	*Acute*: splenomegaly, lymphadenomegaly *Subclinical* (latent): no signs *Chronic*: signs of progressive right heart failure with multiple arrhythmias	Serological testing: IFA Organism identification: blood smears, aspirates, histopathology, PCR	No readily available effective drugs Provide supportive care	Transmission via exposure to infected reduviid bugs and contact with infected blood (mucous, membranes, open wounds, contaminated sharp instruments) Dogs possibly sentinels

TTW, Transtracheal wash; *PCR*, polymerase chain reaction; *IFA*, indirect fluorescent antibody.

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CHAPTER 117

Introduction to Behavioral Diagnosis and Treatment

Sharon L. Crowell-Davis

BEHAVIORAL HISTORY

I. Chief complaint
   A. Obtain detailed descriptions of the actual behaviors that are considered unacceptable.
   B. Words such as *jealous, hates,* and *spiteful* are used by owners to refer to a great variety of behaviors and do not provide useful information about the problem behavior or its motivation.
II. Physical environment
   A. Detailed descriptions of the animal's physical environment
   B. Size of house or apartment, access to fenced-in yard, type of fencing, size of fenced area, map of house, location of litterboxes
III. Social environment
   A. Obtain information on all the people and other animals who frequently interact with the animal and how the animal interacts with them.
   B. In cases of suspected separation anxiety, determine the schedule of all caregivers.
IV. Learning and exercise
   A. Obtain detailed information on the training techniques used, commands taught, and the type and duration of exercise.
   B. Many trainers who use aversive training techniques that produce fear and anxiety incorrectly call themselves "positive trainers."
   C. Discern the specific techniques used, not just the general type of training.
V. Early history
   A. Learn as much about the early history as possible.
   B. In cases of adopted animals, little to no information may be available.
VI. Medical history
   A. Medical problems can incite learned behavior problems (e.g., cats with urinary tract infections may learn to eliminate outside the litterbox and continue to do so even when the infection is resolved).
   B. Medical problems that cause pain and discomfort can be the direct cause of behavior problems.

PSYCHOPHARMACOLOGY

I. Ethical and legal issues
   A. Use of most psychoactive medications in small animals is extra-label.
   B. The Animal Medicinal Drug Use Clarification Act of 1994 requires a valid veterinarian-client-animal relationship to prescribe extra-label medications.
   C. In the case of behavior problems, the veterinarian must conduct a complete behavioral and physical examination.
   D. Recommendations by a trainer or nonveterinary behaviorist are not sufficient for prescribing any medication.
II. Benzodiazepines (Crowell-Davis and Murray, 2006)
   A. Benzodiazepines bind to gamma amino butyric acid (GABA) receptors, thereby facilitating the action of GABA in the central nervous system (CNS).
   B. They reduce anxiety and increase affiliative behavior.
   C. Their use in aggression is controversial; although they reduce the fear that motivates much aggression, they may also cause loss of learned inhibitions.
   D. Treatment of an overdose is primarily supportive.
   E. Flumazenil is a benzodiazepine receptor antagonist.
   F. Side effects include sedation, ataxia, and increased appetite.
   G. Liver failure is a rare complication in cats (Levy et al., 1994; Hughes et al., 1996).
   H. They have a rapid onset of action and can be given as needed.
   I. When prescribing benzodiazepines, use the lowest dose and frequency that adequately addresses the problem (Table 117-1).

TABLE 117-1

Doses for Psychoactive Medications

MEDICATIONS	DOSE FOR DOGS	DOSE FOR CATS
Benzodiazepines		
Alprazolam	0.02 mg/kg PO every 4 hours	0.2-1.0 mg/kg PO BID
Chlordiazepoxide	2.0-6.5 mg/kg PO TID	0.2-1.0 mg/kg PO BID
Clonazepam	0.1-0.5 mg/kg PO TID	0.015-0.2 mg/kg PO TID
Clorazepate	0.5-2.0 mg/kg PO QID	0.5-2.0 mg/kg PO BID
Diazepam	0.5-2.0 mg/kg PO every 4 hours	0.1-1.0 mg/kg PO every 4 hours
Flurazepam	0.1-0.5 mg/kg PO BID	0.1-1.0 mg/kg PO BID
Lorazepam	0.02-0.5 mg/kg PO TID	0.03-0.08 mg/kg PO BID
Oxazepam	0.04-0.5 mg/kg PO QID	0.2-1.0 mg/kg PO BID
Selective Serotonin Reuptake Inhibitors		
Fluoxetine	1.0-2.0 mg/kg PO SID	0.5-1.5 mg/kg PO SID
Fluvoxamine	1.0-2.0 mg/kg PO SID	0.5-1.5 mg/kg PO SID
Paroxetine	1.0-1.5 mg/kg PO SID	0.5-1.5 mg/kg PO SID
Sertraline	0.5-4.0 mg/kg PO SID	0.5-1.5 mg/kg PO SID
Tricyclic Antidepressants		
Amitriptyline	1.0-6.0 mg/kg PO BID	0.5-2.0 mg/kg PO SID-BID
Clomipramine	1.0-3.0 mg/kg PO BID	0.25-1.3 mg/kg PO SID
Doxepin	3.0-5.0 mg/kg PO BID-TID	0.5-1.0 mg/kg PO BID
Imipramine	0.5-2.0 mg/kg PO BID-TID	0.5-2.0 mg/kg PO BID-TID
Azapirones		
Buspirone	0.5-2.0 mg/kg PO BID-TID	0.5-1.0 mg/kg PO BID
Monoamine Oxidase Inhibitors		
Selegiline	0.5-1.0 mg/kg PO SID	0.5-1.0 mg/kg PO SID
Central Nervous System Stimulants		
Dextroamphetamine	0.2-1.3 mg/kg PO BID-TID	Not recommended
Methylphenidate	2.0-4.0 mg/kg PO BID-TID	Not recommended

III. Selective serotonin reuptake inhibitors (SSRIs) (Crowell-Davis and Murray, 2006)
   A. They inhibit the reuptake of serotonin, resulting in down-regulation of the postsynaptic serotonin receptors and increased activity of serotonin in the CNS.
   B. They have antidepressant, anxiolytic, anticompulsive, and antiaggression effects (Charney et al., 1990; Dodman et al., 1996; Larson and Summers, 2001; Olivier and Mos, 1992; Reist et al., 2003).
   C. Side effects include mild sedation and changes in appetite or gastrointestinal (GI) function (constipation or diarrhea).
   D. Overdoses can result in serotonin syndrome, which has a variety of signs (e.g., mental changes, neuromuscular and autonomic changes) (Brown et al,. 1996; Martin, 1996).
   E. Treatment of serotonin syndrome includes discontinuation of all SSRIs, decontamination with activated charcoal, anticonvulsants, thermoregulation, and fluid therapy.
   F. SSRIs should not be given with monoamine oxidase inhibitors (MAOIs).
   G. SSRIs are generally given SID and may take 2 to 6 weeks to produce an effect (see Table 117-1).
   H. Their efficacy is difficult to determine with less than 1 month of therapy.
   I. They must be given per os; no transdermal medication provides comparable blood levels (Ciribassi et al., 2003).

IV. Tricyclic antidepressants (TCAs) (Crowell-Davis and Murray, 2006)
   A. They inhibit the reuptake of both serotonin and norepinephrine, resulting in down-regulation of serotonin and norepinephrine receptors, and increased activity of serotonin and norepinephrine in the CNS.
   B. They also have antihistaminic, anticholinergic effects, and are α-adrenergic antagonists.
   C. They have antidepressant, anxiolytic, antiaggressive, and anticompulsive effects (King et al., 2000; King et al., 2004).

D. Side effects vary widely.
   1. Sedation, vomiting, diarrhea, constipation
   2. Urinary retention, appetite changes, ataxia
   3. Decreased tear production
   4. Rarely, arrhythmias

E. Amitriptyline has been used most often because of its low cost; however, it has a higher incidence of side effects (antihistaminic, antimuscarinic) and is no longer considered the first drug of choice.

F. Clomipramine is the most serotonin-specific of the TCAs.

G. Commonly used TCAs are presented in Table 117-1.

V. Azapirones (Crowell-Davis and Murray, 2006)

A. Azapirones are serotonin 1A agonists and are anxioselective.

B. Although a rapid response can occur, response may require 1 to 4 weeks.

C. Azapirones should not be given in combination with MAOIs.

D. Side effects are rare but include mild sedation and increased anxiety.

E. Buspirone is the only commercially available azapirone (see Table 117-1).

F. Transdermal absorption of buspirone is poor compared with oral absorption (Mealy et al., 2004).

VI. MAOIs

A. They prevent the action of MAO-A, MAO-B, or both.

B. Selegiline hydrochloride slows the progression and reverses some of the symptoms of canine cognitive dysfunction, may increase lifespan, and is sometimes used as an anxiolytic (see Table 117-1) (Milgram et al., 1993; Milgram et al.,1995; Ruehl et al., 1994; Ruehl et al., 1997; Mills and Ledger, 2001).

C. MAOIs should not be given with SSRIs, TCAs, or azapirones, as serious and sometimes life-threatening side effects can occur.

D. When changing from an MAOI to any of these other medications, wait a minimum of 2 weeks.

E. Side effects include agitation, vomiting, disorientation, diarrhea, and diminished hearing.

F. Treat for a minimum of 1 to 2 months.

VII. CNS stimulants

A. CNS stimulants increase synaptic dopamine and norepinephrine.

B. In dogs, CNS stimulants are used to treat attention deficit disorder, which is commonly called *hyperkinesis*.
   1. True canine hyperkinesis is very rare.
   2. Most "hyperactive" dogs are young, inappropriately trained, or inadequately exercised.

C. They should not be given concurrently with an MAOI.

D. They cause increased arousal and activity, and possibly stereotypic behavior in normal dogs and cats.

E. Commonly used CNS stimulants include dextroamphetamine and methylphenidate (see Table 117-1).

VIII. Other drugs

A. It may be necessary to try several different medications or combinations of medications before identifying an effective treatment for any given animal.

B. Acepromazine has sedative properties but is not a true anxiolytic.
   1. It is not used in the treatment of anxiety disorders, except as a supplement to true anxiolytics.
   2. It may be tried in animals in which the behavior is so violent that it risks harm to itself or its environment.

C. Hormones have serious and sometimes life-threatening side effects and are used only as a last resort.

LEARNING

I. Habituation (Domjan, 2003): a natural (not learned) behavior that decreases in intensity and eventually discontinues after repeated exposure to the natural stimulus for the behavior

II. Classic conditioning (Domjan, 2003)

A. A stimulus that does not naturally elicit a response does so through pairing with a stimulus that naturally causes the response.
   1. An unconditioned stimulus causes a natural or unconditioned response.
   2. An example would be the fear that occurs when a dog is hit by a human.
   3. The sight of the human initially does not cause fear (human is a neutral stimulus).
   4. After the human has hit the dog several times, the dog becomes afraid when it sees the human.
   5. The human has now become a conditioned stimulus and the fear that occurs at the sight of the human is a conditioned response.

B. Classic conditioning affects physiological and emotional responses, not voluntary behavior.

C. Stimulus discrimination is the phenomenon in which only a specific, discrete stimulus becomes the conditioned stimulus for the response (e.g., short, blonde humans wearing glasses).

D. Stimulus generalization is the phenomenon in which a broad category of stimuli become the conditioned stimuli for the response (e.g., all humans).

III. Operant conditioning (Domjan, 2003)

A. The probability that a behavior will recur given a specific stimulus is increased or decreased by the consequences of the behavior.

B. An eliciting stimulus informs the animal that if it does not give a particular response, a particular controlling stimulus will not follow the response.

C. Operant conditioning changes voluntary behavior.

D. With positive conditioning, the controlling stimulus occurs after the response.

E. With negative conditioning, the controlling stimulus does not occur or is removed after the response.

F. Reinforcement increases the probability that the behavior will recur given a specific eliciting stimulus; to be effective, reinforcers must occur as the behavior is happening or immediately after the behavior occurs.

G. Punishment decreases the probability that the behavior will recur given a specific eliciting stimulus.

H. Positive reinforcement increases the probability that the behavior will recur, depending on the presence of the controlling stimulus subsequent to the behavior.
   1. Schedules of reinforcement vary and affect both the speed with which the animal learns and resistance to extinction of the behavior.
   2. In continuous reinforcement, the animal's behavior is reinforced every time it engages in the desired behavior.
   3. In variable ratio reinforcement, the animal's behavior is reinforced after a variable number of repetitions.

I. Negative reinforcement increases the probability that the behavior will recur, dependent on the removal or absence of the controlling stimulus subsequent to the behavior.

J. Positive punishment decreases the probability that the behavior will recur, depending on the presence of the controlling stimulus subsequent to the behavior.

K. For punishment to be effective, the following criteria must be met:
   1. It must be *immediate* (occurs as the animal is engaging in the undesired behavior or within 1 second of discontinuation of the behavior).
   2. It must be *consistent* (occurs every time the undesired behavior occurs).
   3. It must be *appropriate* (a type and intensity of behavior that disrupts the undesired behavior, but does not cause a fear response).

L. Negative punishment decreases the probability that the behavior will recur, dependent on the removal or absence of the controlling stimulus subsequent to the behavior.

M. Prompting and fading are learning processes where the animal is prompted (induced to engage in the desired behavior by a strong stimulus), then reinforced, and the intensity of the prompt is progressively decreased as it is repeated.

N. Shaping is a learning process where a behavior that approximates the final desired behavior is reinforced.
   1. Progressively, the animal must engage in a behavior that is more and more like the final, desired behavior to obtain the reinforcer.
   2. An example would be teaching the dog to assume the down position by only giving it a reinforcer when it is sitting and lowers its head a little, then requiring more and more, until it finally lies down.

IV. With desensitization, the animal is exposed to a stimulus that causes an undesired behavior (usually behaviors resulting from fear), but at such a low level that the undesired behaviors do not occur (Crowell-Davis and Murray, 2006).
   A. Over time and with multiple repetitions, the intensity of the stimulus is gradually increased.
   B. Ideally the undesired response is not provoked.

V. Counter-conditioning occurs when a behavior is induced that is both behaviorally and physiologically incompatible with the undesired response (Crowell-Davis and Murray, 2006).

VI. Extinction is the loss of a learned behavior (Domjan, 2003).
   A. Extinction of classic conditioning occurs when the animal is repeatedly exposed to the conditioned stimulus without pairing it with the unconditioned stimulus, and the association between the two is lost.
   B. Extinction of reinforced operant conditioning occurs when the consequences of the response change.
      1. For example, the reinforcer is no longer given or the aversive stimulus is no longer removed.
      2. Eventually the response wanes and discontinues.

CONDITIONS OF BOTH CATS AND DOGS

Dominance

Definition

I. There are various definitions of dominance.

II. A dominance relationship exists between two animals if one animal consistently submits to another in antagonistic interactions at a rate greater than would be predicted by chance (Bernstein, 1981).

III. This definition does not require that the subordinate animal always submit to the dominant animal, only that it submits more than would be predicted if there was no dominant-subordinate relationship between the two animals.

IV. This definition does not require that the dominant animal be aggressive or even exhibit dominance signals to the subordinate, only that the subordinate give submissive signals to the dominant animal.

V. In most interactions, the dominant animal exhibits ritualized dominance behaviors.

VI. This definition does not make any assumptions about the function of dominant-subordinate relationships.

Anxieties and Phobias

Definition

I. Fear is an emotional state that is normal under certain conditions and motivates survival behavior ("fight or flight" response).

II. Animals are assumed to be fearful if they avoid, scream, cry, or engage in other signaling behaviors that are typically associated with fear.
   A. Dogs indicate fear by turning their ears back or down, lowering their tail between their hind limbs, crouching, turning their head or body away from the cause of the fear, whimpering, whining, lip-licking, yawning, retracting the commissure of their lips, salivating profusely, pacing, panting, urinating, defecating, and damaging objects with their teeth or claws.
   B. Cats indicate fear by turning their ears back or down, lowering their tail lateral to one of their hind limbs, crouching, turning their head or body away from the cause of the fear, gaping (opening the mouth wide and

holding it open), hissing, profuse salivation, urination, and defecation.
   C. Some of these behaviors may also occur for other reasons.
III. Fear is identified as being a behavior problem by the context in which it occurs.
   A. A phobia is present if the animal exhibits a consistent, strong behavior indicative of fear to one or more stimuli over multiple exposures to those stimuli, and the fear is not rational or adaptive.
   B. An anxiety disorder is milder than a phobia in terms of intensity of the behavior, but the animal exhibits the behavior over multiple exposures to given stimuli or, in the case of generalized anxiety disorder, to no particular stimulus.

Causes

I. Some strains of dogs and cats appear to be more susceptible to developing fear responses than others, so genetics may contribute (Angel et al., 1982).
II. Early experience in both dogs and cats, such as specific exposure to a variety of nonharmful stimuli, helps make the animal less likely to develop fear-related problems.
III. Learning, particularly classic conditioning, is the main cause of many anxiety disorders and phobias.

Clinical Signs and Diagnosis

I. The animal repeatedly exhibits behaviors indicative of fear to the same stimuli.
II. The animal may be afraid of more than one stimulus.
III. If the animal almost constantly exhibits at least low levels of anxiety, it has generalized anxiety disorder (GAD) (Reisner, 2003).
   A. Animals with GAD may exhibit intense fear responses to certain stimuli because they have become particularly sensitized to those stimuli.
   B. Some animals have multiple phobias (e.g., storms, being alone, meeting strange people), but are calm when none of those stimuli are present, so they do not have GAD.

Treatment and Monitoring

I. Except in mild cases, anxiolytic medications are necessary to significantly improve the signs.
II. Use of antipsychotics (acepromazine) is contraindicated, except when the behaviors are likely to result in bodily harm.
III. Early in treatment, avoid exposing the animal to the fear-inducing conditions.
IV. Desensitize and counter-condition the animal to the stimuli that cause fear responses.
   A. For dogs or cats with separation anxiety, fear of being alone or fear of separation from particular attachment figures, desensitize the animal by a series of short, then progressively longer departures.
   B. Counter-conditioning is generally not possible in these cases, as there is no way to induce competing behaviors in the owner's absence.
   C. For dogs or cats with storm phobia, desensitize and counter-condition the animal to sounds of storms.
   D. For dogs or cats that are afraid of people, desensitize and counter-condition to the approach and physical contact with people.
V. Flooding (i.e., exposure to the fear-inducing stimulus until the animal ceases exhibiting a fear response) is generally an undesirable treatment because the animal may harm itself or the environment before a flooding session has ended.
   A. There are rare exceptions in which flooding can be useful, practical, and not harmful.
   B. Placing a negative ion generator or an artificial waterfall in the house of an animal that is storm-phobic floods the animal to the presence of negative ions, and in the case of the waterfall, the sound of falling water.
VI. Cases of anxieties and phobias vary substantially in their severity, and results of treatment must be monitored closely.

Fear Aggression

Definition

I. Fear-motivated aggression is a very common behavior problem in both dogs and cats.
II. Aggression includes, but is not limited to, growling, snarling, snapping, and biting (dogs), or snarling, biting, scratching, and hissing (cats), which are motivated by anxiety and fear.

Causes

I. Poor socialization as a puppy or kitten to the feared species, usually dogs or humans, is a common cause.
II. Frightening experiences have occurred with the feared species or individuals (e.g., being abused by humans, attacked by other dogs or cats).
   A. Stimulus discrimination may occur in which the dog or cat is afraid only of the individual that caused harm or of individuals that are very similar in appearance, sound, or odor.
   B. Stimulus generalization may occur in which the dog or cat is afraid of a broad spectrum of individuals (all dogs or all humans).
III. Genetics or a lack of early exposure to a variety of stimuli may make the animal more sensitive to fear-inducing stimuli.
IV. Fear is one of the most common reasons for dogs and cats to exhibit human-directed aggression, and use of aversive training techniques is a contributing factor, especially in dogs.

Clinical Signs and Diagnosis

I. Fear is indicated by one or more of the following and is combined with aggressive behavior:
   A. Lowered tail, ears, and head
   B. Crouch or semicrouch, moving away
   C. Avoidance of eye contact
   D. Whining (dogs), gaping (cats), hissing (cats)

II. Some dogs or cats that begin as fear-aggressors subsequently develop body language that includes approaching or even chasing the victim with the tail up (dogs), ears up, and eyes staring.
III. In human-directed fear aggression, the dog or cat may attack when the person has turned around and is walking away.
IV. The underlying emotion motivating the behavior is still fear, even though the overtly visible behaviors have evolved from learning.

Treatment

I. Avoid the aggression by not placing the dog or cat in situations in which fear is likely to be triggered.
   A. Try not to approach, stare at, or reach toward the animal.
   B. In some cases, placing a basket muzzle on a dog while it is in fear-inducing situations may be useful.
   C. With cats, wear protective clothing (pants made of strong cloth, close-toed shoes).
II. Administration of an SSRI or TCA may be helpful (see Table 117-1).
   A. In general, avoid use of benzodiazepines, as they may cause loss of inhibition.
   B. In some cases benzodiazepines can be useful, but they must be used with caution and careful supervision.
III. Institute systematic desensitization and counter-conditioning, beginning with the dogs, cats, or humans to whom the animal exhibits minimal fear.
IV. Do not use aversive training techniques (punishment or negative reinforcement), as these techniques exacerbate the fear that is the underlying cause of the aggression.

Monitoring of Animal

I. Do not place the animal in situations that are likely to trigger incidents of aggression.
II. Communicate with the owner regarding progress every 1 to 2 weeks initially.
III. Communication intervals can be gradually increased if the owner clearly understands the treatment protocol and if the animal is making progress.
IV. Depending on the severity of the problem, it may resolve in a few weeks or a few months.
V. Some cases, especially dogs and cats that have been subjected to abuse by humans, may never resolve, although improvement can usually be achieved with appropriate treatment.

Compulsive Disorder

Definition

I. A stereotypic behavior is a repetitive behavior that is constant in form, serves no obvious goal or function, and occurs in a predictable sequence.
II. A compulsive behavior is a stereotypic behavior that is exhibited regardless of context.
III. Compulsive behaviors are derived from natural behaviors and are typically excessive, intense, performed out of context, or directed toward unnatural stimuli.
IV. Common compulsive behaviors vary from species to species.
   A. In dogs, tail chasing, hunting "invisible game," and excessive self-grooming are common.
   B. In cats, excessive self-grooming, licking, and sucking or chewing on household objects are common.

Causes

I. Stress, including an understimulating or overstimulating environment, can initiate a compulsive disorder.
II. Genetic predispositions make certain individuals more or less susceptible in response to stress.
III. Animals with compulsive disorder undergo neurochemical and even neuroanatomical changes.

Clinical Signs and Diagnosis

I. The animal engages in a stereotypic behavior.
II. Although certain stereotypic behaviors are most common in certain species, any behavior can develop into a compulsive disorder.
III. The behavior is exhibited in a variety of contexts.
IV. The animal spends excessive and increasing amounts of time engaging in the behavior.
V. As the disorder progresses, it may interfere with normal and even essential behaviors, such as play, social interactions, eating, and drinking.
VI. In cases of excessive grooming, the animal eventually harms itself, causing abrasions, lacerations, and in extreme cases, removal of body parts (e.g., toe, end of the tail).

Treatment and Monitoring

I. Do not use any aversive training techniques (punishment, shock, reprimanding).
   A. The disorder is caused by stress and the use of aversive training techniques only increases the stress.
   B. This principle applies to all species.
II. If the problem is mild or just beginning, resolution may be accomplished without medication.
   A. Identify stressors in the environment and remove, decrease, or modify them.
      1. A common stressor is excessive confinement in insufficient space, with too little to do.
      2. Provide the animal with increased time in larger spaces, appropriate toys, and activities.
   B. Using positive reinforcement, teach the animal a variety of commands, so the owner can distract and redirect the animal by giving the command and subsequently redirecting it to another activity.
III. Most cases require medication, such as fluoxetine, clomipramine, other SSRIs, or TCAs (see Table 117-1).
IV. If the animal is very anxious, supplementation with a benzodiazepine may be beneficial.
V. Owners are often very frustrated with this problem, and regular monitoring is necessary to provide appropriate guidance.

Maternal Aggression

Definition and Causes

I. Aggression is exhibited by a female in the context of defending her young.
II. This is a natural behavior that facilitates survival of the offspring.
III. In the domestic dog and cat, both genetics and experience can cause a female to be aggressive to the point where it is problematic.

Clinical Signs and Diagnosis

I. Aggression is exhibited by a female that is otherwise not aggressive when a person or another animal approaches or attempts to handle the young.
II. When the individual approaches, threat behavior, such as growling (dog and cat) or hissing (cat), occurs.
III. If the individual initiates direct interaction with the young, biting or scratching may ensue.

Treatment and Monitoring

I. Prevention is of primary importance.
  A. Ensure that the pregnant female is very familiar and comfortable with everyone involved with her postpartum care.
  B. Provide a suitable and secure nesting area.
  C. Keep animals that are unfamiliar or may present a risk to the young away from the nest.
II. Some females may have such severe aggression that they are not suitable for breeding.
  A. If the female exhibits severe aggression upon her first parturition, she may have a genetic predisposition for strong defense of young.
  B. If the mother undergoes an extremely frightening experience (e.g., someone harms her offspring in her presence), she may become classically conditioned to severe aggression in this context.
III. Most cases of mild to moderate maternal aggression naturally improve over a period of days as the offspring mature.
IV. Supervise the animal closely for the first several days postpartum, without disturbing the puppies or kittens more than is absolutely necessary.

Redirected Aggression

Definition and Causes

I. Aggression is redirected to a secondary target because the primary target cannot be reached.
II. The initial motivators of the aggression are numerous and varied.
III. Humans can become the object of aggression when they get close to or interfere in the actions of a cat or dog that is already motivated to be aggressive toward another subject.

Clinical Signs and Diagnosis

I. Aggression occurs when the animal is already motivated to be aggressive to another animal or person.
II. Examples include but are not limited to the following:
  A. Picking up a cat when it is fighting with a dog or another cat
  B. Taking hold of a dog's collar when it is fighting with another dog or cat, or when it is behaving aggressively toward another person

Treatment and Monitoring

I. Identify the primary cause of the aggression and treat it.
II. Educate owners on prevention of aggressive conditions.
III. The need for monitoring varies substantially, depending on the cause of the primary aggression.

Predatory Aggression

Definition and Causes

I. It is aggression by a dog or cat where specific behaviors preceding the aggression are consistent with normal predatory behavior in these species.
II. Dogs and cats are both predators, and predatory aggression is a natural behavior.
III. For cats, whether the predatory aggression is a behavior problem depends on the context in which the cat is kept.
  A. For example, if the cat is kept on a dairy farm with expectations that it controls the rodent population, the predatory aggression is desirable.
  B. If the cat is allowed to run loose in a wild bird sanctuary or in other habitats where there are small animal populations that can be seriously harmed by predation, its behavior is highly undesirable.
IV. This same general rule also applies to dogs.
  A. If a dog is trained to assist in hunting, its behavior is not considered a problem.
  B. However, dogs may direct their predatory behavior to livestock, pet cats, small dogs, children, and even adult humans.
  C. In these cases the behavior is considered highly undesirable.
V. Genetics contributes to a dog's tendency to engage in particular predatory behaviors.
  A. Herding dogs have a low threshold for stalking and chasing behavior, but a high threshold for biting.
  B. Some breeds have little innate predatory behavior and require a strong stimulus to trigger such behavior.

Clinical Signs and Diagnosis

I. Cats stalk, chase, and pounce on small game and kill it, usually with a fatal bite to the neck.
II. Dogs stalk, chase, and bite the victim of the predatory attack.
III. Dogs often hunt in packs and bring down their prey by multiple bites or by the weight of multiple dogs holding onto the victim.
IV. In the case of predatory dog attacks on babies, small toddlers, small dogs, pet cats, and other small animals, the dog often grabs the victim and violently shakes it.

Treatment and Monitoring

I. Pet cats that live in or near areas where it is undesirable for them to kill small animals must be kept entirely indoors.
II. Although desensitization and counter-conditioning may increase a dog's threshold to engage in predatory attacks, they cannot be entirely relied upon.
III. Because predatory attacks often lead to serious maiming and even death, dogs with a history of independent predatory behavior must always be leashed or restrained in an enclosure from which they cannot escape.
IV. Dogs running loose in packs present a high risk of mass predatory attacks.

Pain-Induced Aggression

Definition and Causes

I. Aggression occurs as a consequence of pain.
II. The existence of this phenomenon is one reason that it is critical for all pets exhibiting aggressive behavior to be thoroughly evaluated by a veterinarian.
III. The cause of the pain may not be obvious to the lay person or even upon a basic physical examination.
IV. Any painful condition, including illness or injury that may or may not be obvious, is a potential cause.

Clinical Signs

I. Onset of aggression is often sudden and severe but may be gradual.
II. Pain-induced aggression is suspected anytime the aggression only occurs when a specific part of the body is reached for or touched (e.g., ears with ear infections, hindquarters with hip dysplasia).

Diagnosis

I. Identify the underlying illness or injury.
II. The cause may not be obvious, or the animal may hide an injury (e.g., a cat may walk without lameness on a limb with a greenstick fracture, but be aggressive to anyone who attempts to touch it).

Treatment and Monitoring

I. Treat the primary problem.
II. Use protective gear (muzzles, leather gloves) to handle the animal, and only use as much restraint as is absolutely necessary.
III. Fear aggression or other fear-based problems may develop secondary to an episode of pain-induced aggression (see Fear Aggression).
IV. Development of fear-related behavior problems secondary to pain-induced aggression is common; therefore monitor behavioral improvement independent of the physical improvement.

Cognitive Dysfunction

Definition and Causes

I. Changes in cognitive function occur as a pathologic process in some aged animals and may involve loss of memory, learning ability, awareness, and perception.
II. Although cognitive dysfunction is a process of aging, not all dogs and cats exhibit this phenomenon.
III. Genetics and environmental factors, including diet, probably affect the likelihood of the animal developing cognitive dysfunction.

Clinical Signs and Diagnosis

I. Multiple changes in behavior occur that are consistent with cognitive decline and cannot be explained by other medical conditions.
   A. Loss of prior learning, such as housetraining, litterbox training, and basic obedience (sit, come)
      1. Dogs may signal to go outside less or even discontinue this behavior.
      2. Dogs may eliminate inside right after they have been outside and may eliminate in front of the owner.
      3. Cats may become erratic in their litterbox usage.
   B. Changes in sleep patterns, increased sleeping
   C. Changes in social interactions
      1. The animal may not recognize family members or may exhibit decreased social interactions with both human family members and other pets.
      2. Dogs that have historically been aggressive to strangers may begin exhibiting aggression to family members.
      3. Cats that have historically hidden when strangers visit may begin hiding whenever anyone, including family members, is home.
   D. Disorientation
      1. The animal may walk behind doors instead of through them, or wander around the house appearing to look for something.
      2. Some animals stand and stare into space for long periods.
      3. Some animals exhibit decreased or no response to auditory stimuli (e.g., doorbell ringing, humans talking).
   E. Possible appetite changes
   F. Changes in type and frequency of activity
      1. Pacing or vocalizing at night
      2. Overall decrease in total activity per 24 hours
   G. Anxious, even with no history of an anxiety problem
II. The diagnosis is based primarily upon owner observations.
III. A comprehensive geriatric medical work-up is indicated to identify or rule out other causes or contributing factors.

Pathophysiology

I. The pathophysiology of canine cognitive dysfunction is very similar to human Alzheimer's disease (Shimada et al., 1992; Uchida et al., 1992; Cummings et al., 1996).
   A. Decreased total brain size and mass
   B. Dilation of the ventricles
   C. Decreased cerebral blood flow
   D. Meningeal fibrosis
   E. Decreased number of cells in the brain
   F. Degeneration of the white matter

II. Neurotransmitter changes include decreased levels, function, and activity of norepinephrine, serotonin, dopamine, and acetylcholine.
III. β-Amyloid plaques develop in the cerebral cortex and hippocampus.

Treatment

I. Selegiline is administered to both dogs and cats at 0.5 to 1.0 mg/kg PO SID (Head et al., 1996; Ruehl et al., 1996; Landsberg, 1999).
   A. It may require 30 to 60 days for improvement to be observed.
   B. Selegiline does not cure the disease.
   C. It only slows the progress and ameliorates many of the signs.
II. Increase the level of antioxidants in the diet.
III. Educate the owner about the disease and the pet's special needs.
IV. For dogs that have lost their house-training, take them outside frequently and reward them for eliminating outside, as for a 6-week-old puppy.
V. For cats that have become inconsistent in litter box usage, add additional litterboxes and place the cat in them several times a day.
VI. Avoid major changes in the environment, if possible.
VII. Provide mental and tactile stimulation (walks), regular training using positive reinforcement, and massage treatments.
VIII. Do *not* ever use aversive stimuli, including punishment, for any reason.

Monitoring of Animal

I. Improvement is gradual, occurring over many weeks.
II. Some animals exhibit little to no improvement, even with aggressive treatment.

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CHAPTER 118

Canine Behavioral Disorders

Sharon L. Crowell-Davis

AGGRESSION

General Considerations

I. With all cases of canine aggression, it is important to inform the owners of the potential risk their dog presents if it is not euthanized.
II. The exact degree of risk varies with the size of the dog, type and severity of the aggression, ability of the owners to adequately restrain the dog, and use of special equipment such as muzzles and head collars.
III. Risk is also affected by the presence or absence of especially vulnerable individuals (children, elderly), or pets that are substantially smaller than the aggressor.

Dominance Aggression Syndrome

Definition

I. A dog behaves as if it were dominant to another dog, human, or other animal (Crowell-Davis, 1991).
II. It is accompanied by actual aggression, including (but not limited) to snarling, snapping, and biting.
III. The term *syndrome* is used because there is no single diagnostic criterion; it is identified by a collection of signs.
IV. True dominance aggression is rare in dogs and is only diagnosed after a thorough behavioral evaluation excludes other possible diagnoses and confirms a consistent pattern of dominant behavior.

Causes

I. The causes are not fully understood.
II. Genetics, early experience, inadequate early socialization, and persistent behavior by owners that the dog interprets as submissive are probably contributing factors.

Clinical Signs

I. The dog frequently exhibits ritualized dominance signals to the target individual, such as staring, directing the ears toward the individual, holding the tail up while staring, and approaching the individual.
II. The dog either does not or rarely exhibits fear, anxiety, or submission toward the individual (i.e., does not turn the head away, avoid eye contact, move away, lower the tail or crouch).
III. Signs occur most commonly in 1- to 3-year-old, intact males.
IV. Signs can occur at any age, in any gender (neutered or intact), and in any breed.

Diagnosis

I. Dominance aggression is a problem based on relationships.
   A. Aggression is usually directed toward family members, people, or dogs the aggressor knows well, rather than toward strangers.
   B. In severe cases, the dog may exhibit intense aggression to both family members and strangers, attempting to establish dominance with any human it meets.
   C. The latter condition is rare and may be secondary to underlying pathologic central nervous system (CNS) findings, such as low serotonin levels (Reisner et al., 1996).
II. Aggression occurs in conjunction with ritualized signals of dominance, including staring, tilting or pulling the ears forward, upright stance, and approaching with the tail up.
   A. The tail may be wagging.
   B. Tail wagging is from arousal, not friendliness.
III. Actual bites are often unpredictable.
   A. The owner may reach to pet the dog and the dog suddenly bites.
   B. This behavior can also occur with fear aggression, and information on the dog's current and historical signaling (behaviors) is important to differentiate.
IV. Spontaneous or unpredictable growling may be reported.
V. Affected dogs are often resistant to learning the "down" command, especially if it is taught with prompting and fading, and may have bitten when attempts were made to force them to lie down in a submissive posture.
VI. Affected dogs commonly jump into their owner's laps and stare at the owner.
   A. This must be differentiated from dogs that have been taught to jump in the owner's lap because the owner pets them when they do so.
   B. The owner may also call the dog to their lap.
VII. Dogs commonly demand to be let out or in, and demand to be petted, and their attention-seeking behavior escalates to aggression if the owner does not perform acts when

the dogs signal that they want such actions from the owner.

VIII. Dogs may physically block the owner's movements in the home, and may attack if the owner attempts to get past them.

IX. Any punishment, verbal or physical, is likely to trigger aggression.

X. Dogs may mount the owner's legs, which must be distinguished from abnormal sexual imprinting and attention-seeking behavior.

XI. Affected dogs may or may not guard food or a sleeping area.

XII. In cases of interdog dominance, establishment of a hierarchy is normal.
   A. Ritualized dominance and submissive signaling that does not include aggression should be allowed.
   B. Dominant and subordinate interactions can escalate to fighting under a variety of circumstances, including but not limited to the following:
      1. Poor early socialization resulting in a dog being unable to recognize and respond appropriately to signals of submission from other dogs.
      2. Poor early socialization resulting in a dog not recognizing ritualized signals of dominance from another dog or not responding with a ritualized submissive behavior.
      3. Two dogs that are evenly matched in size, strength, and motivation may both try to be the dominant dog; these cases are often the most severe and resistant to resolve.
      4. Owner interference in the natural order may contribute to fighting (e.g., owner acts supportive of and gives special attention to a geriatric or sick dog while trying to get a healthy, young adult dog to act deferential to the old dog).

Treatment

I. Human-directed dominance aggression
   A. Open confrontation is likely to lead to human injury and is not recommended.
   B. Castrate intact males.
   C. Instruct the owner to avoid situations in which the dog is likely to behave aggressively.
   D. The owner should frequently give low intensity, ritualized dominance signals that the dog will tolerate (e.g., touching the top of the dog's head).
   E. Teach the dog the "down" command using shaping, not prompting and fading.
   F. Require the dog to obey a command (preferably "down") to get anything it wants (e.g., petting).
   G. Reward ritualized submission (e.g., if the dog looks away from the owner when the owner looks at it), and reinforce that behavior.
   H. Do not allow the dog on furniture, and if it currently defends furniture, call it off for a reward.
   I. Selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants (TCAs) may be helpful (see Table 117-1).
   J. Hormonal treatments (megestrol acetate, medroxyprogesterone acetate) may be considered in dogs that have not responded to more conservative therapy, but are only considered as a last resort.

II. Interdog dominance aggression
   A. Educate owners about normal dog communication and social organization.
   B. Dogs that exhibit dominance aggression to other dogs owing to poor early socialization, as well as failure to recognize submission and inhibit their own aggression, may require muzzling, confinement, or both on an indoor leash with a head collar.
      1. Teach the dog a variety of commands and use these to redirect its behavior whenever it exhibits the intention of being dominant or aggressive to other dogs.
      2. Always supervise the dog when it is in the presence of other dogs.
   C. For dogs that fail to exhibit submissive responses to ritualized dominance signals by other dogs, teach them the "down" command and tell them to go down anytime another dog approaches in a dominant fashion.
   D. When a young, healthy dog attacks a geriatric dog in response to the owner's preferential treatment of the older dog, the owner must give preferential treatment (feed first, pet first, let in and out first) to the young dog.
   E. If owner compliance is a problem, special treatment can be given to the older dog when the young dog is not around.

Monitoring of Animal

I. Dogs with dominance aggression can be very dangerous, especially if they are large.

II. Frequent contact must be made with the family regarding treatment progress.

Possessive Aggression

Definition and Causes

I. It is aggression that occurs while defending an object (e.g., toy, bone, bowl of food).

II. Attempts to control important resources are somewhat normal behaviors for dogs.

III. Extreme manifestations (dog becomes highly aggressive if a person or another dog gets near or enters the same room) develop in part because of learning.
   A. Dogs that have lived on the street may developed aggression to survive.
   B. If a puppy's first attempt to defend a desired object results in a person or another dog backing away, they will learn that aggression is an effective tool.

Clinical Signs and Diagnosis

I. Aggression occurs only in the specific context of defending a certain object or objects.

II. If dogs that defend certain objects exhibit no other signs of aggression or dominance toward the owner or other dogs, they do not have dominance aggression syndrome.

Treatment and Monitoring

I. If the item is discrete and nonessential, removing all examples of the item from the dog's environment can eliminate the problem.
II. If the item cannot be eliminated from the environment, use desensitization and counter-conditioning to alter the dog's response to people and other dogs approaching the item.
III. Owners that use desensitization and counter-conditioning may need daily guidance during the first several days of treatment.

Territorial Aggression

Definition and Causes

I. It is defined as defense of a specific geographical area, which may be as small as a room or as large as a farm.
II. As with possessive aggression, some degree of territorial defense (e.g., brief barking at strangers) is normal.
III. In cases that represent a potential public health problem, the dog barks persistently and loudly, and the behavior may escalate to growling, snapping, and biting.
IV. A combination of genetics and learning contribute to this problem.

Clinical Signs and Diagnosis

I. The aggression is usually directed toward non-family members, humans, or other dogs that enter the dog's perceived territory.
II. When off of its territory, the dog is not aggressive.
III. Occasionally the aggression is directed toward human or canine family members that enter certain areas of the house.

Treatment and Monitoring

I. Do not leave the dog outside unsupervised.
II. If necessary, keep the dog muzzled or on a leash when visitors arrive.
III. Conduct basic obedience training using only positive reinforcement methods.
IV. Desensitize and counter-condition the dog to strangers approaching and entering its territory.
V. Check in with the owner every 2 to 4 weeks, depending on the severity of the case.

Protective Aggression

Definition and Causes

I. Aggression is exhibited in the context of defending a person or another animal.
II. Genetics is a contributing factor, as some breeds have a low threshold for protective behavior.
III. Learning is a significant contributing factor.
   A. Although some owners deliberately train their dogs in protective behavior, others inadvertently encourage it.
   B. Especially in the latter case, the dog may present a significant risk of harm to anyone approaching the owner or handler, because the dog has learned to engage in aggressive behavior toward non-family members, and control of the dog's behavior may not be maintained.

Clinical Signs and Diagnosis

I. Aggression is exhibited anytime someone approaches the person or animal being protected.
II. In some cases, the owner can disrupt the dog's aggression by a command that indicates the individual approaching is welcome.
III. In other cases, the owner has no control over the dog's behavior.

Treatment and Monitoring

I. If necessary, muzzle the dog anytime it is exposed to people against whom it might be aggressive.
II. Head collars are especially useful as they improve the owner's ability to control the dog's head and mouth.
III. Teach the dog basic obedience commands using positive reinforcement training techniques, shifting from continuous reinforcement to variable ratio reinforcement to generate a high level of motivation.
IV. Desensitize and counter-condition the dog to people approaching the owner or to any individual being protected.
V. Training with multiple stimuli is necessary to produce stimulus generalization.
VI. This problem, if severe, typically takes weeks or months to resolve, and the dog may never be truly trustworthy around some people.

ATTENTION DEFICIT DISORDER/ HYPERKINESIS

Definition and Causes

I. A phenomenon similar to human attention deficit disorder is often referred to as *hyperkinesis* in dogs (Corson et al., 1976; Luescher, 1993).
II. It is a rare phenomenon in dogs.
   A. Most dogs that are hyperactive as young, healthy dogs are exhibiting normal behavior for their species and age.
   B. In some cases, the dog is underexercised, and inadequately or inappropriately trained for their environment.
III. The dog is consistently and easily distracted and is usually hyperactive.
IV. Learning is poor, even with a good trainer using appropriate techniques.
V. Cause is unknown, although one group of related dogs with this problem had low levels of norepinephrine, dopamine, and homovanillic acid in the brain (Bareggi et al., 1979).

Clinical Signs and Diagnosis

I. The dog usually performs poorly in any kind of training.
II. Most of these dogs are hyperactive, constantly in motion, or getting into things.
III. The dog may rest only at night.

IV. In the examination room, the dog does not sit or rest.
V. In the examination room, attempts at basic training are likely to be unsuccessful because the dog is constantly in motion.

Treatment

I. Treatment with CNS stimulants, such as methylphenidate or amphetamine, results in less activity and more attentiveness.
II. Because the dog has historically been unable to learn any basic training and has multiple experiences with undesirable behaviors, it does not immediately exhibit good learning and appropriate behavior.
III. If the owners attempt basic training (as if they were just starting with a young puppy), the dog should respond as long as it is on medication.

Monitoring of Animal

I. Owners are often very frustrated with their dog by the time the problem is diagnosed.
II. Frequent communication with the owners and the trainer involved in case management is essential during the first few weeks of treatment.

ELIMINATION PROBLEMS

Definition and Causes

I. These problems consist of urination, defecation, or both in the house or another undesired location.
II. Urine and occasionally feces are used to mark territory.
III. Urination in the house may occur because of an anxiety disorder, such as separation anxiety or storm phobia (see Anxieties and Phobias in Chapter 117).
IV. Dogs urinate as a demonstration of submission to dogs or humans they perceive as being dominant to them.
V. Dogs that are very excited may lose control of their urinary sphincter and urinate while running or jumping.
VI. Dogs may eliminate in the house because they have not been appropriately housetrained or because they have unlearned their housetraining.
VII. See Section 7 for the medical causes of inappropriate urination.

Clinical Signs and Diagnosis

I. Marking is identified by elimination of small volumes of urine or (rarely) feces, on vertical surfaces.
II. Urination associated with anxiety or fear only occurs when the dog is afraid and is typically combined with other indicators of fear.
III. Submissive urination is accompanied by other submissive signals, such as lowering the head, lying down, and rolling over when a person approaches.
IV. Dogs with excitement-induced urination only urinate when exhibiting other signs of excitement, such as barking, jumping, or running.
V. A review of housetraining techniques reveals that appropriate housetraining was not conducted or maintained (e.g., the dog may be kept inside for longer periods than it can reasonably hold its urine).

Treatment

I. Castrate intact male dogs that exhibit territorial marking.
II. Dogs with anxiety disorders or phobias are treated as discussed under Anxieties and Phobias in Chapter 117.
III. Avoid triggering urination in submissive dogs through the following:
   A. Do not reach over the dog's head, approach it quickly, vocalize loudly, stare into the dog's eyes, or pet it on top of the head.
   B. Squat to interact with the dog, but avoid eye contact.
      1. Speak in a gentle, quiet voice and pet the dog under the chin.
      2. If this behavior triggers submissive urination, do not approach the dog, and keep interactions to a minimum.
   C. Dogs with severe submissive urination may require an anxiolytic medication (see Table 117-1) (Creed and Tulloch, 1982).
IV. Avoid reinforcing behaviors of excitement in dogs with excitement-induced urination.
   A. Ignore the dog whenever it is running around, spinning, barking, jumping, etc.
   B. Only give the dog attention when it is calm.
   C. Imipramine or phenylpropanolamine may be useful.
V. Basic housetraining considerations include the following:
   A. Take the dog out frequently to an area where it is acceptable for the dog to eliminate.
   B. Praise the dog every time it eliminates in an acceptable area.
   C. Puppies are taken out after they eat, play, or wake up from a nap.
   D. Do not punish the dog after the fact.
      1. If you find urine or feces in an unacceptable location, do not take the dog back to the location and administer aversive stimuli.
      2. These methods do not help stop the elimination problem.
   E. If the puppy or dog is seen in the act of eliminating in an unacceptable area, disrupt the behavior by calling its name, taking it immediately outside, and praising it when it finishes eliminating outside.
   F. Confine puppies to a small area in the house when not supervised.
   G. Older dogs that have unlearned their housetraining may be kept on a leash attached to the owner for several days so that the owner can continuously monitor them.

Monitoring of Animal

I. The frequency with which cases of inappropriate elimination must be monitored varies with the type of problem.
II. If a relapse of a previously resolved behavioral elimination problem occurs, examine the dog for medical problems.

JUMPING

Definition and Causes

I. The dog repeatedly jumps on people.
II. Jumping can be play- or attention-seeking behavior that is often on a variable ratio reinforcement schedule.
III. The dog is not trying to be dominant to the person.

Clinical Signs and Diagnosis

I. Persistent jumping on people occurs in spite of various attempts by the owner to get the dog to stop.
II. This occurs most commonly in healthy, young dogs.

Treatment and Monitoring

I. Teaching the dog an alternative behavior is critical and more effective than simply attempting to punish the behavior.
II. Teach the dog to "sit-stay" or "down-stay" for a treat, and ask all visitors to do this when they first encounter the dog.
III. If a dog jumps on someone after this training has occurred, turn around and ignore the dog (i.e., do not talk to it, look at it, or touch it).
IV. It is critical that all people who interact with the dog be consistent in reinforcing the appropriate behavior.

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CHAPTER 119

Feline Behavioral Disorders

Sharon L. Crowell-Davis

AGGRESSION

Introduction of a New Cat

Definition and Causes

I. It is aggression by a new cat to cats already living in the household or by the household cats toward a new cat.
II. Cats are highly social and form discrete social groups called *colonies* (Crowell-Davis, 2005).
III. Members of the colony recognize other members and nonmembers, and they reject attempts by nonmembers to interact with the colony.
IV. Cats that have lived in isolation from their own species since youth or for several years may have poor social skills.
V. All introductions of a new cat to a household have the potential to lead to aggression, especially if one or more cats have poor social skills.

Treatment

I. Introduction should always be gradual.
II. Place the new cat in its own room with its own food, water, bed, and litterbox.
III. If glass or screened doors are not available within the house, a solid door can be propped open by about one-inch, which allows the cats to hear, see, and smell each other without being able to interact aggressively.
IV. Rotate bedding among the cats.
V. Gently and playfully rub a small cloth on each cat's perioral area to facilitate familiarizing the cats with each other's scent.
VI. In some cases, systematic desensitization and counterconditioning may be useful.
   A. Place one or more cats in a harness or in cages.
   B. It is critical that fear not be induced (e.g., placing cat in a cage of which it is already frightened).
VII. In refractory cases, tricyclic antidepressants (TCAs) or selective serotonin reuptake inhibitors (SSRIs) may be useful (see Table 117-1).

Monitoring

I. Advise owners that introductions should be done gradually to prevent a serious incident that makes it difficult for the cats to adapt to each other.
II. Well-socialized and friendly cats may become comfortable with each other in a matter of minutes or hours.
III. Poorly socialized cats may require weeks or months to be comfortable with another cat.

Dominance Aggression

Definition and Causes

I. Aggression, combined with multiple dominance signals, is directed toward a cat or a human with whom the cat is familiar (Crowell-Davis et al., 1997).
II. Cats that are not well socialized as kittens are particularly prone to being the aggressor or the victim in this problem.
III. Genetics contribute to the ease with which a cat is socialized.
IV. A variety of changes in the cat's environment or traumatic events may trigger dominance conflicts.
   A. If a high-ranking cat is removed from the household for a period (e.g., because of illness), its status in the household may not be acknowledged upon its return.
   B. The addition of a new cat may disrupt the existing hierarchy and coalitions.
   C. If a major fight is triggered by a disruptive event that causes displaced or arousal-related aggression (e.g., new cat growls at the household cats through a screened door), a previously stable hierarchy may be disrupted.

Clinical Signs and Diagnosis

I. Cats that previously got along well begin exhibiting aggression involving intense signaling of dominance or submission.
II. The aggressor approaches the victim with a stiff-legged walk.
III. The base of the tail is elevated, with the remainder drooping.
IV. The cat stares at the victim or may exhibit a slow, side-to-side head wag.
V. Subordinate cats may trigger attacks by otherwise nonaggressive dominant cats by exhibiting intense displays of running away when they see the dominant cat.
VI. Human-directed dominance aggression is extremely rare in the cat.

Treatment

I. Separate the cats that are in conflict when they are not being supervised.

II. Make sure that all cats have access to essential resources without having to encounter cats with whom they are in conflict.
III. Cats that get along are rotated among the cats that are in conflict so that their stable, amicable relationships are not disrupted.
IV. Conduct desensitization and counter-conditioning in neutral areas; do not conduct treatment sessions in any of the cats' favorite or core areas.
V. Medication with SSRIs or TCAs may be useful in some cases (see Table 117-1).

Monitoring of Animal

I. These cases often require weeks or months of consistent treatment.
II. Resolution is possible but does not always occur.

Play Aggression

Definition and Causes

I. Biting and scratching occurs in the context of play.
II. Inadequate or inappropriate socialization to humans or cats when they are kittens is a cause.
III. Inappropriate play by one or more humans (using the hands or feet as a toy) teaches the kitten that it is acceptable to bite or claw at hands or feet.
IV. Genetics and other factors that contribute to a cat's general level of arousal may contribute to the problem.
V. Some cats appear to become overly aroused in the context of play.

Clinical Signs and Diagnosis

I. The cat approaches, stalks, and chases the owner, leaps on to them, and may bite or claw (usually deeply).
II. Postures characteristic of predatory cats may be observed before attacks, especially tail twitching and focused stares.
III. The cat is more likely to attack moving targets rather than stationary targets.
IV. In the case of intercat play aggression, normal play may escalate into fighting.

Treatment

I. This problem can usually be prevented by providing kittens and adult cats with adequate opportunities for acceptable play and vigorous exercise.
II. Never encourage a cat to bat at or otherwise play with hands or feet.
III. If a cat has significant human-directed play aggression, it is important that all the people being attacked wear sturdy, protective clothing when around the cat until the problem is resolved.
IV. Jumping, running, and vocalizations made by people can stimulate the cat to further attack as part of the "game."
V. Provide the cat with multiple toys and opportunities for interactive play, either alone or with the owner.
VI. For cats whose bouts of normal wrestling escalate into actual fights, disrupt the play when escalation first begins.
VII. For cats that become highly aroused, treatment with SSRIs or TCAs may be useful (see Table 117-1).

Monitoring of Animal

I. Although the cat's biting and scratching are a form of inappropriate play, this form of human-directed aggression is the one that most often leads to serious injury.
II. Some owners become afraid of their cat even when they wish to pursue treatment.
III. Regular contact with the owner during early phases of treatment is important.

Petting Intolerance

Definition

I. The cat begins growling, biting, and scratching when petted.
II. Some cats only exhibit this problem if petting is initiated by the human, during a certain type of petting, or after a certain amount of petting.

Causes

I. The cause of petting intolerance is not fully understood.
II. With intercat interactions, grooming (licking) is typically directed to the head and neck of the cat being groomed, so humans who pet other areas of the cat's body may trigger a defensive response.
III. Genetics is probably a contributing factor, with some strains of cats being more or less likely to develop this problem.
IV. Early experience and habituation to human handling makes this problem less likely to develop.
V. Owner-initiated interaction with the cat has a significant effect on this problem.
   A. At one extreme, some owners have minimal physical interaction with their cat.
   B. At the other extreme, some owners want to carry their cat around, hold it in their lap, and pet it for long periods.

Clinical Signs and Diagnosis

I. The cat becomes aggressive only when handled and petted.
II. Although some owner's may initially claim that the cat gives them no warning of its intention to bite or scratch, careful observation invariably reveals that the cat is giving signals that the owner is missing (e.g., twitching tail, twitching ears, rippling skin, low volume growling).

Treatment

I. It is important to recognize that some cats have thresholds for tactile contact and handling beyond which they are not comfortable.
   A. If a cat only becomes aggressive when petted a certain way, avoid petting it that way.
   B. If a cat only becomes aggressive when a human (rather than the cat) initiates petting, then pet the cat only when it initiates or seeks petting.

C. If the cat becomes aggressive after a certain amount of petting, only pet it for brief periods.

II. Sometimes an owner and cat are not a good match, so adoption of another cat that has a preference for or high tolerance of petting may be desirable.

III. Progressive desensitization and counter-conditioning may increase the cat's tolerance of petting.

IV. Treatment with an SSRIs or TCAs may be helpful (see Table 117-1).

Monitoring of Animal

I. Clarifying goals about this problem at the first visit is critical.

II. The problem may be resolved almost immediately if the owner understands the cat's needs and interacts with it appropriately.

III. Owners who do not fully understand the situation may continue to engage in behaviors that stimulate aggression.

ELIMINATION PROBLEMS

Definition

I. Failure to use the litterbox includes defecating or urinating large volumes of urine on a horizontal surface.

II. Urine marking primarily occurs when the cat backs up to a vertical object and ejects a small amount of urine onto the object.

III. With urine marking, the tail is held straight up with the tip twitching, or it may be held aside in a J shape.

IV. Sometimes urine-marking cats partially squat and spray the lower part of vertical surfaces, such as baseboards or the bottom of curtains.

V. A small number of urine-marking cats pass large volumes of urine in a single marking episode, whereas others assume the position of marking but do not pass any urine.

VI. Medical problems are common causes of elimination behavior problems, so a thorough medical evaluation must be conducted before pursuing behavioral issues (see Section 7).

VII. In some cats, a medical problem initiates a behavioral elimination problem through learning.

Causes

I. Failure to use the litterbox is generally caused by aversion to some aspect of the litter, the litterbox, the location of the box, or by preference for some other substrate or location.

II. Multiple causes may be present and may change over time.

III. There is no single cause of urine marking.

A. Urine marking is not used to mark territory or territorial boundaries.

B. Because there is a higher rate of urine marking among estrous females and intact males, it is probable that urine marking gives information about sexual status.

C. Feral cats may use urine marking to give information to other colony members about their location.

D. Urine marking in household cats is often associated with environmental stress, such as overcrowding and major changes in the household.

E. Not all cats subjected to stress develop urine marking.

Clinical Signs

I. Urine and feces are found outside the litterbox.

II. Failure to use the litterbox is discriminated from urine spraying by location (horizontal versus vertical surface) and the volume of urine.

Diagnosis and Treatment

I. Diagnosis is determined by evaluating potential problems, correcting them, and evaluating whether the cat responds in a desired fashion.

II. Litterboxes are checked and cleaned at least BID.

A. If this resolves the problem, the diagnosis is aversion to soiled litterbox.

B. A small number of cats will not use litterboxes that have any soiled material in them.

III. If nonclumping litter is used, completely change it every 2 to 3 days.

IV. If clumping litter is used, completely change it every 1 to 4 weeks.

V. If the cat spends little time digging (0 to 8 seconds), litter aversion is a possibility (Horwitz, 1997; Sung and Crowell-Davis, 2006).

A. Cats with litter aversion may stand with one or more paws on the rim of the litterbox, or they may vigorously shake their paws upon exiting.

B. Offer cats multiple litterboxes of the same type and in the same location with several different kinds of litter.

C. Some cats prefer one type of litter for urination and another litter for defecation.

D. In general, most cats prefer unscented, fine-grained, clumping litter.

E. Certain cats reject this kind of litter and prefer something unusual (e.g., potting soil, cloth); for cloth preference, using cloth baby diapers in the litterbox may be the best solution.

VI. Litterbox aversion can occur in a variety of ways.

A. If a cat has an unpleasant experience at the litterbox (e.g., painful defecation), it may become conditioned to fear the litterbox, so a new type and location of the box may help.

B. Litterboxes themselves may be undesirable for a variety of reasons.

1. The box may be too small.
   a. The box should be at least 1.5 times the length of the cat.
   b. Plastic storage boxes may be preferable.
2. Cats do not normally enter small caves to eliminate and many cats find hooded boxes aversive.
3. The box may be located in an inappropriate place, where high traffic, loud noises, drafts, or other unpleasant conditions make the cat avoid the area.
4. Kittens and geriatric cats may not be able to enter high-sided litterboxes.

VII. Cats sometimes have a location preference for elimination where there is no litterbox.
  A. They may prefer to eliminate in a location close to where they spend most of their time.
  B. Cats sometimes develop a location preference because of inappropriate litterbox management.
  C. Confirm appropriate management, then make the preferred area inaccessible (closed doors, stacked baby gates or furniture, food bowls over the area) or undesirable (placing a citrus room deodorizer nearby).

VIII. Cats may prefer to eliminate on a substrate the owner does not want them to use, such as carpet or linoleum.
  A. These problems often begin with inappropriate litterbox management, so appropriate management must be verified before other treatment is initiated.
  B. If the cat prefers carpet (one of the most common problems), there are two main approaches to retraining.
    1. Isolate the cat from carpeting except under supervision.
      a. It is essential that the cat have supervised time on carpet every day for this technique to work.
      b. Several weeks may be required.
    2. Place carpet squares in the litterbox regularly and discard them as they become soiled, or place a carpet frame around the box so that the cat can have tactile contact with carpet while eliminating in the box.
  C. If the cat prefers smooth surfaces (linoleum, vinyl), try multiple boxes that have no litter in them or that contain pieces of linoleum or vinyl.

IX. Overcrowding can contribute to elimination behavior problems.
  A. Social conflict may result in one or more cats keeping a cat away from the litterbox.
  B. In multicat households, have as many boxes as there are cats plus one more, and place the litterboxes in multiple locations.
  C. Make sure timid and low-ranking cats can reach a box without having to encounter other cats.
  D. Litterbox cleanliness is a special challenge in households with several cats, so it is imperative that owners check and clean the boxes several times a day.

X. A coprophagic dog in the household may disturb the cat while it is attempting to defecate.
  A. In this case, a covered litterbox may be useful.
  B. The litterbox can be kept in a room to which the dog does not have access.

XI. Long-haired cats with elimination problems sometimes show substantial improvement if the hair between their toes and around their perineum is clipped.

XII. Stressors, including owner absence, can sometimes cause elimination behavior problems.
  A. Identify and attempt to remove the stressor or desensitize and counter-condition the cat to the stressor.
  B. Medications with anxiolytic activity may be necessary.

XIII. Placing the litterbox in an extremely dark location can sometimes cause elimination behavior problems, so try adding a night light or some other light source to the area.

XIV. Some cats respond well to toilet training.
  A. Place a frame that holds litter over a toilet.
  B. The cat is encouraged to use it by such means as burying catnip in the litter and playing with the cat at the location.
  C. Cats that are generally attracted to the toilet are the easiest to toilet train.
  D. Once the cat is using the litter frame over the toilet, gradually decrease the amount of litter and eventually remove the frame.
  E. Do not train the cat to flush the toilet, as some cats will do this dozens of times a day.

XV. Spraying is significantly enhanced by environmental stressors.
  A. If the cat is an intact male, castrate it (Hart and Barrett, 1973).
  B. If possible, identify, decrease, or eliminate stressors, or desensitize and counter-condition the cat to the stressor.
  C. Anxiolytic medications (buspirone, clomipramine, fluoxetine, paroxetine,) are often helpful, particularly in cases of spraying (Hart et al., 1993; Pryor et al., 2001; King et al., 2004)
  D. They may also be helpful for nonspraying problems when the anxiety of the cat is obviously high.

XI. Since learning is involved in many elimination behavior problems, several days are allowed between changes in management to identify whether the cat is responding.

SCRATCHING OBJECTS

Definition and Causes

I. Even though it is a common complaint among cat owners, scratching is a normal behavior.

II. Scratching is part of normal grooming and serves to remove the outer layer of the claw.

III. Scratching leaves a visual and an olfactory marker from scent deposited from the interdigital glands.

Treatment and Monitoring

I. A common error in managing this problem is for the owner to select a commercially available scratching post and, if the cat does not scratch it, assume a designated scratching post is not an option.

II. It is important to realize that each cat is unique in terms of its preferences, and the scratching post must fit its preferences.

III. The following must be taken into consideration:
  A. Identify if the cat prefers to scratch in a particular location and make the scratching post available in that location.
  B. Identify if the cat prefers to scratch on vertical, horizontal, or sloping surfaces, or some mixture of these.
  C. Identify the textures the cat prefers to scratch.

D. While carpet-covered scratching posts are probably the most available type, various other textures may be tried, including natural wood with bark, cardboard and rope.
E. Some cats have a specific texture preference that is not available commercially.
   1. Identify the cat's preference by examining the objects in the house that are being scratched.
   2. Try to make a post with a texture that matches those surfaces.
F. To help train a cat to use a scratching post, play with the cat in the vicinity of the post, or rub catnip on the post.

IV. It is important to contact owners regularly during the early training period so that they do not become frustrated after trying one or two options.

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CHAPTER 120

Introduction

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Animal Factors

I. Dogs and cats eat to meet energy requirements and maintain body mass based on the following:
   A. Signalment: species, breed, age, gender
   B. Life stage: growth, adult, pregnancy, lactation
   C. Individual variation
   D. Environmental factors: temperature, housing, presence of other animals
II. Perform a good physical examination at every appointment.
   A. Record body weight at every examination.
   B. Body condition score is an important measurement.
      1. Provides assessment of overall nutritional status
      2. Either a 5- or 9-point scale for dogs and cats (see Chapter 1; Table 120-1)

Dietary Factors

I. Acquire a good dietary history including type and amount of food consumed, frequency of feeding, exposure to other foods or foreign matter, and administration of supplements.
II. An adequate diet is complete, balanced, and of sufficient palatability so that the animal eats an appropriate amount.
III. Inspect the food when possible and any time a concern exists about the food.
   A. Physically inspect the food for appearance, presence of foreign material, and odor.
   B. Pet foods are available in different forms.
      1. Dry diets are produced from dry ingredients (e.g., grains, meals) that are mixed to a doughy consistency, cooked, and extruded.
         a. Antioxidants and low moisture content preserve food and prevent fat oxidation.
         b. Digest is sprayed on the extruded food to increase palatability and to provide acidification for cat foods.
         c. Dry diets are the most economical and convenient to feed.
      2. Semimoist and semidry diets are more calorically dense, palatable, and expensive to feed than dry diets and require chemical preservation.
      3. Canned diets often contain whole ingredients, are highly digestible and palatable, require chemical preservation, and are more expensive to feed than other forms.
      4. Frozen diets are often composed of whole ingredients, but do not typically contain preservatives.
      5. Liquid diets are used to provide nutrition for critically ill animals and as milk replacement for neonates.
IV. Inspect the pet food label for information on the diet.
   A. The product display panel contains the product identity, information on whether the food is for dogs or cats, the net weight of the product, and marketing vignettes.
   B. The information panel contains the ingredient list, guaranteed analysis, nutritional adequacy statement, feeding guidelines, and manufacturer or distributor information.
      1. Ingredients are listed in descending order according to preprocessed weight.
         a. Ingredient names are set by the American Association of Feed Control Officials (AAFCO).
            (1) Information panel does not give information as to quality of ingredients.
            (2) Panel does not give information as to exact amount of ingredient present.
         b. A specific component of the diet may come from two different sources, which appears further down the list.
         c. Ingredients with chemical-like names are vitamins, minerals, and preservatives, and must be recognized by AAFCO as being "generally regarded as safe."
      2. The guaranteed analysis lists major dietary components as percentages (as fed).

TABLE 120-1

Semiquantitative Body Condition Scoring System

DESCRIPTOR	FINDINGS	POINT SCALE (1-5)	POINT SCALE (1-9)
Cachectic	Ribs are easily palpated, with no fat cover Bony structures are prominent and easy to identify Muscle tone and mass often decreased Little to no subcutaneous fat Hair coat often poor Pronounced abdominal tuck	1	1
Underweight	Ribs are easily palpated, with little fat cover Bony structures are palpable but not prominent Muscle tone and mass may be good or slightly decreased Hair coat may be poor Abdominal tuck is present	2	3
Ideal	Ribs are easily palpated, but fat cover is present Bony prominences are palpable but not visible Some subcutaneous fat present, but no large accumulations Good muscle tone and mass Hair coat quality is good Hourglass shape and abdominal tuck are present, but not pronounced	3	5
Overweight	Ribs are difficult to palpate owing to overlying fat accumulation Cannot identify bony prominences Subcutaneous fat obvious, with some areas of accumulation Good muscle tone and mass Hair coat quality may be decreased Hourglass shape is not prominent and abdominal tuck is absent	4	7
Obese	Ribs are impossible to palpate owing to overlying fat Subcutaneous fat is obvious and accumulations are present in the neck, tail-base, and abdominal regions Muscle tone and mass may be decreased Hair coat quality may be decreased Hourglass shape is absent and animal may have a round appearance	5	9

a. Pet food content must guarantee the following:
   (1) Minimum amount of crude protein
   (2) Minimum amount of crude fat
   (3) Maximum amount of crude fiber
   (4) Maximum amount of moisture
b. Values are based on "crude" analytical procedures and do not refer to the quality of the ingredient.
c. Compare different forms of food by converting nutrients to a "dry matter" basis:

% nutrient as fed ÷ (100 – % moisture) = % nutrient dry matter (DM)

d. Another and perhaps better way to compare information is based on the food's caloric density:

amount of nutrient as fed (e.g., grams) ÷ energy density of diet (kilocalories) = amount of nutrient per kilocalorie of energy

3. The nutritional adequacy statement ensures that if the diet is fed as the sole source of nutrition, it will adequately sustain an animal during certain life stages.
   a. It includes wording such as "complete and balanced," the life stage for which the food is intended (adult, pregnancy, lactation, growth), and how the product was found to be adequate.
   b. The two methods used to determine adequacy are calculation of nutrient profile by chemical analysis or feeding trials.
   c. Therapeutic diets do not often have a nutritional adequacy statement.
   d. Supplements and treats are not designed to be fed as the sole source of nutrition.
4. Feeding guidelines must be included to provide a general recommendation as to the amount of food that should be fed to a dog or cat.
5. Name and address of manufacturer or distributor are provided for contact purposes.
6. The Universal Product Code is present on the label.

Feeding Factors

I. How the nutrition is provided is as important as what is fed.

II. The appropriate diet must be provided in the appropriate amount.

Formulate a Feeding Plan

I. Once assessments are made, a nutritional plan is formulated that includes the food and feeding method.
II. Monitor the animal and reformulate the nutritional plan as needed, especially when the margin of safety for nutrition is narrow and nutrient demands are high.

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CHAPTER 121

Nutrition in Health

Susan D. Lauten | Joseph W. Bartges | Claudia A. Kirk

ADULT DOGS

Animal Factors

I. A wide margin of safety exists for nutritional requirements in healthy adult dogs; however, the margin becomes narrower with stressful physiological or pathologic states.
II. The American Association of Feed Control Officials (AAFCO) mandates adequate nutrition for all life stages (AAFCO, 2006), whereas the National Research Council (NRC) provides recommended allowances for all life stages (NRC, 2006).

Dietary Factors

I. Energy requirement is based on energy expenditure (e.g., physiological status and activity) (Table 121-1).
   A. It can be estimated using one of the following formulas:
      1. Linear: 1.1 to 2.0 × (30 × body weight in kilograms [BW_{kg}] + 70) (Hand et al., 2000)
      2. Exponential: 80 to 200 × $BW_{kg}^{0.75}$ (NRC, 2006)
      3. Lower estimated values used for less-active and neutered dogs, and dogs prone to obesity
      4. Higher estimated values used for more active and reproductively intact dogs
   B. These formulas are estimates; only 60% of dogs need the calculated energy requirements.
II. Protein requirement is 18% to 25% of the diet (dry matter [DM] basis); 25% to 50% of the maintenance energy requirement (MER); or 4.0 to 6.5 g of digestible protein per 100 kcal of metabolizable energy (ME).
III. Fat requirement is 8% to 12% (DM) or 20% to 50% of MER.
   A. Linoleic acid is an essential fatty acid.
   B. NRC recommends inclusion of α-linolenic, docosahexaenoic (DHA), and eicosapentaenoic (EPA) acid in diets (NRC, 2006).
IV. There is no carbohydrate requirement for dogs.
V. Average dietary characteristics are as follows:
   A. Energy: 3.5 to 4.5 kcal ME/g
   B. Crude protein: 18% to 30% DM
   C. Crude fat: 10% to 20% DM
   D. Crude fiber: 5% DM
   E. Calcium: 0.5% to 1.0 % DM
   F. Calcium-to-phosphorous ratio: 1:1 to 2:1

Feeding Factors

I. May be dictated by lifestyle of owner or dog (Hand et al., 2000)
   A. Feed one to two meals per day.
   B. Cost of food may influence feeding choices.
   C. Dry food can be fed ad libitum, whereas moist and canned foods are fed as meals.
II. Monitor body condition and body weight (BW), and adjust intake to maintain ideal body condition.

TABLE 121-1

Comparison of Typical Nutrient Content in Dog Diets

NUTRIENT	SENIOR DIET	ADULT MAINTENANCE DIET	DIFFERENCE
Energy (kcal/g of DM)	3.7 to 4.7	4.1 to 4.5	−0.4 to 0.2
Protein			
(g/100 kcal)	4.6 to 7.1	5.3 to 6.8	−0.7 to 0.3
(% kcal)	16 to 29	18 to 26	−2 to 3
Fat			
(g/100 kcal)	2.4 to 4.4	2.8 to 4.3	−0.4 to 0.1
(% kcal)	19 to 42	23 to 38	−4 to 4
Carbohydrate			
(g/100 kcal)	11.8 to 17.6	10 to 13.4	1.8 to 4.2
(% kcal)	29 to 62	37 to 53	−8 to 9
Fiber (% DM)	0.2 to 2.4	0.2 to 0.7	0 to 1.7

DM, Dry matter.

ADULT CATS

Animal Factors

I. Cats are true carnivores.
II. They are more suited to animal protein-based diets because they cannot down-regulate hepatic enzymes involved in protein metabolism.

Dietary Factors

I. Cats require less energy per kg BW for maintenance than dogs, but resting energy requirements are similar (NRC, 2006).

A. Cats derive part of their energy from dietary protein.
B. Energy requirements can be estimated using one of the following formulae:
   1. Linear: 0.8 to 1.5 × (30 × BW_{kg} + 70) (Hand et al., 2000)
   2. Exponential: 70 to 199 × $BW_{kg}^{0.75}$ (NRC, 2006)

II. Adult cats require 26% to 30% protein (DM) or 6.0 to 8.0 g/100 kcal ME.
   A. Protein increases palatability of foods for cats.
   B. Requirements include certain amounts of specific amino acids.
      1. Taurine is a sulfur-containing amino acid, and diets should contain 0.1% DM (extruded diets) or 0.2% DM (canned diets).
      2. Arginine requirements are higher in cats than in dogs (Hand et al., 2000).

III. Dietary fat requirements are 10% to 20% DM.
   A. Linoleic and arachidonic acids are essential fatty acids.
   B. Cats cannot convert linoleic to arachidonic acid (Case et al., 2000).
   C. Arachidonic acid is found primarily in animal tissues.
   D. NRC recommends inclusion of EPA and DHA in diets (NRC, 2006).

IV. Cats cannot convert beta-carotene to vitamin A; therefore, it must be supplied in the diet.

V. Cats cannot convert tryptophan to niacin, so it must also be supplied in the diet.

VI. Cats require more pyridoxine (vitamin B_6) than dogs.

VII. No calcium-to-phosphorus ratio has been established by AAFCO for cat diets.

VIII. Average dietary characteristics include the following:
   A. Energy: 4.0 to 5.0 kcal ME/g
   B. Crude protein: 30% to 45% DM
   C. Crude fat: 10% to 30% DM
   D. Crude fiber: <5% DM
   E. Calcium: 0.5% to 1.0 % DM
   F. Calcium-to-phosphorous ratio: 0.9 to 1.5:1.0 considered safe (Hand et al., 2000)

Feeding Factors

I. Ad libitum feeding helps to maintain an acidic urinary pH in cats.

II. Feeding meals is associated with a postprandial alkaline tide and alkaluria.

III. Cats generally consume many small meals throughout the day (Case et al., 2000).
   A. Dry food is more appropriate for this feeding behavior.
   B. Dry foods are generally carbohydrate-based, not animal protein–based.
   C. Canned and semimoist foods are appropriate for meal feeding.

GERIATRIC DOGS AND CATS

Animal Factors

I. Defining *geriatric* is difficult in dogs and cats.
   A. Cats may be considered geriatric at 7 years.
   B. Small-breed dogs can be considered geriatric at 9 years, medium- and large-breed dogs at 7 years, and giant-breed dogs at 5 years.

II. Older dogs have decreased metabolic rates, glucose tolerance, and renal function, as well as increased protein requirements.

III. Body condition and physical activity determine the nutritional needs of geriatric animals.

Dietary Factors

I. Types of diets that can be fed include the following:
   A. Adult maintenance diet
   B. Senior diet (lower in energy, protein, and fat, higher in fiber and carbohydrate) compared with an adult maintenance diet
   C. Calorically (energy) dense diet: growth diet
   D. Therapeutic diets: depending on diseases present

II. Type of appropriate diet is determined by physiological, metabolic, and clinical characteristics of the individual animal.
   A. Physiologically young, efficient metabolism, clinically healthy: adult diet
   B. Physiologically old, efficient metabolism, gains weight easily, clinically healthy: calorie-restricted diet
   C. Physiologically old, inefficient metabolism, loses weight easily, clinically healthy: calorie-dense diet
   D. Physiologically old, inefficient metabolism, clinically unhealthy: disease-specific diet

Feeding Factors

I. Older animals may not eat as well as younger dogs; therefore, it may be necessary to offer food free choice or feed several meals daily.

II. Changes in body condition can occur quickly in geriatric animals, which make frequent follow-up evaluations essential.

WORKING ADULT DOGS

Animal Factors

I. Dogs may be required to perform work at a wide range of activity levels.

II. Maintain body condition and BW to achieve these desired activity levels.

Dietary Factors

I. Feed seasonal working dogs (e.g., hunting dogs) a maintenance diet during the off season.

II. Transition to a calorie-dense diet before training and conditioning, and continue to feed this diet during heavy activity.

III. Additional protein intake is not advantageous but is not harmful.

IV. Average dietary characteristics include the following:
   A. Energy: >3.8 kcal/g
   B. Crude protein: >26% DM
   C. Crude fat: 17% DM
   D. Crude fiber: <2% DM

Feeding Factors

I. Maintain an ideal body condition during the off season (NRC, 2006).
II. Extended periods of exercise deplete glycogen stores rapidly.
  A. Energy requirements are met by utilization of fat.
  B. If fat is not available, the body catabolizes protein to provide energy.
III. Feeding high fat diets are appropriate.
IV. Carbohydrate loading is not effective for intermediate or endurance exercise but helps to restore glycogen levels for sprint-type exercise (Reynolds et al., 1997).
V. An additional, small meal can be given the night before heavy exercise.
VI. Consider feeding a meal several hours before heavy exercise, but realize it may predispose to fatigue and bloat.
VII. Give treats during rest periods or breaks.
VIII. Maintain hydration.

PREGNANT DOGS

Animal Factors

I. Before breeding, the dam should be in good physical condition and at ideal BW.
II. For the first 4 to 5 weeks of pregnancy there is no increase in energy or nutritional needs.
III. Fetuses do not grow in size until the last 3 to 4 weeks of gestation.
IV. By the end of gestation, the dam should be eating 60% >MER on average (Meyer et al., 1985).

Dietary Factors

I. Feed a diet suitable for gestation through peak lactation.
  A. Average dietary characteristics are as follows:
    1. Energy: >3.8 kcal/g
    2. Crude protein: >26% DM
    3. Crude fat: >17% DM
    4. Crude fiber: <2% DM
    5. Calcium: 1.0% to 1.5% DM
    6. Calcium-to-phosphorous ratio: 1.1 to 1.5:1.0
  B. Majority of ingredients should be of animal origin.
    1. Plant-based protein diets tend to have lower digestibility, nutrients of less bioavailability, and inadequate zinc levels.
    2. High-carbohydrate diets may not contain enough protein and energy for pregnancy and lactation.
II. Dietary supplementation is not recommended and may be detrimental.
III. Vitamin D and calcium supplementation may result in eclampsia.
IV. Some dogs experience anorexia briefly during week 4 or 5 of pregnancy, with a 2- to 3-day duration being normal; longer durations may indicate fetal loss.

Feeding Factors

I. Dry foods are fine, but higher water intake is needed to promote milk production.
II. During the last trimester of pregnancy, dam may be fed free choice (if dry food) or given multiple small meals because the enlarging uterus decreases space for gastric expansion at feeding (Case et al., 2000).
III. Transition the food to a growth/pregnancy/lactation diet at midpregnancy.
  A. Increase food volume by approximately 15% per week from weeks 5 to 9.
  B. Dam should be consuming about 60% >MER by end of pregnancy, with a gain in BW of 5% to 10% (excluding weight of fetuses).
IV. Free choice feeding may be necessary to maintain proper body condition.
V. During the 12 to 24 hours before whelping, food intake decreases.

PREGNANT CATS

Animal Factors

I. They are similar to dogs but with some exceptions.
II. Cats gain weight throughout gestation.
  A. Kittens grow primarily during the last 3 weeks of gestation.
  B. Early pregnancy weight gain is body fat.
  C. Weight gain is proportional to the number of kittens.

Dietary Factors

I. Pregnancy is accompanied by an increased demand for protein, fat, vitamins, minerals, and caloric density of food.
II. Average dietary characteristics include the following:
  A. Energy: 4.0 to 5.0 kcal/g
  B. Crude protein: 35% to 50% DM
  C. Crude fat: 18% to 35% DM
  D. Crude fiber: <5% DM
  E. Taurine: 1000 ppm (dry diet) or 2500 ppm (canned diet)

Feeding Factors

I. A canned product may be more palatable and calorically dense, and provides moisture for lactation.
II. As pregnancy progresses, feed as free choice or multiple, small meals.
III. At parturition, queen should be consuming 1.25 to 1.5 × MER.
IV. Appetite decreases within 24 to 48 hours of parturition.

LACTATION IN DOGS

Animal Factors

I. The dam quits eating 12 to 24 hours before whelping.
  A. At whelping, dam should weigh >5% to 10% prebreeding weight.
  B. Dam should be consuming 1.6 × MER.
II. Lactation represents the greatest nutrient demand (Hand et al., 2000)
  A. Dam must eat, digest, absorb, and use large amounts of nutrients to produce milk and maintain milk production.

B. Most dams require 2 to 4 × MER.
C. Other nutrient requirements are also increased.

Dietary Factors

I. Protein content is a major determinant of milk production (Kronfeld, 1975).
II. Average diet characteristics include the following:
  A. Energy: >3.8 kcal/g
  B. Crude protein: >26% DM
  C. Crude fat: >17% DM
  D. Crude fiber: <2% DM
  E. Calcium: 1.0% to 1.5% DM
  F. Calcium-to-phosphorous ratio: 1.1 to 1.5:1.0
III. The first two or three ingredients listed should be of animal origin, because they are of higher digestibility and nutrient bioavailability.
IV. Feed canned food or moistened dry foods and have clean, fresh water available at all times.

Feeding Factors

I. Dam needs to eat free choice or have multiple, small meals.
II. At peak lactation, energy intake can be as high as 4 × MER.
III. If moistened dry or canned growth diet is available, puppies can be weaned to this diet.
  A. Weaning occurs around 5 to 6 weeks after birth.
  B. On first day of weaning, remove food, but not water, from dam and do not allow puppies access to the dam, to reduce milk production.
    1. The following day, give 25% to 35% of daily food volume to dam.
    2. On the third day, give 50% to 65% of daily food volume to dam.
  C. Feed full ration to the dam thereafter.
    1. If body condition is good, switch to adult maintenance diet gradually over the next few days.
    2. If body condition is reduced, continue with growth diet and then gradually switch to adult maintenance diet when BW and condition have improved.

LACTATION IN CATS

Animal Factors

I. Peak lactation occurs around 2 weeks after parturition.
II. Nutrient demands at peak lactation are often 2 × MER.

Dietary Factors

I. Growth/gestation/lactation diet is started after breeding.
II. Average dietary characteristics are as follows:
  A. Energy: 4.0 to 5.0 kcal/g
  B. Crude protein: 35% to 50% DM
  C. Crude fat: 18% to 35% DM
  D. Crude fiber: <5% DM
  E. Taurine: 1000 ppm (dry diet) or 2500 ppm (canned diet)
III. This diet is suitable for kittens to consume before and after weaning.

Feeding Factors

I. Maintain body condition during lactation.
II. Free-choice feeding or providing small meals is needed.
III. Kittens begin eating solid food around 21 to 28 days after birth.
IV. Weaning begins at about 6 weeks of age and may take up to 9 weeks to accomplish (NRC, 2006).
V. Weaning is done in a manner similar to dogs.
  A. If body condition is good, switch to adult maintenance diet gradually over the next few days.
  B. If body condition is reduced, continue with growth diet and then gradually switch to adult maintenance diet when BW and condition have improved.

GROWTH IN DOGS

Animal Factors

I. The growth period involves the time from birth to adulthood.
II. Between birth and weaning, nutrition is obtained from dam's milk.
  A. In the first 1 to 2 days of life, puppies must nurse to receive antibody-rich colostrum.
  B. Serum may be given orally if neonates are unable to obtain colostrum from the dam.
III. Neonates are unable to regulate body temperature and must be kept in a warm, draft-free environment.
IV. They have little fat and glycogen stores and must nurse periodically throughout the day.
V. Birth weight doubles within the first 7 to 10 days and increases 6 to 10 times by weaning.
  A. Puppies should gain 2 to 5 g/day/kg of anticipated adult weight.
  B. Energy requirements are approximately 4 × MER at birth and decrease to approximately 2 × MER by weaning.
  C. Weight gain occurs in a stepped fashion, not continuously.
  D. As puppies grow, they will eat available solid food and nurse less often.
  E. Weaning is initiated around 6 weeks of age.
VI. Following weaning, puppies are fed three to four times a day.
  A. Rate of growth depends on the breed, but approximately 50% of adult weight and size is reached by 5 to 6 months of age.
  B. Energy requirements decrease from weaning to adulthood, when requirements are MER.
  C. Other nutrient requirements are higher than in adults in order to promote growth.

Dietary Factors

I. Average diet characteristics include the following:
  A. Energy: >3.8 kcal/g
  B. Crude protein: >26% DM
  C. Crude fat: >17% DM
  D. Crude fiber: <2% DM
  E. Calcium: 1.0% to 1.5% DM
  F. Calcium-to-phosphorous ratio: 1.1 to 1.5:1.0

II. Make clean water available at all times.
III. Additional nutrient supplementation is unnecessary and can be detrimental.

Feeding Factors

I. During weaning, the diet consumed is typically what the dam is eating.
II. Following weaning, a dry food or canned growth diet are fed.
III. Meal feeding is preferred over free-choice feeding.
IV. Monitor body condition frequently and adjust dietary intake as needed.
V. Food can be changed to an adult diet after 50% of adult weight is reached.

GROWTH IN LARGE- AND GIANT-BREED DOGS

Animal Factors

I. Large-breed puppies are at risk for developmental orthopedic diseases (DOD), such as hip dysplasia, osteochondrosis desiccans, joint laxity, ligament laxity, and hyperextended joints.
II. Rate of growth, specific nutrients, food consumption, and feeding methods affect the onset of DOD.

Dietary Factors

I. Excess energy intake results in rapid growth and obesity, which are associated with DOD; therefore, maintain optimal body condition during growth.
II. Excess dietary protein (>27% DM) does not contribute to DOD.
III. Calcium directly influences DOD.
   A. Calcium intake of >3% DM is associated with DOD.
   B. For example, supplementation with 2 level teaspoons of calcium carbonate to a 15-week-old, large-breed puppy eating a growth diet more than doubles the calcium intake.
IV. Vitamin C is necessary for hydroxylation of proline and lysine during biosynthesis of collagen (Geesin and Berg, 2001).
   A. No known dietary vitamin C requirement exists for dogs.
   B. Supplementation to puppies for 147 to 154 days did not affect growth and development (Dzanis, 1995).
V. Vitamin D excess and deficiency affects DOD.
   A. Deficiency results in disturbance of calcium metabolism; however, it is difficult to induce when feeding commercial diets.
   B. Excess may occur with vitamin-mineral supplementation (Richardson and Toll, 1997).
VI. Copper and zinc deficiency also impair normal development.
VII. Average diet characteristics are as follows:
   A. Energy: 3.2 to 3.8 kcal/g
   B. Crude protein: >26% DM
   C. Crude fat: 9% to 12% DM
   D. Crude fiber: <2% DM
   E. Calcium: 0.7% to 1.2% DM
   F. Calcium-to-phosphorous ratio: 1.1:1.0 to 1.5:1.0

Feeding Factors

I. Free-choice feeding increases risk of DOD when compared with meal feeding.
II. Rapid growth rate increases risk of DOD.
III. Feed large-breed growth diet as meals to decrease risk of DOD.
IV. Adult food can be fed after 6 months of age, but it may limit protein, vitamin, and mineral intake, which may be detrimental.

GROWTH IN CATS

Animal Factors

I. Growing cats have higher nutrient requirements than adults.
II. Cats have higher protein and energy requirements than dogs.
III. Adult weight is reached around 6 to 8 months of age.

Diet Factors

I. Growth diet is fed before and after weaning.
II. Average dietary characteristics include the following:
   A. Energy: 4.0 to 5.0 kcal/g
   B. Crude protein: 35% to 50% DM
   C. Crude fat: 18% to 35% DM
   D. Crude fiber: <5% DM
   E. Taurine: 1000 ppm (dry diet) or 2500 ppm (canned diet)

Feeding Factors

I. During weaning, the diet consumed is typically what the dam is eating.
II. After weaning, a dry food or canned growth diet are fed.
III. Meal feeding is preferred over free-choice feeding.
IV. Monitor body condition frequently and adjust dietary intake as needed.
V. Diet can be changed to an adult diet after 50% of adult weight is reached.

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CHAPTER 122

Nutrition in Disease

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ADVERSE REACTIONS TO FOOD

Animal Factors

I. Although providing nutrition to companion animals is relatively easy and safe, situations arise where an adverse reaction to a diet or nutrient, or exposure to a food hazard, occurs.
II. Reactions may occur to components that are present normally but are unbalanced, or they may occur to components that are not present normally.

Dietary Factors

I. Nutrient imbalances may occur with problems in the formulation or manufacture of a diet, or if the owner supplements a complete and balanced diet with an incomplete and unbalanced food or supplement (Tables 122-1 and 122-2).
II. Certain food components are toxic.
    A. Onion poisoning causes a Heinz body hemolytic anemia in cats.
    B. Chocolate toxicity causes vomiting, diarrhea, and seizures from the effects of theobromine.
    C. Raisins and grapes have been associated with acute renal failure in dogs.
III. Certain food additives may cause problems.
    A. Ethoxyquin is an antioxidant that may cause reproductive disorders, dermatological problems, and immune-mediated diseases.
    B. Most pet food manufacturers no longer use ethoxyquin.
    C. Other synthetic or so-called natural antioxidants are usually mixed with tocopherols, ascorbic acid, or both.
IV. Contamination may occur from contaminated foodstuffs or the food may become contaminated after production.
    A. Mycotoxins occur sporadically in dry foods and cause hepatic failure and death.
    B. Pet foods may become contaminated if mold is allowed to grow, especially if the food becomes moist or if the fat becomes rancid.
    C. Bacterial contamination may occur with *Salmonella* spp., *Campylobacter* spp., and *Clostridium* spp.
    D. Ingestion of animal tissues containing residues of toxic substances (e.g., warfarin) may result in disease.
V. An *adverse reaction to food* is defined as a clinically abnormal response attributed to an ingested food substance, and it may be categorized as immunological or non-immunological.
    A. Food hypersensitivity is an immune-mediated reaction to ingested food.
        1. A particular foodstuff activates one or more immunological pathways.

TABLE 122-1

Nutrient Excesses

NUTRIENT CLASS/ELEMENTS	ASSOCIATED DISEASES/CONDITIONS
Energy	
	Obesity Increased risk for other diseases Developmental orthopedic diseases in growing large- and giant-breed dogs
Protein	
	May result in imbalanced or deficient diet
Carbohydrate	
	Lactose intolerance Diarrhea, bloating
Minerals	
Calcium, phosphorous	Developmental orthopedic diseases in growing large- and giant-breed dogs
Magnesium	Struvite-related urolithiasis and urethral plugs
Sodium	Hypertension, congestive heart failure, fluid retention
Vitamins	
Vitamin A	Cervical osteocartilaginous hyperplasia in cats
Vitamin D	Soft tissue calcification
Trace Elements	
Iron	Vomiting, diarrhea, neurological signs
Copper	Chronic active hepatitis
Zinc	Hemolytic anemia
Iodine	Hyperthyroidism

TABLE 122-2

Nutrient Deficiencies

NUTRIENT CLASS/ELEMENTS	ASSOCIATED DISEASES/CONDITIONS
Energy	
	Malnutrition Poor growth and body condition
Protein	
Total protein	Poor hair coat, hypoproteinemia, edema/ascites, vacuolar hepatopathy
Taurine (cats)	Dilated cardiomyopathy, retinal degeneration, poor reproductive performance
Fat	
Linoleic, arachidonic (cats)	Poor hair coat, vitamin deficiencies
Minerals	
Calcium, phosphorous	Nutritional secondary hyperparathyroidism
Magnesium	Calcium oxalate urolithiasis, cardiac dysfunction
Sodium	Poor appetite
Potassium	Polymyopathy
Vitamins	
Vitamin A	Dermatological and ophthalmologic disease
Vitamin D	Rickets
Thiamine	Seizures
Niacin	Pellagra/black tongue
Biotin	Poor hair coat
Vitamin E	Cats: steatitis Dogs: muscle disease, decreased immunocompetence
Trace Elements	
Iron	Anemia
Copper	Anemia, depigmentation of skin
Zinc	Parakeratosis, poor hair coat
Iodine	Goiter, alopecia
Selenium	Muscular weakness

2. After development of this response, subsequent ingestion of the foodstuff causes clinical signs.
3. Factors that lead to hypersensitivity are speculative.
   a. Heat- and acid-stable glycoproteins with molecular weights (MW) of 18,000 to 30,000 Daltons (D) are most frequently implicated.
   b. Most basic food ingredients can potentially induce an allergic response, although proteins are thought to cause most of the reactions.
   c. Causative dietary components include cow's milk, beef, mutton, pork, chicken, rabbit, horse meat, fish, eggs, oatmeal, wheat, corn, soy, rice flour, potatoes, kidney beans, canned foods, cod liver oil, dry food, pet treats, and food additives.
4. Clinical signs include pruritus, skin erythema, otitis externa, pyoderma, and inflammatory bowel disease.

B. Food intolerance is a nonimmunological, abnormal response to a food item.
   1. The reactions may be toxic, pharmacological, metabolic, or idiosyncratic (i.e., the animal is unable to digest or process a dietary component).
   2. Lactose intolerance, gluten intolerance, reactions to dietary vasoactive amines, and reactions to histamine-containing foods or foods that stimulate histamine release are examples.

C. Food hypersensitivity can be treated in several ways.
   1. Elimination diets are the most useful and reliable way to diagnosis dietary sensitivity and involve the feeding of a restricted diet, followed by dietary challenge with a test meal.
      a. The diets are individualized based on previous dietary exposure.
      b. Identify foods that have not been fed before and use them to formulate a nutritionally balanced diet that is hypoallergenic.
      c. Clinical signs may subside in 3 to 5 days, but may it take 4 to 6 weeks.
   2. A restricted antigen diet may be used that contains only one or two potential allergens, preferably ones that the animal has not eaten in the preceding month.
      a. Many homemade diets are incomplete and unbalanced (e.g., cottage cheese and rice, chicken and rice).
      b. Supplementation with vitamins and minerals is encouraged, but avoid use of supplements that contain potentially offending foodstuffs (e.g., beef, pork).
      c. Commercially prepared, hypoallergenic diets are complete and balanced and may be used for convenience.
         (1) Many diets are available that contain novel protein and carbohydrate sources (e.g., duck, potato)
         (2) Because proteins >18,000 D are incriminated as antigens, modification of proteins to compounds with lower MW may be beneficial.
         (3) Protein modification is a process that alters the physical characteristics of protein molecules, presumably reducing the antigenicity and rendering them less able to elicit an immune response.
         (4) To be effective, protein hydrolysates are <18,000 D.

D. Introducing the presumed offending antigen may be done to confirm a dietary allergy.

E. Long-term management of food hypersensitivities may involve the following:
   1. It is preferable to change from a home-prepared elimination diet to a commercially prepared diet of a selected protein to provide a nutritionally balanced and complete diet.
   2. There are many single-protein diets available, including diets that contain duck, venison, lamb, rabbit, and kangaroo.
   3. A homemade diet may be continued, but must be formulated to be complete and balanced.
   4. A protein hydrolysate diet may be fed.
   5. If the animal does well, emphasize that the owner must not give table scraps or treats, or change the diet even if clinical signs do not recur.

VI. Other adverse food problems include the following:
   A. Mechanical injuries: ingestion of bones
   B. Poisonous plants and chemical toxins
   C. Metals and minerals: lead, zinc, salt

Feeding Factors

I. Management of adverse reactions to food involves changing the diet.
II. It may also involve changing feeding patterns to more or less frequent feedings.

NUTRITION AND CANCER

Animal Factors

I. Four stages of metabolic alterations may occur with cancer.
   A. Phase 1 is a preclinical phase with no obvious clinical signs; metabolic changes include hyperlactatemia, hyperinsulinemia, and altered amino acid profiles.
   B. Phase 2 is associated with early clinical signs, such as anorexia, lethargy, and weight loss; metabolic changes are similar to phase 1.
   C. Phase 3 is associated with advanced clinical signs, such as cachexia, anorexia, lethargy, and increased morbidity associated with cancer treatment; metabolic changes are more profound than in phases 1 and 2.
   D. Phase 4 is recovery and remission; metabolic changes usually persist.
II. Cancer causes many alterations in metabolism.
   A. Abnormalities in carbohydrate metabolism include glucose intolerance, insulin resistance, delayed glucose clearance, abnormal insulin secretion, increased glucose turnover, increased gluconeogenesis, hyperlactatemia, and increased Cori cycle activity.
   B. Abnormalities of fat metabolism include excess depletion of body fat relative to protein loss, decreased total body lipid content, increased lipolysis, decreased lipogenesis, hyperlipidemia, increased free fatty acid and glycerol turnover rates, failure of glucose to suppress free fatty acid oxidation, and decreased serum lipoprotein lipase activity.
   C. Abnormalities in protein metabolism include increased whole-body protein turnover, increased liver protein fractional synthetic rates, reduced muscle fractional synthetic rates, decreased incorporation of amino acids into muscle, increased hepatic protein synthesis, muscle breakdown, and decreased plasma branched-chain amino acids.
   D. Depending on the location and distribution of the cancer, malnutrition may occur from interference with eating and digestion.
III. Treatment of cancer also induces problems.
   A. Surgery increases nutritional requirements, especially for energy and protein, and may impair food intake or result in malassimilation.
   B. Chemotherapy may induce anorexia, vomiting, mucositis, infections, and organ injury.
   C. Radiation therapy may cause mucositis or dermatitis.
   D. Complications may increase if multimodality therapy is used.
IV. Immunosuppression occurs with malnutrition, which promotes tumor growth, infections, and impaired wound healing.
V. Cachexia and malnutrition can occur with any type of cancer.
   A. Hormones, cytokines, and neurotransmitters associated with cancer can affect food intake.
   B. Tumor necrosis factor produced by monocytes causes anorexia.

Dietary Factors

I. Animals with lymphoma may not utilize carbohydrates efficiently; therefore, a low carbohydrate diet (<20% dry matter [DM]) may be beneficial.
II. Animals with lymphoma may preferentially utilize fat, so fat content should be 25% to 50%.
III. Greater protein intake may help maintain protein balance; therefore, protein content should be 25% to 40% DM for dogs and 40% to 50% DM for cats.
IV. Other nutrients may be of benefit in animals with cancer.
   A. Fish oils containing omega-3 fatty acids are anti-inflammatory.
   B. Glutamine is an amino acid that is an energy source for enterocytes.
   C. Antioxidants, such as retinoids, vitamin C, and vitamin E, may improve immune function and help in treating cancer.
V. Preventing obesity decreases the risk of cancer in general and of certain types of cancer (e.g., mammary cancer).

Feeding Factors

I. Because many animals have decreased appetite or anorexia, take a good dietary history.
II. Getting an animal to eat may involve changing food type, texture, or feeding patterns, or may involve stimulating appetite.
III. Nutritional support is individualized.
   A. If possible, feed enterally; however, parenteral nutrition may be required.
   B. Goals of nutrition include maintaining body condition and lean muscle mass, and minimizing nutritional support of the actual cancer.

IV. Select a food.
  A. The diet should contain more fat and protein, and fewer carbohydrates.
  B. It should contain omega-3 fatty acids (>5% DM) and have an omega-6:omega-3 ratio of <3:1.
V. Most importantly, the animal should eat the diet.
VI. The goal is to maintain body condition and weight and to provide a good quality of life.

NUTRITION AND CARDIOVASCULAR DISEASE

Animal Factors

I. Obesity results in blood volume expansion with elevated cardiac output, increased plasma and extracellular fluid volume, increased neurohumoral activation, reduced urinary sodium and water excretion, tachycardia, abnormal systolic and diastolic ventricular function, exercise intolerance, and systemic arterial hypertension.
II. Cachexia associated with heart disease or failure results in negative nitrogen and energy balance.
III. Cats have a dietary requirement for taurine because they have limited ability to synthesize it, and because it is used exclusively for bile acid conjugation.
IV. L-Carnitine is a conditionally essential nutrient involved with transport of long chain fatty acids from the cytosol into the mitochondria where they undergo beta-oxidation for energy production.
V. Hypokalemia and hypomagnesemia are associated with arrhythmias, decreased myocardial contractility, and muscle weakness.

Dietary Factors

I. Average dietary recommendations are as follows:
  A. Restrict calories if obese; however, increase caloric intake if cachectic.
  B. Protein content must be adequate or greater than normal.
  C. Omega-3 fatty acids may be beneficial in an omega-6: omega-3 ratio of 5:1.
  D. Sodium restriction (<0.05% to 0.3% DM) is indicated with congestive heart failure.
  E. Adequate potassium, phosphorous, magnesium are important.
  F. Taurine can be supplemented to cats at 250 to 500 mg PO SID to BID and to dogs at 500 to 1000 mg PO TID.
  G. For L-carnitine deficiency, supplement dogs with 50 to 100 mg/kg PO TID.
II. Commercial diets formulated for dogs and cats with cardiovascular disease are available.

Feeding Factors

I. Some animals require feeding of frequent small meals.
II. Additional nutrients that may be beneficial include the following:
  A. Coenzyme Q10 is required for energy reactions and is an antioxidant.
  B. Antioxidants may decrease oxidative stress in dogs with dilated cardiomyopathy.

NUTRITION AND COGNITIVE DYSFUNCTION

Animal Factors

I. Dogs can develop cognitive dysfunction from certain brain pathologies.
II. Oxidative stress with aging results in brain pathology.
III. Animals with cognitive dysfunction have increased sleep time; decreased activity; loss of learned behaviors (e.g., house training); and decreased recognition of familiar people, things, and places.

Dietary Factors

I. Provide balanced antioxidants.
  A. Vitamin E: membrane radical scavenger, decreases lipid peroxidation
  B. Vitamin C: protects against radical-mediated effects
  C. Flavonoids
  D. Minerals: cofactors for antioxidant enzymes
  E. Coenzyme Q: regenerates vitamin E
  F. Enzymes: catalase, superoxide dismutase, glutathione peroxidase
  G. Nonenzymatic scavengers: uric acid, glutathione, coenzyme Q, transport protein (transferrin, ferritin, lactoferrin, ceruloplasmin)
II. Diets designed for dogs with cognitive dysfunction are available and contain increased levels of vitamins C and E, lipoic acid (an antioxidant), L-carnitine, selenium, and omega-3 fatty acids.

NUTRITION AND CRITICAL CARE

Animal Factors

I. Critical illnesses may be caused by factors such as trauma and acute or chronic disease.
II. Nutritional support is indicated in animals that have not eaten for 3 to 5 days, have poor body condition, or have increased needs for nutrition.

Dietary Factors

I. Provide a complete and balanced diet, if possible.
II. Provide specific nutrients for specific diseases.

Feeding Factors

I. Provide nutrition enterally when possible, because it is the most physiological, easiest, and safest route.
II. Nutrition may be provided orally using one of several techniques.
  A. Try a different flavor or texture of diet.
  B. Add water and warm to near body temperature (especially cats).
  C. Consider forced oral feeding.
  D. Syringe feeding may be tried.
    1. Use food gruel and inject it into oral cavity.

2. Risk of aspiration pneumonia is high and it is difficult to meet requirements with this method.

E. Orogastric feeding tubes are usually used for neonates.

III. Appetite may be stimulated pharmacologically.

A. Benzodiazepines are used cautiously in animals with liver disease and may cause sedation.
1. Diazepam is given at 0.05 to 0.15 mg/kg IV, IM, PO as needed, or at 1 mg PO SID.
2. Oxazepam works better in dogs than cats, and the dosages are 0.2 to 1 mg/kg PO SID to BID in dogs and 2 mg PO SID to BID in cats.
3. Alprazolam is used for behavioral disorders but may stimulate appetite.
   a. Dogs: 0.01 to 0.1 mg/kg PO as needed; maximum 4 mg/day
   b. Cats: 0.05 to 0.2 mg/kg PO SID to BID
4. Flurazepam dosage is 0.2 to 0.4 mg/kg PO every 4 to 7 days in both dogs and cats.

B. Anabolic steroids are not as effective as benzodiazepines and may cause hepatopathy.
1. These testosterone derivatives are given IM and have a delay between initiation of treatment and effect.
2. Nandrolone decanoate dose in dogs is 5 mg/kg IM every 7 days, with a maximum of 200 mg per dose.
3. Stanozolol dose in dogs is 1 to 4 mg PO BID or 25 to 50 mg IM every 7 days, and in cats the dose is 1 to 2 mg PO BID or 25 mg IM every 7 days.

C. Glucocorticoids are catabolic and mobilize muscle (resulting in atrophy), redistribute adipose tissue, and induce insulin resistance.
1. Prednisone 0.2 to 0.5 mg/kg PO SID to QOD
2. Triamcinolone
   a. Initial dosage is 0.11 mg/kg PO SID and may be increased to 0.22 mg/kg PO SID if initial response is unsatisfactory.
   b. Quickly taper to 0.028 to 0.055 mg/kg PO SID.

D. Megestrol acetate has been associated with insulin-resistant diabetes mellitus.
1. It is rarely used for appetite stimulation.
2. Dose in dogs is 0.5 to 1.0 mg/kg PO SID.
3. Dose in cats is 0.25 to 0.5 mg/kg PO SID for 3 to 5 days, then every 48 to 72 hours.

E. Cyproheptadine is a serotonin antagonist that works in cats, but not in dogs.
1. It may cause sedation and liver disease.
2. Dosage is 1 to 4 mg PO SID to BID.

F. B-vitamin deficiency is associated with anorexia and is often supplemented at a dosage of 1 to 2 mL/L of IV fluids; however, no proof of its efficacy exists.

G. Interferon α-2b is used in cats at 30 units PO SID.

IV. Several choices of feeding tubes are available.

A. Nasogastric feeding tubes are inserted through the nasal cavity into the esophagus and stomach.
1. They are placed using topical anesthesia.
2. A 3.5 to 5 French tube is used in small cats and dogs and a 5 to 8 French tube is used in average-size cats and larger dogs.
3. Liquid diets or very watery gruels are fed.
4. Do not use if the animal is comatose, lacks a gag reflex, or has esophageal motility problems because of the increased risk of aspiration pneumonia.
5. Complications include rhinitis, dacryocystitis, esophageal reflux, vomiting, aspiration, pneumonia, inadvertent tube removal, and tube obstruction.

B. Esophagostomy feeding tubes are inserted directly into the cervical esophagus.
1. Use size 12 French tubes or larger.
2. They do not interfere with voluntary consumption of food.
3. Gruels may be used because of the size of the tube used.
4. Insert surgically or by blind percutaneous techniques, with the animal under heavy sedation or anesthesia.
5. Esophagitis usually does not occur unless the distal tip passes through the lower esophageal sphincter.

C. Gastrostomy feeding tubes are inserted directly into the stomach and exit through the lateral abdominal wall.
1. They may be placed surgically through a small laparotomy incision; at the time of abdominal surgery; endoscopically or via nonendoscopic techniques.
2. Gastrostomy tubes can be used in animals with esophageal or oral disease, are usually large-bore tubes (16 to 24 French) through which gruels of canned foods can be administered, are usually well tolerated, and can be left in place for months to years.
3. Disadvantages and complications include vomiting, aspiration pneumonia (often associated with rapid administration of cold foods), peritonitis from dislodgement of the tube, and difficulty in maintaining the tube and associated bandages.

D. Low-profile gastrostomy tubes can be left in place for years and have the advantage of not requiring bandage material; however, they are expensive and must be inserted surgically or percutaneously, after another gastrostomy tube has been in place for at least a month.

E. Enterostomy feeding tubes are inserted surgically into the small intestine.
1. A 5 French tube is inserted into the small intestine for $\geq$ 20 cm.
2. Because they by-pass the stomach, they can be used in animals that are vomiting, have had gastric surgery, or have pancreatitis.
3. They require use of a liquid diet.

V. Parenteral nutrition may be used for short-term nutritional support, if enteral nutrition cannot be used or to supplement enteral food intake.

A. Total parenteral nutrition (TPN) provides protein (amino acids), carbohydrate (dextrose), fat (lipids), vitamins, minerals, and electrolytes to meet daily nutritional requirements.
1. Nonprotein calories are divided between carbohydrate and fat.

2. Solutions are hypertonic and must be administered through a central venous catheter.
3. Formulations depend on the animal's underlying disease.

B. Partial parenteral nutrition is administered through a peripheral venous catheter.
1. A TPN formulation may be diluted until it is isotonic or only certain components may be administered.
2. The solution must be isotonic.
3. It meets only part of the daily nutritional requirements.

NUTRITION AND DERMATOLOGICAL CONDITIONS

Animal Factors

I. Nutritional factors affect the skin and coat.
II. Clinical signs associated with nutritional abnormalities include a sparse, dry, dull, and brittle hair coat that epilates easily, slow hair growth, abnormal scale accumulation, alopecia, erythema, crusting, decubital ulcers, and slow wound healing.

Dietary Factors

I. Inadequate energy intake is associated with keratinization abnormalities, depigmentation, changes in epidermal and sebaceous glands, and increased susceptibility to trauma.
II. Protein deficiency is associated with similar clinical signs.
III. Essential omega-6 fatty acids include linoleic acid (>1% DM dogs, >0.5% DM cats) and arachidonic acid for cats (>0.02% DM).
A. Omega-3 fatty acids can supply part of the omega-6 fatty acid component.
B. Clinical signs of essential fatty acid deficiency include scaling, matting of hair, loss of skin elasticity, dry and dull haircoat, erythema, epidermal peeling, otitis externa, and slow hair growth.
IV. Certain mineral deficiencies may affect the skin (see Table 122-2).
A. Copper deficiency is associated with loss of normal hair coloration, decreased density or lack of hair, and rough or dull haircoat.
B. Many dermatological conditions may occur with zinc deficiency and respond to zinc supplementation.
1. Dietary phytate binds zinc, resulting in clinical signs of deficiency.
2. Clinical signs of zinc deficiency include erythema, alopecia, and hyperkeratosis.
V. Certain vitamins may affect the skin.
A. Vitamin A deficiency is associated with skin lesions and focal sloughing of skin.
B. Vitamin E deficiency occurs in cats in association with steatitis.
1. Clinical signs include erythema and keratinization defects.
2. Vitamin E–responsive dermatoses include discoid lupus erythematosus, systemic lupus erythematosus, pemphigus erythematosus, sterile panniculitis, acanthosis nigricans, dermatomyositis, and ear margin vasculitis.
VI. Dermatological conditions also arise from food allergies (see Adverse Food Reactions).

Feeding Factors

I. Evaluate the quality and amount of diet fed.
II. Consider a dietary change (see Adverse Food Reactions).
III. Feed a better quality diet if a nutritional deficiency is suspected.
IV. Supplement specific nutrients for dietary deficiencies.
A. Dogs with seborrhea may respond to essential fatty acid supplementation even if they are consuming an adequate diet.
B. Omega-3 fatty acid supplementation may decrease inflammation.
C. Give zinc supplementation for zinc-responsive dermatoses.
1. Zinc sulfate 10 to 15 mg/kg/day PO
2. Zinc methionine 2 mg/kg/day PO
3. Not given with food
D. Supplement vitamin A for vitamin A–responsive dermatoses.
1. Tretinoin topically SID to BID
2. Isotretinoin 1 to 3 mg/kg/day PO
3. Etretinate 0.75 to 1 mg/kg/day PO
E. Vitamin E is given to dogs at 200 to 800 IU PO BID.

NUTRITION AND DIABETES MELLITUS

Animal Factors

I. Metabolic pathways (protein, lipid, carbohydrate, energy) are disrupted with diabetes mellitus.
II. Animals with insulin-dependent diabetes mellitus (IDDM) have a ravenous appetite, lose weight, are polyuric and polydipsic (PU/PD), and develop ketoacidosis.
III. Animals with non–insulin-dependent diabetes mellitus (NIDDM) have insulin resistance, are obese, and do not commonly develop ketoacidosis.

Dietary Factors

I. Dehydration may occur from PU/PD and from vomiting with ketoacidosis.
II. Obesity and hyperlipidemia may induce insulin resistance.
III. Protein catabolism results in loss of muscle mass.
IV. In cats, avoid fructose and simple sugars, which are found in semimoist diets.
V. Moderate to high intake of fiber decreases obesity and increases insulin responsiveness.
VI. Omega-3 fatty acids may be beneficial in dogs and cats.
VII. Hypokalemia may occur from PU/PD, decreased food intake, and vomiting with ketoacidosis.
VIII. Hypophosphatemia may occur when treating ketoacidosis.

IX. Chromium, manganese, iron, and zinc may be important in the management of diabetes mellitus; however, their role is unclear.

Feeding Factors

I. Nutritional modification complements the treatment of IDDM.
   A. The goal is to achieve optimal body condition and weight.
   B. Different diets have been recommended.
      1. High-fiber diets may help decrease obesity but are less calorically dense.
      2. Moderate-fiber diets may be as effective as high-fiber diets in dogs.
      3. High-fat, low-carbohydrate diets are beneficial in some cats.
   C. Match dietary intake with insulin administration.
      1. Most animals require insulin BID.
      2. Feed two to four meals a day, if possible.
II. Weight reduction is important with NIDDM.
   A. Nutrient requirements are similar to IDDM.
   B. Reduce weight carefully in obese cats because of the risk of hepatic lipidosis.
III. Diabetic ketoacidosis requires intensive hospital care.
   A. Parenteral nutrition may be required.
   B. Regular feedings are usually begun once vomiting stops, and then intensive insulin therapy is switched to maintenance insulin.

NUTRITION AND GASTROINTESTINAL DISEASES

See Section 5 and Table 122-3.

NUTRITION AND HEPATIC DISEASE

Animal Factors

I. Liver failure is associated with disruption of several metabolic processes.
II. Hepatoencephalopathy is a neurological manifestation of liver failure.

Dietary Factors

I. Maintain adequate caloric intake to reverse fat mobilization.
II. Restrict dietary protein if hepatoencephalopathy is present.
III. Decrease copper intake for copper-associated hepatopathy.
   A. Chelating agents may be required.
   B. Zinc decreases hepatic copper levels.
IV. Omega-3 fatty acids may be helpful for inflammatory hepatic disease.
V. Taurine may be administered to induce choleresis.

Feeding Factors

I. Consider changing the diet or supplementing the current diet.
II. Feed small meals frequently or use a feeding tube.

NUTRITION AND MUSCULOSKELETAL DISEASES

Developmental Orthopedic Diseases

See Chapter 121.

Osteoarthritis

Animal Factors

I. Degenerative joint disease (DJD) or osteoarthritis has multiple etiologies and is characterized by pathologic changes of synovial or diarthrodial joints that are accompanied by pain and disability.
II. Although an association exists between obesity and DJD, cause and effect are unproven.
   A. Obesity may cause excessive forces on joints and articular cartilage, which result in inactivity and further weight gain.
   B. Abnormal forces are placed on joints.
   C. A vicious cycle ensues.

Dietary Factors

I. Manage obesity if present.
II. Consider supplementing specific nutrients.
   A. Omega-3 fatty acids alter inflammation associated with DJD.
      1. Arachidonic acid is metabolized to prostaglandins, leukotrienes, and thromboxanes, which are pro-inflammatory, vasoactive substances.
      2. Substituting an omega-3 fatty acid for arachidonic acid results in production of cytokines that have less proinflammatory and vasoactive effects.
      3. Omega-3 fatty acids derived from fish oil have been shown to be of benefit for DJD.
   B. Antioxidants scavenge free radicals that are increased with DJD, and may also be beneficial.
   C. Cartilage-modulating agents, such as chondroitin sulfate and glucosamine, may slow progression or alter processes involved with DJD.
      1. They stimulate cartilage matrix synthesis and hyaluronate by synovial membranes, and inhibit catabolic enzymes.
      2. Some commercial diets contain chondro-modulating agents.

Feeding Factors

I. Manage obesity, if present.
II. Consider changing from ad libitum to meal feeding.

NUTRITION AND OBESITY

Animal Factors

I. Obesity is defined as body weight ≥15% over ideal weight that is associated with fat deposition.
II. It is the most common nutritional disease, with 25% to 50% of dogs and cats being obese.

TABLE 122-3

Dietary Recommendations for Gastrointestinal Diseases

DISEASE	DIETARY RECOMMENDATIONS
Dental	
	Feed a dry diet with fiber-like texture to promote mechanical cleaning. Consider a diet with microcleansing crystals.
Pharyngeal, Esophageal	
	Feed a diet of high calorie, fat, and protein content. Feed small volumes of food frequently in an upright position.
Gastric, Small Intestinal	
Gastritis, gastric motility problems	Use a low fat diet. Feed small volumes of food frequently.
Gastric dilatation-volvulus	Feed an adult dry food. Feed several meals a day. Avoid rapid consumption of food and large amounts of water.
Acute gastroenteritis	Withhold food for 1-2 days. Feed a highly digestible diet with moderate fat content.
Inflammatory bowel disease	Feed a novel protein diet or protein hydrolysate diet.
Protein-losing enteropathy	Feed a high-protein, low-fat, calorically dense diet. Consider feeding small meals frequently.
Small intestinal bacterial overgrowth, exocrine pancreatic insufficiency	Feed a highly digestible, moderate-fat-content diet. Dietary fructooligosaccharides may be beneficial. Incubate food with pancreatic digestive enzymes for pancreatic exocrine insufficiency.
Large Intestinal	
Inflammatory colitis	Feed a hypoallergenic diet or a high-fiber diet.
Constipation, megacolon	Some animals respond to a high-fiber diet. A low-fiber diet may be beneficial for megacolon.
Flatulence	Feed a highly digestible diet containing alpha-galactosidase. Do not feed diets containing fermentable fiber. Do not feed sulfur-containing vegetables.
Pancreatitis	
Acute	After vomiting subsides, begin small amounts of fluids. Then start small meals. Feed a highly digestible diet containing moderate fat, and moderate protein diet during recovery.
Chronic, hyperlipidemia	Feed a low-fat, high-fiber diet.

III. Associated health risks include musculoskeletal and cardiovascular disease; hypertension; diabetes mellitus; hyperlipidemia; hepatic lipidosis in cats; higher incidence of transitional cell carcinoma and mammary cancer in dogs; possible anesthetic and surgical complications; decreased heat tolerance and stamina; and reproductive problems.

IV. Assessment of body composition is important.
   A. Compare current weight to ideal body weight in early adulthood.
   B. Body condition scoring (BCS) incorporates body weight and overall condition (see Chapter 1).
      1. It may be based on a 9- or 5-point scale.
      2. The middle of the scale (5/9 or 3/5) is ideal.
         a. Lower numbers: underconditioned
         b. Higher numbers: overconditioned
      3. Optimal body condition (5/9 or 3/5) is equivalent to 15% to 20% body fat.
         a. BCS of 3/9 or 2/5 = 7% to 15% body fat
         b. BCS of 1/9 or 1/5 = 1% to 6% body fat
         c. BCS of 7/9 or 4/5 = 20% to 30% body fat
         d. BCS of 9/9 or 5/5 > 30% body fat and possibly >50% body fat

V. Obesity occurs when energy intake exceeds energy expenditure and other risk factors are present.
   A. Certain breeds (e.g., Labrador retriever, Cairn terrier, American cocker spaniel, dachshund, basset hound, beagle) have increased incidence.

B. Females have higher incidence.
C. Gonadectomy increases risk of obesity in dogs and cats because metabolic rates are 20% to 25% below those of reproductively-intact animals.
D. Obesity occurs commonly in middle-aged animals because of decreased activity.
E. Feeding calorically dense, highly palatable foods increases risk of obesity.
F. Free choice feeding increases risk of obesity.
G. Obese pets are more likely to be owned by middle-aged or older humans who are also obese.
H. Hypothyroidism and hyperadrenocorticism are associated with obesity.

Dietary Factors

I. Body weight and condition are determined by the nutrient composition of the diet, amount of diet eaten, and activity level.
II. Obesity develops when daily intake of energy exceeds daily energy expenditure over a period.
  A. Obesity occurs in a stair-step fashion.
  B. Often animals require fewer calories than estimated to maintain the obese state.
III. Take a good dietary history to determine how much food the animal is eating.
  A. From the amount of food eaten and from the package information, estimate the caloric content of the diet.
  B. Also include calories from treats and table scraps.
IV. Change the diet and feeding method to induce weight loss.
  A. Feeding less of the same food is usually unsuccessful.
    1. Calorically dense foods contain more fat than weight-reduction diets.
    2. Digestibility of food is inversely proportional to total amount eaten.
    3. When less of a calorically dense food is fed, the proportion digested increases.
  B. Low-carbohydrate, high-fat diets are recommended in some cats because peripheral fat is mobilized.
  C. Less calorically dense diets are preferred.
    1. Diets formulated for weight reduction contain <3.4 kcal/g (DM) for dogs and <3.6 kcal/g (DM) for cats.
    2. They contain reduced fat and increased fiber, as well as air or moisture that induces a feeling of satiety.

Feeding Factors

I. Weight loss is better achieved with meal feeding than free-choice feeding.
II. Limit access to other food, table scraps, and treats.
III. Weight-reduction programs involve a multistep approach that involves good owner commitment, a feeding plan, an exercise plan, and repeated communication and montoring.
  A. Owners must recognize that their pet is obese and understand the health risks.
    1. Use BCS charts or posters as a visual aid.
    2. Use other tests (e.g., radiographs, hyperlipidemic serum) to demonstrate associated abnormalities.
    3. Educate owners as to the costs of cruciate repair or management of diabetes mellitus.
  B. Institute a feeding plan.
    1. Detailed history of food and caloric intake is essential.
    2. Set the amount of calories to be fed.
      a. Use optimal body weight.
        (1) Estimate maintenance energy requirement (MER) at optimal body weight.
        (2) Feed 50% to 75% of this MER.
        (3) Compare the estimated MER with current caloric intake, because many animals require less than the estimated MER and caloric intake may need further restriction.
      b. Determine how much to feed to induce a 1% to 4% loss of body weight per week.
    3. Select the diet and feed as meals.
    4. Eliminate or account for treats, snacks, and table scraps.
    5. In multianimal households, feed the obese animal away from other animals or have the animal work for its meal.
    6. Increase exercise.
  C. Communication is extremely important.
    1. Obesity is a disease and requires periodic reassessment.
    2. Weigh the animal every other week.
    3. The goal is for 1% to 2% loss of body weight per week on average.
    4. Use positive reinforcement.
    5. Reward animals and owners as milestones are reached.
    6. Graph weight reduction as a visual reinforcement.
    7. Take photographs before and after initiating the weight loss program.
IV. Prevention of obesity is critical.
  A. Prevent obesity from occurring in growing animals.
  B. When adult animals successfully finish a weight reduction program, make a weight maintenance program available.
    1. It may include feeding a maintenance diet that is less calorically dense and higher in fiber.
    2. Certain diets labeled as *light* can be used, but are not as effective.
  C. Treats, snacks, and table scraps should be <5% of total caloric intake.

NUTRITION AND UROLOGICAL DISEASES

Chronic Renal Failure

Animal Factors

I. Appetite may be decreased.
II. Evidence of chronic disease includes decreased body weight, loss of muscle mass, poor haircoat, and pale mucous membranes.
III. Signs of uremia include oral ulcers, dehydration, hematochezia, and melena.

Dietary Factors

I. Water requirements are increased; therefore, feed a canned food, add water to dry food, or supplement with PO or SC fluids.
II. Increase caloric density of the diet to compensate for anorexia.
III. Decrease protein fed to 1.25 to 1.75 g/kg body weight/day or 15% to 20% DM for dogs and to 3.8 to 4.4 g/kg/day or 28% to 32% DM for cats.
IV. Hypokalemia may occur, especially in cats; therefore, feed a diet replete in potassium (0.3% to 0.5% DM for dogs and 0.8% to 1.2% DM for cats) or provide supplementation.
V. Decrease sodium content if the animal is hypertensive (<0.25% DM for dogs and <0.35% DM for cats).
VI. Feed an alkalinizing diet to offset metabolic acidosis or supplement with an alkalinizing agent (e.g., potassium citrate).
VII. Decrease phosphorous to 0.15% to 0.3% DM for dogs and 0.4% to 0.6% DM for cats.
VIII. Omega-3 fatty acids may be beneficial in dogs when fed at an omega-6:omega-3 ratio of 5:1.

Feeding Factors

I. Anorexia is often present from uremic gastroenteritis; therefore administer histamine-2 receptor antagonists or antacids.
II. Feed small meals frequently.
III. Feeding tubes may be required.

Urolithiasis

Animal Factors

I. Uroliths may be composed of several different types of minerals (see Section 7).
   A. In pediatric dogs and cats, infection-induced struvite and urate uroliths occur most commonly.
   B. In young adults, infection-induced struvite (dogs), sterile struvite (cats), urate, and cystine are the most common types.
   C. In geriatric adults, infection-induced struvite and calcium oxalate occur most commonly.
II. Urolith formation is associated with varying underlying causes.
   A. Infection-induced struvite uroliths are associated with systemic or local diseases that result in a bacterial urinary tract infection with urease-producing microbe.
   B. Sterile struvite uroliths are associated with the feeding of meals and dry foods, and alkaluria.
   C. Calcium oxalate uroliths are associated with hypercalcemia (idiopathic hypercalcemia in cats) or hypercalciuria (e.g., hyperadrenocorticism).
   D. Urate uroliths are associated with liver disease or an underlying defect in uric acid metabolism.
   E. Cystine uroliths are associated with an inborn error of cystine reabsorption in the renal proximal tubule.

Dietary Factors

I. Struvite, urate, and cystine uroliths can be dissolved medically.
   A. For dissolution of struvite uroliths, feed a low-magnesium, low-phosphorous, low-protein, acidifying, and diuretic diet, and administer antibiotics if the uroliths are associated with infection.
   B. For dissolution of urate uroliths, feed a low-protein, alkalinizing, and diuretic diet, and administer allopurinol.
   C. For dissolution of cystine uroliths, feed a low-protein, alkalinizing, and diuretic diet, and administer 2-mercaptopropionyl glycine.
II. Prevention of uroliths may involve dietary changes.
   A. For infection-induced struvite uroliths, no dietary change is required.
   B. For sterile struvite uroliths, feed a diet that is low in protein, magnesium, and phosphorous, and that induces aciduria.
   C. Dietary management of calcium oxalate uroliths is dependent on whether the animal is normocalcemic or hypercalcemic.
      1. In animals that are normocalcemic, feed an oxalate-preventative diet that is low in calcium, replete in magnesium, and induces a neutral to alkaline urine pH.
      2. In cats with idiopathic hypercalcemia and in dogs that are intolerant of higher fat intake, feed a higher fiber diet and supplement with potassium citrate.
   D. For urate uroliths, feed a low-protein, alkalinizing, and diuretic diet, with or without administration of allopurinol.
   E. For cystine uroliths, feed a low-protein, alkalinizing, and diuretic diet, with or without administration of 2-mercaptopropionyl glycine.

Feeding Factors

I. Feeding a canned diet may decrease risk of recurrence of sterile struvite, calcium oxalate, urate, and cystine uroliths by decreasing concentrations of calculogenic compounds in the urine.
II. Monitor response to diet using urine specific gravity, urine pH, and absence of crystalluria.

Feline Idiopathic Cystitis

Animal Factors

I. Idiopathic cystitis usually occurs in young adult cats (see Chapter 50).
II. Males may obstruct from matrix-crystalline urethral plugs that are often composed of struvite.

Dietary Factors

I. Dry diets may result in concentrated urine and increased concentration of crystallogenic compounds.
II. Canned diets increase water intake and urine volume, and decrease urine specific gravity, which may be beneficial.

Feeding Factors

I. Free-choice feeding is associated with persistent aciduria.
II. Feeding a canned diet increases volume and frequency of urination.

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CHAPTER 123

Introduction

Petra A. Volmer

DECONTAMINATION

Definition

I. Decontamination is the removal or neutralization of poisonous or otherwise harmful substances in the body and enhancement of their elimination.
II. There is no one correct approach to decontamination; the process must be adapted to address the needs of the individual animal.

Gastrointestinal Decontamination

Emesis

I. Emesis is one of the most rapid, safe, and easiest methods for removing substances from the gut.
II. Effectiveness of emesis is dependent on the physical properties of the toxin ingested, time from ingestion to emesis, the volume of gastric contents, and the emetic agent used.
III. Recovery of gastric contents varies widely (from 9% to 75%) (Peterson, 2006).
IV. Contraindications to emesis include the following:
    A. Clinical signs of central nervous system (CNS) stimulation or depression
        1. Induction of emesis in the stimulated animal can induce a seizure and cause aspiration.
        2. This is also true for rapidly acting agents that may produce CNS stimulation before the emetic action takes effect.
        3. Animals with CNS depression may have a compromised gag reflex, thereby risking aspiration.
    B. Ingestion of a volatile hydrocarbon
        1. Volatile hydrocarbons readily evaporate at ambient temperatures and pressures.
        2. Volatile hydrocarbons enter the pulmonary tree and can cause fairly rapid changes, such as inflammation, edema, and hemorrhage (chemical pneumonitis).
    C. Ingestion of a corrosive or caustic substance
        1. Corrosives (acids) or caustics (alkalis) can cause coagulative and liquefactive necrosis of mucosa and submucosa.
        2. Cationic detergents are strong surfactants that disrupt cell walls.
        3. Oral and esophageal burns are possible, with subsequent stricture formation.
    D. Species that cannot vomit are rabbits and rodents.
V. Emesis is not recommended or is of questionable benefit under the following circumstances:
    A. If the animal has already vomited
    B. If the animal has a preexisting medical condition that may make vomiting hazardous
    C. If the exposure was via inhalation or intravenously
    D. If the exposure occurred more than 2 hours previously
        1. Exceptions include extended-release medications or some plant materials that digest slowly.
        2. In these cases emesis may be rewarding for up to 4 hours, if no clinical signs are present.
VI. Emetics work best with food in the stomach; if possible, feed a small, moist meal prior to inducing emesis.
    A. Hydrogen peroxide (3%)
        1. Hydrogen peroxide is thought to act by causing gastric irritation, and can be administered by the veterinarian or the owner.
        2. The recommended dose is 1 to 2 mL/kg PO for dogs and cats; the dose can be repeated one time if emesis does not occur within 20 minutes.
        3. Gentle agitation, such as walking, may promote emesis.
    B. Apomorphine hydrochloride
        1. Apomorphine acts directly on the chemoreceptor trigger zone.
        2. Apomorphine is usually used in the dog.

3. Although a safe and effective dose has not been established in the cat, it has been used successfully in this species by some clinicians.
4. Administration is by instillation in conjunctival sac.
   a. Tablet or a portion of the tablet is placed in the inferior conjunctival sac.
   b. Apomorphine can also be dissolved in water and instilled in the eye.
   c. After emesis, the tablet or residue is removed and the conjunctiva is rinsed.
5. Apomorphine can also be injected at 0.03 to 0.04 mg/kg IV, 0.04 to 0.08 mg/kg IM, or 0.08 mg/kg SC (Plumb, 2005).
6. CNS depression is possible and can be reversed with naloxone 0.04 mg/kg IV, IM, or SC in dogs and 0.05 to 0.1 mg/kg IV in cats (Plumb, 2005).

C. Xylazine *(Rompun)*
1. Xylazine is a centrally acting α-2 adrenergic agonist.
2. It has been recommended as an emetic in cats at 0.44 mg/kg IM, but is not a reliable emetic in dogs.
3. Sedation can be reversed with an α-2 adrenergic antagonist (e.g., yohimbine 0.1 mg/kg IV).

D. Syrup of Ipecac
1. It is no longer routinely recommended, because it is not as reliable as other emetics.
2. It causes emesis by gastric irritation; however when absorbed, emesis also occurs from stimulation of the chemoreceptor trigger zone.
3. Overdoses can cause cardiotoxicity.
4. Because of its unpleasant taste, it usually requires administration via a stomach tube.
5. Dose in the dog is 1 to 2.5 mL/kg PO and in cats is 3.3 mL/kg PO, diluted 50:50 with water.

VII. The following methods of emesis are not recommended because they are ineffective, dangerous, and waste valuable time.
A. Sodium chloride (table salt): inconsistent emesis, sodium ion toxicosis possible
B. Liquid dishwashing detergent: emesis inconsistent
C. Placing fingers or other objects in the back of the throat: risk of injury to the human or animal, inconsistent results

VIII. Emetics may not remove all material from the stomach and may propel some ingesta into the duodenum.

IX. Other measures to evacuate the gut or prevent absorption are gastric lavage, enterogastric lavage, and the use of activated charcoal and cathartics.

Gastric Lavage

I. Gastric lavage: evacuation of stomach contents by gastric intubation and irrigation

II. Indications
A. Emetics have failed.
B. Animal is exhibiting clinical signs.
C. Other conditions prevent the safe use of emetics.

III. Contraindications
A. If caustic or corrosive substances have been ingested
B. If volatile hydrocarbons have been ingested
C. Large chunky material in stomach

IV. Procedure
A. Animal may be anesthetized or unconscious, with a cuffed endotracheal tube inflated in the airway.
B. Pass a large bore stomach tube, keeping the head lower than animal's chest.
C. Gently force warm water into the stomach tube using a stomach or bilge pump.
1. Approximately 5 to 10 mL/kg of fluid is used per rinse.
2. Allow water to mix with stomach contents.
D. Using gravity, allow fluid to drain from tube, retrieving the approximate amount that was administered, and repeat until the water comes out clear.
E. Administer activated charcoal prior to removal of tube, then occlude the end of tube and withdraw it.
F. Retrieved fluid is saved for future toxicological testing.
G. The procedure may result in esophageal perforation or accidental tracheal intubation.

Enterogastric Lavage

I. This procedure is an extension of gastric lavage, with additional decontamination of the intestines.

II. Perform gastric lavage as described above, leaving the lavage tube in place.

III. Perform tepid water enema.

IV. Attach enema tube to faucet with an adapter.
A. At low pressure, continuously run water into the colon while applying mild digital pressure around anus (to prevent leakage).
B. Intestines will fill with water.
C. Atropine 0.02 mg/kg IV may be required to relax the smooth muscle of gut.

V. Monitor for intestinal distension using abdominal palpation.

VI. Observe for fluid draining from the gastric tube and continue infusion until this fluid runs clear.

VII. Contraindications are similar to those for gastric lavage.

Activated Charcoal

I. Activated charcoal is a highly porous material capable of trapping a wide range of organic substances.

II. Powdered and liquid activated charcoal products have surface-binding areas of 900 to 1500 m^2/g.

III. Tablet and capsule formulations are unsuitable for the treatment of poisoning, because they have surface-binding areas of only 2 to 4 m^2/g (Rosendale, 2002).

IV. Burnt toast, charcoal briquettes, or wood ashes are inert and are *not* substitutes for activated charcoal.

V. Not all toxic substances bind equally to activated charcoal; alcohols, hydrocarbons, metals, inorganic minerals, and corrosive/caustic agents do not adsorb well.

VI. Contraindications to the use of activated charcoal are as follows:
A. The substance ingested poses a significant danger of aspiration (volatile hydrocarbons).
B. Esophageal or gastrointestinal perforation is suspected.

C. The animal is experiencing severe vomiting.

VII. Administration is as follows:
- A. Powdered activated charcoal is given at 1 to 2 g/kg PO, mixed with 50 to 200 mL of water to make a slurry.
  1. Liquid preparations are also available and may contain sorbitol.
  2. *ToxiBan Suspension* (Lloyd, Inc., Shenandoah, Iowa) has a recommended label dose of 10-20 mL/kg PO.
- B. Charcoal stains clothing and other surfaces, so consider administration in a bathtub or other easily cleanable area.
- C. Administration is repeated every 6 to 12 hours at half the original dose for delayed release substances or for those suspected of undergoing extensive enterohepatic recirculation.
- D. If the animal is exhibiting signs, administer charcoal with a stomach tube under sedation, with a cuffed endotracheal tube in place.
- E. Activated charcoal may also be administered with a syringe or turkey baster to the unanesthetized animal, although this increases the risk of aspiration.
- F. Some animals may ingest the charcoal if it is mixed with a small amount of food.

VIII. Several precautions exist.
- A. Aspiration of activated charcoal can lead to pulmonary complications.
- B. Administration has been associated with electrolyte disturbances (hypernatremia).

Gastrotomy

I. Gastrotomy or physical removal is indicated for some toxins.

II. Examples include polyurethane glues (e.g., *Gorilla glue*) in which other methods of decontamination are inadequate.

Cathartics

I. Cathartics: hasten passage of material through the gastrointestinal tract

II. Contraindications
- A. The animal has diarrhea.
- B. The animal is dehydrated.
- C. Gastrointestinal ileus or obstruction is present.

III. Osmotic cathartics
- A. Magnesium sulfate (Epsom salts) and sodium sulfate (Glauber's salts)
  1. Saline cathartics
  2. Dose: 250 mg/kg PO added to charcoal slurry
  3. Magnesium sulfate
     a. It is used with caution in animals with slowed gastrointestinal transit time or those with renal insufficiency.
     b. Excess magnesium may be absorbed.
- B. Sorbitol
  1. It is a nonabsorbable sugar.
  2. Some activated charcoal slurries contain sorbitol as a cathartic.
  3. Dose is 1 to 2 mL/kg of a 70% solution added to a charcoal solution.

IV. Bulk cathartics
- A. They add bulk to the ingesta.
- B. They are particularly useful for encouraging passage of physical objects.
- C. Psyllium *(Metamucil)* is given at 3 to 10 g in dogs and 3 g in cats, and mixed with food SID to BID.
- D. Canned pumpkin (unspiced) added to food or a high-fiber pet food can also be tried.

Dermal Decontamination and Bathing

I. Stabilize animals before initiating bathing.

II. Liquid dish detergents are recommended over shampoos or hand soaps.

III. Do not use insecticidal shampoos, detergents designed for automatic dishwashers, or citrus-based cleaners.

IV. Repeated bathing is required in some instances, followed by thorough rinsing and drying.

V. Bathing alone may not be sufficient for some sticky or viscous substances.

VI. Hand cleaners such as *Goop* (Critzas Industries, St. Louis, Mo.) may work well to remove some thick, petroleum-based products, followed by thorough bathing with a detergent.

VII. In some cases, clipping or shaving the hair coat may be required to remove the offending substance.

Ocular Decontamination

I. Clinical effects may range from mild irritation to severe damage of the cornea or conjunctiva.

II. Immediate irrigation can be initiated by the owner, followed by more extensive irrigation by the veterinarian.

III. Rinse with copious amounts of appropriate fluid for 20 to 30 minutes.
- A. Tap water, lactated Ringer's solution, or normal saline at body temperature are used for irrigation.
- B. Rinse from the medial aspect of the eye to the lateral aspect, to avoid contamination of the opposite eye.
- C. For severe exposures, sedation may be required.

PRACTICAL CONVERSIONS

I. Perform calculations to determine exposure based on the amount of toxic agent per unit of body weight.

II. Most toxicities are reported in milligrams of toxic substance per kilogram of body weight (mg/kg).

III. Table 123-1 provides useful conversions to use in estimating exposure.

DIAGNOSTIC TOXICOLOGY

I. Arriving at a toxicological diagnosis requires cooperation among the owner, veterinarian, and diagnostic toxicologist.

II. Communicating with the diagnostic laboratory is one of the most important steps that can be taken prior to collecting and submitting samples.

III. The most common reason for an inadequate analytical result is the lack of an appropriate sample or insufficient sample quantity.

TABLE 123-1

Useful Conversions for Calculating Exposures to Toxicants

AMOUNT	APPROXIMATE EQUIVALENT
1 teaspoon (tsp)	5 g dry or 5 mL wet
1 tablespoon (Tbsp)	15 g dry or 15 mL wet
2.2 lb	1 kg dry or 1 L wet
1 lb	454 g
1 g	15.4 grains
1 grain	65 mg
1 oz	28 g dry, 29.6 mL wet
1 cup	237 mL
1 gal	3.785 L
1 qt	0.946 L
1 mg/kg	1 ppm
1 µg/kg	1 part per billion (ppb)
1 part per million (ppm)	0.0001%

IV. Provide a thorough and complete history.
   A. A comprehensive, yet succinct, history helps narrow down and prioritize the possible list of toxic agents.
   B. Include information on the recent circumstances surrounding the illness in question.
      1. Breed, sex, age, weight and relevant medical history and current medications
      2. Total number of animals in environment and number affected
      3. If known, substance ingested, time ingested, signs noted, and response to treatment
      4. Results of any clinical pathologic tests
      5. Environmental factors, such as sources of food and water, and possible access to hazardous sub stances
      6. Relationship of owners with others, such as neighbors
      7. Recent visitors to home who may have misplaced medications
      8. Supervision of animal while outdoors
      9. Vaccination status of animal
      10. Children in home who may have innocently fed the animal inappropriate substances
   V. Be as specific as possible regarding requested analyses; there is no such thing as a "poison screen."
   VI. Submit appropriate specimens.
      A. Considering the toxicokinetics of the agent helps to determine the most appropriate tissue to submit.
      B. Submit a large quantity of the specimen to allow for repeated analyses or searching for other toxicants.
      C. Submit specimens refrigerated or frozen.
      D. Package, store, and label each tissue individually.
   VII. Triple-bag specimens and ship as quickly as possible on ice or dry ice.
   VIII. Avoid shipping on weekends or holidays, as specimens may sit for days in hot conditions.

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CHAPTER 124

Rodenticides

Donna Mensching | Petra A. Volmer

ANTICOAGULANT RODENTICIDES

Sources

I. First-generation anticoagulant agents
   A. Hydroxycoumarin agents
      1. They include short-acting compounds (warfarin and dicoumarol) and long-acting compound (coumafuryl and fumarin).
      2. Duration of vitamin K_1 epoxide reductase inhibition is 4 to 6 days (half-life, 14.5 hours in the dog).
      3. Brand names include *D-Con, Mouse Prufe II, Havoc, Jaguar, Talon-G, Final Blox, Enforcer, Contrac,* and *Just One Bite.*
      4. Warfarin-containing products are generally 0.025%.
      5. Toxicosis typically requires repeated ingestion.
   B. Indandione agents
      1. They include long-acting pindone, valone, and chlorphacinone.
      2. Trade names include *Pival Parakake, Eaton's A-C Formula 50, Purina Rat Kill, Contrax P, Enforcer,* and *Tri-Ban.*
      3. Formulations are typically 0.025%, but the previously listed products range from 0.011% to 0.14%.

II. Second-generation anticoagulant agents were formulated as a result of resistance against the first-generation anticoagulant agents.
   A. Formulations
      1. Second-generation anticoagulant agents are usually 0.005%, but exceptions do occur.
      2. Toxicosis can occur with one dose.
      3. Relay toxicosis—clinical effects that occur in a predator that has consumed prey that succumbed to the anticoagulant—is more likely as a result.
   B. Hydroxycoumarin agents
      1. They include brodifacoum and bromadiolone.
      2. Duration of vitamin K_1 epoxide reductase inhibition is 30 days for brodifacoum and 21 days for bromadiolone.
      3. Half-lives are 4 to 6 days in the dog.
   C. Indandione agents
      1. They include diphacinone and difethialone.
      2. Agents are derivatives of indane-1,3-dione.
      3. Duration of vitamin K_1 epoxide reductase inhibition is 1 to 4 weeks.
      4. Brand names include *Assassin, Gold Crest, Diphacine, Contrax-D, Rozol, Ditrac, Kill-Ko, D-Cease, Mouse and Rat Bait,* and *Tomcat*.
      5. Difethialone-containing products are generally 0.0025%.

Action

I. Inhibition of vitamin K_1 epoxide reductase prevents formation of vitamin KH_2 (hydroquinone), a necessary cofactor of the enzyme vitamin K_1 carboxylase, which activates clotting factors II, VII, IX, and X via carboxylation.
II. Upon consumption of the liver's store of vitamin K_1, clotting factors can no longer be carboxylated and remain inactive in the prozymogen state.
III. Spontaneous and fatal hemorrhage can then occur.

Clinical Signs

I. Signs of toxicosis depend on the location of the hemorrhage and are often nonspecific.
II. Signs may include lethargy, dyspnea, acute collapse, pale mucous membranes, lameness, paralysis, petechiae, ecchymoses, hematomas, hematuria, hemoptysis, epistaxis, hematochezia, weakness, or sudden death.

Diagnosis

I. Evidence of hemorrhage, significant prolongation of the prothrombin time (PT), and historical evidence of exposure within the preceding 3 to 7 days are diagnostic of anticoagulant rodenticide toxicosis.
II. In the postmortem specimen, evidence of massive internal hemorrhage is consistent with anticoagulant rodenticide ingestion, and the diagnosis can be confirmed by detecting anticoagulant rodenticide residues in the liver.

Differential Diagnosis

I. Any disease that results in a coagulopathy, bleeding diathesis (see Chapters 67 and 68), or severe anemia is considered.
II. Examples include von Willebrand disease, immune-mediated thrombocytopenia, immune-mediated hemolytic anemia, disseminated intravascular coagulation (DIC), hemangiosarcoma, inherited platelet disorders, trauma, rickettsial diseases, and severe liver disease.

Treatment

I. Asymptomatic animal
   A. Decontamination with emesis and one dose of activated charcoal (6.6 to 11 mL/kg PO with sorbitol) is indicated if the toxicant was ingested within 2 to 3 hours of presentation.
   B. Initiate additional treatment if the calculated dosage is >0.02 mg/kg and decontamination does not decrease the dosage below this level, based on one tenth of the lowest reported LD_{50} dose ranges in dogs and cats (ASPCA, 2006).
   C. Vitamin K_1 is given at 1 to 1.5 mg/kg PO TID (or daily equivalent) for the duration of effect of the ingested anticoagulant.
      1. Two weeks of therapy are recommended for first-generation anticoagulant ingestions (ASPCA, 2006), 3 weeks for bromadiolone, and 1 month for other second-generation anticoagulants.
      2. If in doubt as to the identity of the anticoagulant, then treat for 30 days.
      3. Vitamin K_1 is well absorbed orally, particularly if given with a fatty food, so giving injectable vitamin K_1 to an asymptomatic animal is not necessary.
      4. Subcutaneous and IV administration has been associated with anaphylactic reactions; the IV route is not recommended.
      5. When the weight of the animal is so small that available capsule sizes are too large, the injectable product can be given orally.
II. Symptomatic animal
   A. Vitamin K_1 administration is given as for the asymptomatic animal.
      1. Subcutaneous vitamin K_1 is given if the animal is vomiting or otherwise unable to take oral medications.
      2. Once able to take oral medications, oral vitamin K_1 is supplemented for the duration of action of the anticoagulant.
   B. Whole blood transfusion is indicated for active bleeding.
   C. Plasma transfusion may serve as a source of clotting factors if whole blood is not available (see Chapter 71).
   D. Oxygen supplementation is indicated for the dyspneic or severely anemic animal.
   E. Strict rest and gentle handling are instituted until the PT has normalized.

Monitoring of Animal

I. Measurement of PT 48 and 72 hours after ingestion can determine if vitamin K_1 therapy is indicated.
   A. If PT is normal at 48 hours, then repeat the measurement at 72 hours to be sure that clotting factors have not become depleted in the intervening 24 hours.
   B. Administration of vitamin K_1 before drawing blood for PT can result in falsely normal values.
II. Monitor packed cell volume (PCV) and clotting times in symptomatic animals.
III. For animals treated with vitamin K_1, perform a PT test 48 and 72 hours after cessation of therapy.
IV. Closer monitoring is warranted in more susceptible animals, such as young and hypothyroid animals, as well as those with underlying coagulopathies or liver disease, because prolonged therapy and adjustment of vitamin K_1 dosages may be required.
V. Closer monitoring is also warranted for animals on drugs that have potential metabolic interactions with anticoagulant rodenticides, such as metronidazole, cimetidine, chloramphenicol, sulfonamides, allopurinol, and anabolic steroids.
VI. Drugs that are highly protein-bound (e.g., aspirin, phenylbutazone, erythromycin, ketoconazole, propranolol, diazoxide) can displace anticoagulant rodenticides and increase the amount of free anticoagulant available.

BROMETHALIN

Sources

I. Formulations are typically 0.01% bromethalin in pellets or blocks.
II. Brand names include *Assault, Trounce, Real-Kill, Hot Shot, Top Gun, Fastrac, Rampage,* and *Vengeance.*
III. Talpirid is more concentrated (0.025%) and marketed to kill moles.

Action

I. Bromethalin is a secondary amine that exerts its neurotoxic effects via uncoupling of oxidative phosphorylation in mitochondria.
II. Spongy degeneration and edema of the white matter of the brain, spinal cord, and optic nerves occur as a result of separation and fluid accumulation within the myelin lamellae.
III. Lesions are irreversible.
IV. Bromethalin's active metabolite, desmethyl bromethalin, is the compound responsible for the toxicosis.
V. Because guinea pigs are deficient in N-demethylate, they are relatively resistant to bromethalin toxicosis.

Clinical Signs

I. Ingestion of dosages at or near the LD_{50} (0.40 to 0.71 mg/kg in cats; 2.38 to 5.6 mg/kg in dogs; ASPCA, 2006) can result in clinical signs within 2 to 4 hours, but more commonly by 8 to 12 hours.
II. Acute signs include hyperexcitation, tremors, seizures, paralysis, and death.
III. At lower dosages (about 0.30 to 0.45 mg/kg in cats; 1.67 mg/kg in dogs; ASPCA, 2006), the onset of signs may develop gradually over several days and can include ataxia, pelvic limb paresis, decreased sensory response, labored respiration, depression, coma, seizures (generalized or focal motor), and death.
IV. Sublethal clinical effects may be slowly reversible or permanent.

Diagnosis

I. History of exposure
II. Consistent clinical signs
III. Positive analysis of bromethalin in gastric contents
IV. Postmortem detection of the active metabolite in gastrointestinal contents, liver, brain, or adipose tissue
V. Histopathologic findings: severe spongiosis of the white matter of the central nervous system (CNS)

Differential Diagnosis

I. Seizure-inducing agents: lead, metaldehyde, strychnine, tremorogenic mycotoxins, methylxanthines, organophosphates, carbamates, methamphetamine, pseudoephedrine, phenylpropanolamine
II. Other CNS disorders: intracranial neoplasia, infectious meningitis

Treatment

I. Asymptomatic animal
  A. Induce emesis and administer multiple doses of activated charcoal.
    1. Activated charcoal is beneficial because bromethalin undergoes enterohepatic recirculation.
    2. If >0.1 mg/kg of bromethalin has been ingested (ASPCA, 2006), then emesis (if <4 hours postexposure) and activated charcoal are recommended.
    3. Give activated charcoal 6 to 11 mL/kg PO TID for 48 hours with large exposures.
  B. Further treatment guidelines are presented in Tables 124-1 and 124-2.
II. Symptomatic animal
  A. Attempt to manage seizure activity caused by cerebral edema.
    1. Osmotic agents (mannitol), corticosteroids, and furosemide have not been very effective.
    2. Administration of diazepam, barbiturates, inhalant anesthetics, and propofol can be tried.
  B. An extract of *Gingko biloba* (100 mg/kg PO) has experimentally reduced cerebral edema and lipid peroxidation of the brain when given to rats immediately after a lethal dose of bromethalin, but its efficacy in dogs and cats has not been proven.
  C. Supportive care includes IV fluids and regulation of seizure-induced hyperthermia.

TABLE 124-1

Treatment Guidelines for Bromethalin Exposure in Dogs

TIME SINCE INGESTION	AMOUNT INGESTED	TREATMENT RECOMMENDATIONS
<4 hours	0.1-0.49 mg/kg	Emesis or one dose of activated charcoal
>4 hours	0.1-0.49 mg/kg	One dose of activated charcoal
<4 hours	0.5-0.75 mg/kg	Emesis and three doses of activated charcoal
>4 hours	0.5-0.75 mg/kg	Three doses of activated charcoal
<4 hours	>0.75 mg/kg	Emesis and three doses of activated charcoal
>4 hours	>0.75 mg/kg	Three doses of activated charcoal for 48 hours

TABLE 124-2

Treatment Guidelines for Bromethalin Exposure in Cats

TIME SINCE INGESTION	AMOUNT INGESTED	TREATMENT RECOMMENDATIONS
<4 hours	0.05-0.1 mg/kg	Emesis or one dose of activated charcoal
>4 hours	0.05-0.1 mg/kg	One dose of activated charcoal
<4 hours	0.1-0.3 mg/kg	Emesis and three doses of activated charcoal
>4 hours	0.1-0.3 mg/kg	Three doses of activated charcoal
<4 hours	>0.3 mg/kg	Emesis and three doses of activated charcoal
>4 hours	>0.3 mg/kg	Three doses of activated charcoal for 48 hours

CHOLECALCIFEROL

Sources

I. Cholecalciferol is vitamin D_3 marketed commercially as a rodenticide and dietary supplement.
II. Brand names include *Quintox, Rampage, Ceva True Grit, Ortho Mouse-Be-Gon* and *Rat-B-Gon.*
III. Formulations are typically pelleted, but may also be sold as seed mixtures or bait chunks.
IV. Products are generally 0.075% cholecalciferol.

Action

I. Cholecalciferol is metabolized in the liver to 25-hydroxycholecalciferol (calcifediol or 25-(OH) vitamin D_3), which is then metabolized by the kidney to the actively toxic compound 1,25-dihydroxycholecalciferol (calcitriol or 1,25-$(OH)_2$ vitamin D_3).
II. Calcitriol increases intestinal absorption and renal tubule reabsorption of calcium, and stimulates bone resorption, resulting in hypercalcemia and hyperphosphatemia.
III. When serum calcium × phosphorus calculations are ≥60, soft tissue mineralization may occur.
  A. Because the kidneys are uniquely susceptible to dystrophic mineralization, renal failure ensues.

B. Other soft tissues, such as the cardiovascular and gastrointestinal systems, may also undergo mineralization.

Clinical Signs

I. Initial signs of exposure may appear as early as 12 hours (typically in 36 to 48 hours), and include lethargy and vomiting.
II. As the kidneys fail, the animal may become anorexic, polydipsic, and polyuric.
III. In end-stage kidney failure, anuria may occur.
IV. Significant signs may be seen at oral doses of 0.5 mg cholecalciferol/kg in the dog.
V. Sudden death may occur after initial exposure from mineralization of soft tissues (e.g., rupture of a mineralized aorta).

Diagnosis

I. History of exposure
II. Consistent clinical signs
III. Laboratory findings: elevated calcium, phosphorus, blood urea nitrogen (BUN); creatinine, dilute urine
IV. Abnormal endocrine assays
  A. Suppressed serum parathyroid hormone (PTH) level (normal values: dog, 2 to 13 pmol/L; cat, 0 to 4 pmol/L) in conjunction *with*
  B. Markedly elevated serum 25-$(OH)_2$ vitamin D_3 (normal values: dog, 60 to 215 nmol/L; cat, 65 to 170 nmol/L)
V. Analysis of bile or kidney 25-$(OH)_2$ vitamin D_3 levels on necropsy

Differential Diagnosis

I. *Dovonex* ingestion containing calcipotriene, a synthetic analogue of calcitriol
II. *Cestrum diurnum* (day jessamine, China berry, inkberry) ingestion
III. Hypercalcemia of malignancy (see Chapter 73)
IV. Other causes of renal failure (see Chapter 48)
V. Renal secondary hyperparathyroidism, primary hyperparathyroidism
VI. Blastomycosis: hypercalcemia
VII. Hypoadrenocorticism

Treatment and Monitoring

I. Fluid diuresis is done with 0.9% sodium chloride (NaCl) IV for 4 days postingestion or until resolution of hypercalcemia and azotemia.
  A. Treatment may be required for several weeks.
  B. Avoid fluids containing calcium (lactated Ringer's solution).
II. Furosemide is started at 2.5 to 4.5 mg/kg IV TID to QID or as a 5 mg/kg/hr IV constant rate infusion (CRI), after an initial 5 mg/kg IV dose.
  A. Diuretic therapy is continued until hypercalcemia resolves.
  B. Thiazide diuretics are contraindicated because they are calcium-sparing.
III. Prednisolone is also given (1 to 3 mg/kg PO BID), until hypercalcemia abates, and is then tapered over several weeks, as long as calcium levels remain normal.
IV. Salmon calcitonin or pamidronate may be tried for persistent hypercalcemia.
  A. Salmon calcitonin is given at 4 to 6 IU/kg SC or IM BID to TID.
  B. Pamidronate is given as a slow IV infusion of 1.3 to 2.0 mg/kg over 2 hours and may be repeated in 5 to 7 days.
V. Oral phosphate binders (e.g., *Amphojel* 10 to 30 mg/kg PO TID) are indicated to bind dietary phosphorus.
VI. Gastrointestinal protectants may be needed for uremic gastritis.
  A. Sucralfate 0.5 to 1 g PO TID in dogs and 0.25 to 0.5 g PO BID to TID in cats
  B. Famotidine 0.5 mg/kg PO, SC, IM, IV SID to BID
VII. See Chapter 48 for additional therapy of renal failure.
VIII. BUN, serum creatinine, calcium, phosphorus, urine output, and hydration status are monitored SID for 4 days in the asymptomatic animal.
IX. In the hypercalcemic and/or azotemic animal, these parameters are monitored frequently until they normalize, then intermittently throughout the tapering of corticosteroid therapy.

ZINC PHOSPHIDE

Sources

I. Zinc phosphide (Zn_3P_2) is a metallophosphide rodenticide used predominantly to kill moles and gophers.
II. Formulations are almost exclusively 2% but can be as high as 10%.
III. Brand names include *Sweeney's Poison Peanuts, Prozap, Forces, Bonide, Gopha-Rid, Revenge, Black Leaf, True Grit,* and *Tomcat.*
IV. Relay toxicosis is possible if enough of the bait is present in the gut of the consumed prey.

Action

I. Zinc phosphide is converted to phosphine gas (PH_3) in the acidic environment of the stomach.
II. Phosphine gas is an irritant to the stomach and lungs.
III. Intracellularly, phosphine is thought to block cytochrome oxidase, thereby inhibiting mitochondrial oxidative phosphorylation and causing cell necrosis, particularly in organs with high oxygen demand (heart, brain, kidneys, and liver).
IV. Formation of free radicals contributes to the oxidative damage.
V. Metabolic acidosis is a common finding.
VI. Residual zinc phosphide can be absorbed, resulting in delayed hepatic and renal failure (5 to 14 days postexposure).

Clinical Signs

I. Within 4 hours of ingestion, clinical signs of vomiting (frank blood or "coffee grounds" appearance if digested), lethargy, tachypnea and dyspnea (pulmonary edema), abdominal pain, ataxia, weakness, recumbency, tremors, hypersalivation, seizures, shock, and death may be seen.

II. Garlic or rotten fish odor on the breath is characteristic of the formation of phosphine gas.
III. LD_{50} in various mammals ranges from 20 to 50 mg of zinc phosphide/kg.
IV. Signs may be seen at one-tenth LD_{50} in the sensitive individual.

Diagnosis

I. Definitive diagnosis relies on a history of exposure, consistent clinical signs, the characteristic smell of the phosphine gas on the breath, and possible confirmation of the gas in the vomitus or gastric contents.
II. Samples for analysis must be placed in an airtight container and frozen before shipping.
III. Presumptive diagnosis can be made based on elevated zinc levels in the serum (royal blue blood tubes used), liver, and kidneys.

Differential Diagnosis

I. Aluminum phosphide
II. Metaldehyde

Treatment and Monitoring

I. Asymptomatic animal
   A. Administration of aluminum and magnesium hydroxide–containing products (*Maalox* 90 to 180 mg/kg PO TID) increases the gastric pH and slows the conversion of zinc phosphide to phosphine gas.
      1. A mixture of the two hydroxides is recommended because magnesium hydroxide raises the gastric pH higher and faster than aluminum hydroxide, which has a longer duration of action.
      2. If a large volume has been ingested, then gastric lavage with *Maalox* may be an option (ASPCA, 2006).
   B. Induction of emesis with apomorphine is recommended.
   C. Providing adequate ventilation upon induction of emesis or upon passing a lavage tube is critical, because phosphine gas is toxic to attending personnel even at levels below which it can be smelled.
   D. Obtain baseline laboratory tests to monitor for the possible development of delayed renal or hepatic damage.
II. Symptomatic animal
   A. Respiratory support with supplemental oxygen and ventilation is indicated in the severely affected animal.
   B. Institute treatment for shock (IV crystalloids or colloids, see Chapter 132).
   C. Fluids containing magnesium *(Normosol-R*, *Plasma-Lyte)* may correct mild hypomagnesemia.
   D. Metabolic acidosis is treated with addition of sodium bicarbonate to IV fluids as indicated by the degree of base deficit.
   E. Control seizures with diazepam, barbiturates, or inhalant anesthetics (see Chapter 22).
   F. Administer aluminum and magnesium hydroxide as for the asymptomatic animal.
   G. Gastrointestinal protectants are indicated for hemorrhagic gastroenteritis.
      1. Sucralfate 0.5 to 1 g PO TID in dogs and 0.25 to 0.5 g PO TID in cats
      2. Famotidine 0.5 mg/kg PO, SC, IM, IV SID to BID
      3. Misoprostol 1 to 3 μg/kg PO TID
   H. Hepatoprotective therapies may be used to minimize damage from reactive oxygen species.
      1. S-Adenosyl-methionine (SAMe) 17 to 20 mg/kg PO SID in dogs and 200 mg/day PO in cats
      2. Milk thistle (silymarin) 20 to 50 mg/kg/day PO
      3. N-Acetylcysteine as a loading dose of 140 mg/kg PO, IV followed by 70 mg/kg PO, IV QID
   I. Regulation of seizure-induced hyperthermia may be warranted.
   J. Monitor acid-base status and electrolytes, and reevaluate renal and hepatic values 1 week after recovery from the initial crisis.

STRYCHNINE

Sources

I. Strychnine is a bitter alkaloid extracted from the seeds of *Strychnos nux vomica* trees.
II. Strychnine use is restricted to burrowing rodents, such as moles and gophers.
III. Brand names include *Monterey Go Die Gopher, Force's Poison Peanuts, Sweeney's Poison Peanuts,* and *Wilco Gopher Getter.*
IV. Formulations typically range from 0.3% to 0.5%.
V. Baits are often dyed red, green, or blue, and combined with grain.
VI. Mammalian median lethal dosages range from 0.5 to 3 mg/kg.
VII. Over-the-counter availability varies across the United States.
VIII. *Nux vomica* is a homeopathic formulation of *Strychnos nux vomica* that is used as an appetite stimulant and for indigestion caused by atonic dyspepsia.

Action

I. Strychnine competitively and reversibly binds to postsynaptic glycine receptors in the Renshaw cells of the spinal cord and medulla.
II. Antagonizing the action of this inhibitory neurotransmitter results in continuous muscle and CNS stimulation that progresses to violent seizures and death owing to exhaustion or anoxia (inability to relax muscles of respiration).
III. Margin of safety is narrow with 3.5 g (<1 teaspoon) of a 0.3% bait considered to be a lethal dosage for a 15-kg dog.

Clinical Signs

I. Anxiety, stiff muscles (especially extensor muscles of limbs), sawhorse stance, tremors, tetanic seizures
II. Tachypnea, apnea, dyspnea
III. Myoglobinuria

IV. Strained expression from facial muscle contracture
V. Death 10 to 120 minutes postingestion

Diagnosis

I. Diagnosis is based on a history of exposure, consistent clinical signs, and positive analysis of strychnine in bait and gastric contents or lavage washings.
II. If the animal does not die peracutely, strychnine may be detected in the urine.
III. The liver, bile, and kidneys may be analyzed for strychnine at necropsy, but peracute death may preclude sufficient amounts in the tissues for confirmation of the toxicosis.

Differential Diagnosis

I. Certain toxicoses: metaldehyde, zinc phosphide, tremorgenic mycotoxins, organophosphate compounds, 1080 (fluoroacetate), fluorouracil *(Efudex),* nicotine
II. Tetanus
III. Liver disease
IV. Other causes of seizures: idiopathic epilepsy, congenital brain anomalies, intracranial neoplasia, etc. (see Chapter 22)

Treatment

I. Asymptomatic animal
   A. Because clinical signs may begin as early as 10 minutes after ingestion, the opportunity to induce emesis is often lost.
      1. If the exposure is witnessed and emesis can be induced immediately, then it may be efficacious.
      2. Emesis is contraindicated once signs are present because of the risk of inducing a seizure.
   B. Administer activated charcoal with a cathartic agent (e.g., sorbitol) at 6.6 to 11 mL/kg PO.
   C. Enterogastric lavage, although an extreme measure, may be lifesaving following a known lethal ingestion.
II. Symptomatic animal
   A. Manage seizures with diazepam (rarely efficacious alone), barbiturates, or inhalant anesthetic agents (see Chapter 22).
   B. Methocarbamol 55 to 220 mg/kg IV to effect (maximum of 330 mg/kg/day) can be given for muscle relaxation not controlled by barbiturate administration.
   C. IV fluid support is indicated to prevent renal injury from myoglobinuria.
      1. Forced diuresis with IV fluids at twice the maintenance rate may also be helpful.
      2. Acidification of the urine with ammonium chloride 50 mg/kg PO QID can maximize the excretion of strychnine but is contraindicated with myoglobinuria or lactic acidosis.
      3. Consider IV administration of bicarbonate for severe lactic acidosis (based on evaluation of pH and base deficit).
   D. Manage hyperthermia induced by muscle rigidity and/or seizure activity with cooled IV fluid therapy.
   E. Minimize stimulation because of the hyperesthetic state.
   F. Provide ventilatory support if the animal is not adequately oxygenated.
   G. Hypertension and tachycardia may be seen, especially with sublethal exposures.
   H. Monitor acid-base status and for the onset of severe lactic acidosis.

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CHAPTER 125

Insecticides and Molluscicides

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METALDEHYDE

Sources

I. Metaldehyde is a tetramer of acetaldehyde and is used primarily to kill snails and slugs.
II. Brand names include *Deadline, Prozap, Snarol, Turf King, Eliminator, Terminide, Ortho Bug-Geta,* and *Soilserv Sevin* (in combination with carbaryl, an organophosphorus compound).
III. Formulations are commonly 2% to 3% active ingredient but may be as high as 7.5%.

Action

I. Exact mechanism is unclear; however, decreased gamma-aminobutyric acid (GABA), serotonin, and norepinephrine may be involved in the toxic mechanism of metaldehyde.
II. Alterations in monoamine oxidases and 5-hydroxytryptamine may also be involved.
III. Metabolic acidosis results from the metabolism of metaldehyde to acetaldehyde.
IV. As little as 1 teaspoon of bait can be lethal to a 2.5-kg dog.

Clinical Signs

I. Tremors, seizures, hypersalivation, hyperesthesia
II. Tachycardia, hyperpnea, cyanosis, acidosis
III. Ataxia, nystagmus, anxiety, mydriasis
IV. Hyperthermia, diarrhea
V. Depression and death
VI. Signs as early as 1 hour postingestion, typically within 4 hours
VII. Liver failure possible 2 to 3 days postexposure

Diagnosis

I. History of exposure, consistent clinical signs, and analysis of gastric contents for acetaldehyde help to confirm metaldehyde toxicosis.
II. Metaldehyde can also be confirmed in a bait sample or detected in liver, urine, and plasma.

Differential Diagnosis

I. Any toxicant that causes seizures including strychnine: organophosphate and carbamate compounds, tremorgenic mycotoxins, 1080 (fluoroacetate), zinc phosphide, bromethalin, organochlorine insecticides, 5-fluorouracil *(Efudex)*
II. Other causes of seizures: see Chapter 22

Treatment and Monitoring

I. Asymptomatic animal
  A. Decontamination with induction of emesis is warranted if the ingestion was within 1 hour.
  B. Activated charcoal with a cathartic is recommended thereafter.
  C. Monitor the animal closely for a minimum of 4 hours.
  D. Gastric lavage is an alternative to inducing emesis, particularly if a large volume of metaldehyde has been ingested.
II. Symptomatic animal
  A. Manage muscle tremors with methocarbamol 55 to 220 mg/kg IV to effect (maximum of 330 mg/kg/day).
  B. Control seizures with diazepam, barbiturates, or inhalant anesthetics (see Chapter 22).
    1. Diazepam may be preferred because barbiturates compete with an enzyme that metabolizes acetaldehyde.
    2. Acepromazine (to effect) can also be helpful with managing central nervous system (CNS) excitation (APSCA, 2006).
  C. Perform baseline laboratory tests to evaluate liver function, electrolytes, and acid-base status.
  D. Institute IV fluid therapy to combat dehydration and acidosis.
  E. Sodium bicarbonate can be added to the IV fluids as needed for severe acidosis.
  F. Oxygen and ventilation may be needed if respiration is significantly depressed.

ORGANOPHOSPHORUS INSECTICIDES

Sources

I. Organophosphorus (organophosphate) insecticides (OPs) are a class of insectiides that inhibit acetylcholinesterase (AChE) activity by irreversibly phosphorylating the enzyme.
II. OPs are widely available commercially.

III. Some representative brand names include *Bonide/Ortho Systemic Rose and Flower Care* (disulfoton), *Dursban* and *Lorsban* (chlorpyrifos), *Wellmark's Paramite* (phosmet), *Maltox* (malathion), *Hartz 2-in-1 Collar* for dogs (tetrachlorvinphos), and *Orthene* (acephate).
IV. Use of many OPs, such as diazinon, is restricted.
V. Exposure to older OP formulations continue, however, because of prolonged storage of the chemical in areas such as garages, sheds, and barns.
VI. Formulations vary widely in concentration, carrier, and form; they include sprays, dips, powders, food mixtures for ant and roach baits, and impregnated collars.

Action

I. OPs irreversibly inhibit AChE, the enzyme that normally hydrolyzes the neurotransmitter acetylcholine to acetic acid and choline.
   A. This results in an excess of the neurotransmitter at the neuromuscular junction and at synapses of the parasympathetic and sympathetic nervous system.
   B. Overstimulation of postsynaptic muscarinic and nicotinic cholinergic receptors results in clinical signs.
II. If a covalent bond forms between the OP and the enzyme, a process termed *aging*, then the bond becomes irreversible.
   A. Not all OPs "age," and the rate at which those that age differs with different OPs.
   B. For example, the warfare agents sarin and VX age within seconds.
   C. Abatement of signs then relies on the body's synthesis of new AChE.

Clinical Signs

I. Muscarinic signs include salivation, lacrimation, increased urination, diarrhea, dyspnea, and emesis, as well as bradycardia, miosis, and bronchoconstriction.
II. Nicotinic signs include muscle tremors, seizures, and weakness.
III. Catecholamine-induced tachycardia may override muscarinic-induced bradycardia.
IV. Onset of clinical signs varies widely with the type of OP and the amount ingested; a potent OP (e.g., disulfoton) may cause clinical signs within minutes, whereas chlorpyrifos may take days.
V. Organophosphate-induced delayed neuropathy syndrome occurs 1 to 4 weeks after exposure.
   A. It is an axonal dying-back neuropathy that results in irreversible paralysis.
   B. An intermediate syndrome occurs in cats exposed to chlorpyrifos in which weakness, anorexia, and depression are exhibited for several days after exposure and are thought to be related to subnormal cholinesterase (ChE) levels.

Diagnosis

I. Inhibition of ChE is detectable in the live animal by determination of ChE activity in whole blood (ethylenediamine tetraacetic acid [EDTA] tube).
   A. Markedly decreased ChE activity (<25% of normal) is diagnostic for OP intoxication.
   B. Normal canine ChE activity in whole blood is 1.46 ± 0.33 μm/mL/min, and normal feline ChE activity in whole blood is 1.37 ± 0.42 μm/mL/min (University of Illinois, 2006).
II. In the postmortem specimen, ChE activity can be determined in the retina or the brain, and OP compounds can be detected in the liver, skin, or stomach contents.
III. Administration of a test dose of atropine (0.02 mg/kg IV) can be given to determine if the muscarinic signs are from a source other than intoxication with an OP or carbamate insecticide.
   A. If the heart rate increases and the other signs abate with this small dose of atropine, then the signs are *not* likely to be the result of an OP or carbamate.
   B. Ten times the preanesthetic dose of atropine is required to appreciably change the clinical signs associated with OP or carbamate intoxication because atropine acts by competitively inhibiting excess acetylcholine at the muscarinic receptor.

Differential Diagnosis

I. Carbamate toxicosis must be ruled out.
II. Anatoxin-a(s), produced by cyanobacteria, inhibits AChE in the peripheral nervous system but does not cross the blood-brain barrier.

Treatment and Monitoring

I. Asymptomatic animal
   A. Decontamination via induction of emesis and administration of activated charcoal with a cathartic agent is done for oral exposures.
   B. For dermal exposures, remove the treated collar and/or bathe with a liquid dishwashing detergent.
   C. Monitor the animal for development of clinical signs.
II. Symptomatic animal
   A. Institute oxygen therapy for dyspnea.
   B. Atropine 0.05 to 0.5 mg/kg IV and 0.15 to 1.5 mg/kg SC, IM is indicated for life-threatening muscarinic signs.
      1. These include severe bradycardia and/or dyspnea from excessive bronchial secretions.
      2. Give atropine to effect, but use with caution because atropine toxicosis can occur with excessive administration.
   C. Pralidoxime (2-PAM; *Protopam chloride*) 10 to 15 mg/kg IM, SC is an AChE reactivator that binds to the OP after it binds with AChE.
      1. 2-PAM and the OP complex is excreted, thereby freeing the enzyme.
      2. 2-PAM is indicated for predominantly nicotinic signs and is ineffective after aging occurs.
      3. Because the aging process varies with the particular OP, administration of 2-PAM may be beneficial days after the initial exposure.
      4. 2-PAM administration is discontinued after three doses if steady improvement is not seen.

5. The drug has the ability to inhibit AChE itself at high doses (LD_{50}, 190 mg/kg).

D. Diazepam is given for seizures (5 mg increments IV to effect) and may be protective against additional CNS effects and bradycardia.

E. The most critical parameters to monitor are heart rate, oxygenation status, and CNS status.

CARBAMATES

Sources

I. Carbamates are carbamic acid–derivative insecticides that inhibit AChE.

II. Brand names include *Sevin* (carbaryl), *Temik* (aldicarb), *Golden Malrin* (methomyl), *Furadan* (carbofuran), and *Baygon* (propoxur).

Action

I. Carbamate insecticides inhibit AChE in a reversible fashion by carbamylating the enzyme.

II. Clinical signs with aldicarb intoxication, for example, appear within minutes to hours and may spontaneously resolve within 4 to 12 hours as AChE is freed from the carbamate.

Clinical Signs

I. Signs are identical to those of the OP insecticides.

II. Because of the reversible nature of carbamate's action, spontaneous recovery is possible.

III. Clinical signs of acute toxicosis may be severe enough to be life-threatening.

Diagnosis

I. Decreased whole blood ChE activity (<25% normal) is diagnostic for both OPs and carbamates.

A. Distinguishing between the two is possible if the analysis is repeated 1 hour later.

B. If ChE activity has increased, then decarbamylation has occurred, freeing the enzyme from the carbamate, whereas activity after OP exposure is not expected to increase.

C. Because of the rapid reversibility of carbamates, the timing of analysis is critical.

II. A negative atropine response test is indicative of either OP or carbamate intoxication (see previous discussion).

Differential Diagnosis

I. OP toxicosis

II. Anatoxin-a(s) toxicosis

Treatment and Monitoring

I. The main difference between treatment of a carbamate versus an OP intoxication is the lack of efficacy of 2-PAM with carbamates; reactivation of the enzyme is not necessary because decarbamylation occurs readily with time.

II. All other treatment and monitoring recommendations are identical to OP intoxication (see previous discussion).

ORGANOCHLORINE INSECTICIDES

Sources

I. This class of insecticides is also known as *chlorinated hydrocarbons* or *organochlorines* (OCs).

II. OCs can be divided into three main categories: diphenyl aliphatics (dichlorophenylethanes), aryl hydrocarbons (chlorinated benzenes and cyclohexanes), and cyclodiene insecticides.

III. Examples of diphenyl aliphatics include dichlorodiphenyltrichloroethane (DDT), DDD, dicofol, ethylan, chlorobenzilate, and methoxychlor.

IV. Examples of aryl hydrocarbons include hexachlorobenzene (paradichlorobenzene) and lindane.

V. Examples of the cyclodiene insecticides include chlordane, heptachlor, aldrin, and dieldrin.

VI. Lindane is the active ingredient in *Kwell,* a human ectoparasiticide product.

VII. Mitotane (o,p'-DDD), a metabolite of DDT, is approved for the treatment of pituitary-dependent hyperadrenocorticism in dogs.

Action

I. The mechanism of action of OCs involves slowing of sodium (Na^+) influx and inhibiting potassium (K^+) efflux from neurons.

II. This results in a decreased threshold for the next action potential and sustained neurotransmission.

III. Cyclodienes also inhibit postsynaptic binding of GABA, adding to the neuronal stimulation.

Clinical Signs

I. Acute toxicoses from OCs are rare today.

II. Although all species can be affected, the cat is the most sensitive species.

III. Clinical signs can include hypersalivation and vomiting followed by behavioral changes, such as agitation, apprehension, aggression, and/or hyperexcitability.

IV. Incoordination, tremors, tonic-clonic seizures, hyperthermia, respiratory depression, coma, and death may then occur.

V. Signs may last for days owing to enterohepatic recirculation and the lipophilicity of the OCs, which allows them to accumulate in adipose tissue.

VI. Acute toxicosis may occur, with rapid weight loss as lipid stores are liberated.

VII. Chronic effects are more common as a result of the bioaccumulative potential of OCs.

A. Accumulation in body fat is particularly an issue for predators at the top of the food chain.

B. Dichlordiphenylethane (DDE), a long-lived metabolite of DDT, has been implicated in the thinning of eggshells and decline of many birds of prey, including the bald eagle.

Diagnosis

I. Diagnosis relies on a history of exposure, consistent clinical signs, and confirmation of the OC or metabolite in blood, brain, liver, or fat (including milk fat).
II. Samples are collected in glass containers because plastics may interfere with the analysis.

Differential Diagnosis

I. Any toxicant causing seizures (see previous discussion of OP toxicity)
II. Any disease process causing seizures (see Chapter 22)

Treatment and Monitoring

I. Asymptomatic animal
   A. Decontamination with activated charcoal and a cathartic is indicated for oral exposures, and repeated doses may be needed because of enterohepatic recirculation.
   B. Dermal exposures require bathing with a liquid dishwashing detergent.
II. Symptomatic animal
   A. No specific antidote exists for OC intoxication, so treatment is largely supportive and symptomatic.
   B. Seizures are treated with diazepam, barbiturates, inhalant anesthetics, or propofol (see Chapter 22).
   C. Muscle tremors are treated with methocarbamol 55 to 220 mg/kg IV to effect (maximum of 330 mg/kg/day).
   D. Supplemental oxygenation or intubation may be necessary for the severely depressed animal.
   E. Other supportive measures, such as managing hyperthermia, nutritional support and IV fluids, may be indicated.
   F. CNS status, peripheral oxygenation, body temperature, electrolytes, and acid-base status are closely monitored.

AMITRAZ

Sources

I. Amitraz is a formamidine antiparasitic agent commonly used in small animals to treat demodicosis and ascarids.
II. It is also used as an agricultural pest control agent.
III. *Mitaban* (19.9% amitraz) is approved for use in dogs and for treatment of demodicosis.
IV. *Preventic* collars (9% amitraz) are approved for dogs >12 weeks old (2500 mg of amitraz in each collar, 25 inches in length).
V. Products labeled for use in large animals such as *Taktic* (12.5% amitraz) and *Point-Guard* (2% amitraz) may be diluted and used in dogs.

Action

I. Amitraz possesses α_2-adrenergic activity, and its clinical effects may be mediated via α_2 receptors.
II. Its exact mechanism of action is not completely understood.
III. Amitraz is thought to inhibit monoamine oxidase and to possess weak serotonin antagonist properties.
IV. The potential for inducing ileus is caused by inhibition of smooth muscle contractility.
V. Hyperglycemia may be mediated by suppression of insulin release.

Clinical Signs

I. Clinical signs may occur with appropriate use of amitraz products and include sedation, ataxia, bradycardia, vomiting, diarrhea, hypothermia, and transient hyperglycemia.
II. Toy and small breeds are more susceptible to adverse effects with appropriate use.
III. Clinical signs may also be more likely if the animal has a deep pyoderma with cutaneous ulceration.
IV. Use of amitraz must be done cautiously in a diabetic animal, given the risk of hyperglycemia.
V. In addition to the previously mentioned signs, an overdose may also cause disorientation, ileus, hypertension or hypotension, coma, respiratory depression, seizures, and death.

Diagnosis

I. Diagnosis of amitraz toxicosis relies on a history of exposure and presence of consistent clinical signs.
II. Analysis for amitraz may be performed in urine, plasma, skin, blood, or gastric contents.

Differential Diagnosis

I. Any toxicant causing CNS depression: alcohol, ethylene glycol, avermectins, marijuana, benzodiazepines, barbiturates, phenothiazines
II. Other causes of bradycardia: hyperkalemia, hypoadrenocorticism, β-adrenergic blocking agents, urethral obstruction, bladder rupture, calcium channel blocker toxicosis, primary cardiac diseases

Treatment and Monitoring

I. Asymptomatic animal
   A. Decontamination via emesis followed by administration of a cathartic agent is indicated; although activated charcoal can be helpful, its use must be weighed against the potential development of ileus.
   B. For dermal exposures, bathe the animal with warm water and a liquid dishwashing detergent.
   C. If an ingested collar containing amitraz is not recovered with emesis, then endoscopic retrieval is warranted before the development of severe clinical signs.
II. Symptomatic animal
   A. Yohimbine *(Yobine)* and atipamezole *(Antisedan)* are α_2-adrenergic antagonists that can be used to specifically reverse the life-threatening clinical effects of amitraz toxicosis.
      1. Yohimbine is given at 0.11 to 0.2 mg/kg IV slowly; because of its short half-life (1.5 to 2 hours in dogs), it may need to be repeated.
      2. Atipamezole is given at a dosage of 50 μg/kg IM, and its longer half-life (2 to 3 hours in the dog) allows less frequent administration than yohimbine.
   B. Supportive care such as IV fluid therapy and management of hypothermia are important.

C. Endoscopic or surgical removal of an amitraz-containing collar may be necessary, given the potential for severe ileus and prolonged duration of signs from continued release of the drug from the collar.
D. Activated charcoal adsorbs amitraz, yet its use must be weighed against the potential for ileus and anticipation of a possible gastrotomy or enterotomy to remove an ingested collar.
E. Seizures may be treated with diazepam (5-mg increments IV to effect).
F. Atropine is *not* recommended for bradycardia.
G. Monitoring of heart rate, rhythm, and blood pressure is critical.
H. CNS status is also closely monitored, especially for the onset of extreme depression and seizures.
I. Blood glucose is monitored because of the potential for hyperglycemia.

PYRETHRINS AND PYRETHROIDS

Sources

I. Pyrethrins are a group of six insecticides that are derived from pyrethrum, a natural insecticide from the flowers of *Chrysanthemum cinerariaefolium* and *Chrysanthemum cineum*.
II. Natural pyrethrins include pyrethrin I and II, cinerin I and II, and jasmolin I and II.
III. Pyrethroids are synthetic analogues of pyrethrins, with a longer duration of action, higher toxicity, and greater stability than their natural counterparts.
  A. Type II pyrethroids are distinguished from type I by the presence of a cyano group at the alpha position, which further increases their potency.
  B. Type I pyrethroids include allethrin, bifenthrin, permethrin, phenothin, resmethrin, sumithrin, tefluthrin, and tetramethrin.
  C. Type II pyrethroids include cyfluthrin, cyhalothrin, cypermethrin, deltamethrin, fenvalerate, flumethrin, fluvalinate, and tralomethrin.
IV. Pyrethrins and pyrethroids are readily marketed as flea treatments for dogs and cats and commonly available for insecticidal use in homes.
V. Formulations vary widely in concentration and include sprays, liquids, spot-ons, foggers, and gels.

Action

I. Pyrethrins and pyrethroids exert their insecticidal properties by binding to the membrane of neurons near sodium channels to slow their opening and closing.
II. Type I pyrethroids result in repetitive discharging of the neuron while type II pyrethroids cause membrane depolarization.
III. Neurological signs can be seen with <1% of sodium channels affected.
IV. Paresthesia can occur and is thought to be a direct action of pyrethroids on sensory nerve endings.

Clinical Signs

I. Cats
  A. Exposure of cats to flea treatments containing low concentrations (<2%) of pyrethrin and pyrethroid insecticides is not expected to cause severe clinical signs.
  B. Dermal application may result in a local reaction such as erythema and paresthesia ("pins and needles" tingling sensation), as a result of stimulation of local nerve endings within minutes to a few hours after application.
    1. Cats may react to this feeling by flicking the tail, twitching the ears and skin, shaking the paws, walking abnormally, or exhibiting other behavioral aberrations.
    2. Signs typically resolve within 24 to 48 hours.
  C. Spot-on flea treatments labeled for dogs contain higher concentrations of permethrin (45% to 65%) in particular and may induce severe systemic signs in cats.
    1. Signs include hyperesthesia, tremors, and seizures.
    2. Signs are expected within 12 to 18 hours after exposure.
    3. Secondary effects include possible hypoglycemia, myoglobinuric renal failure, and hyperthermia.
    4. Death is possible if appropriate treatment is not administered.
    5. Cats are often exposed by rubbing against or grooming a recently treated dog or by intentional treatment with a product when the labeled instructions are not followed.
  D. Oral exposures to any pyrethroid may result in hypersalivation from a taste reaction and gastrointestinal irritation, often from the product carriers.
II. Dogs
  A. Exposure to pyrethroids in dogs is not expected to cause severe signs unless the exposure is massive or the dog is otherwise predisposed (e.g., a young age, underlying liver disease, debilitated as with a severe flea infestation).
  B. Local dermal reactions identical to those described for cats are possible in dogs.
  C. Oral ingestion is expected to cause mild to moderate gastroenteritis; however, with appropriate care, signs usually resolve within 24 hours.

Diagnosis

I. History of exposure and consistent clinical signs are sufficient in most cases to make a diagnosis of pyrethrin or pyrethroid intoxication.
II. A "greasy" spot on the back or detection of the odor of the product on the coat is evidence of exposure.
III. Fur may be tested to confirm exposure.
IV. Postmortem, the compounds may also be detected in the liver.

Differential Diagnosis

I. Consider any neurotoxicant that results in CNS stimulation.

II. Clinical signs of intoxication with strychnine, metaldehyde, 1080 (fluoroacetate), 5-fluorouracil *(Efudex),* 4-aminopyridine, caffeine, theobromine, amphetamine, cocaine, OPs, carbamates, OCs, cationic surfactants, and tremorgenic mycotoxins resemble those of pyrethroid intoxication.

Treatment and Monitoring

I. Asymptomatic animal
   A. With dermal exposure, bathe the animal with a liquid dishwashing detergent to remove the residue.
   B. Monitor for gastrointestinal upset and signs consistent with paresthesia within a few hours of exposure, for tremors and seizure activity within 12 to 18 hours postexposure, and for local skin irritation in the first 24 hours.

II. Symptomatic animal
   A. Treat tremors, hyperesthesia, or seizures with a slow injection of methocarbamol 55 to 220 mg/kg IV (maximum of 330 mg/kg/day) to effect, and repeat as needed as long as CNS depression is not present.
   B. Seizures refractory to methocarbamol may be controlled by barbiturates, inhalant anesthetics, or propofol (see Chapter 22).
   C. Once the animal is stable, treat any dermal exposure with thorough bathing in warm water using a liquid dishwashing detergent.
   D. Tremors and seizures may cause significant hyperthermia, yet the bathing process may result in hypothermia, which can enhance the toxicosis.
   E. Supportive care including IV fluids and IV dextrose supplementation may be indicated.
   F. Canned food or a tasty treat may be given to the hypersalivating animal suspected of reacting to the adverse taste of the dermal products.
   G. For animals exhibiting paresthesia and local dermal irritation, liquid vitamin E may be applied to the affected skin after adequate bathing to remove the product residue.
   H. Gastrointestinal irritation is treated symptomatically and supportively (see Chapter 31).

AVERMECTINS

Sources

I. Avermectins are macrolide parasiticides commonly used as a heartworm *(Dirofilaria immitis)* preventative and as a treatment for mite infestations such as scabies (*Sarcoptes* spp.), demodicosis (*Demodex* spp.), and ear mites (*Otodectes* spp.).
II. Certain members of the class are also used in ant and roach baits.
III. Macrolide parasiticides are fermentation products of *Streptomyces* spp. fungi.
IV. Brand names include *Heartgard, Ivomec, Tri-Heart* (ivermectin); *Revolution* (selamectin); *Proheart* (moxidectin); *Interceptor* (milbemycin); and *Avomec, Raid,* and *Hot Shot MaxAttrax* (abamectin).

Action

I. Macrolides cause death of their target species by binding to GABA-containing neurons in the parasite's neuromuscular junction and to glutamate-gated chloride channels in the CNS.
II. This binding causes an influx of chloride ions into the postsynaptic neuron, hyperpolarization that prevents subsequent action potential initiation or propagation, and ultimately flaccid paralysis.
III. The normal mammalian blood–brain barrier prevents high concentrations of macrolides from accumulating in the brain by using the P-glycoprotein efflux pump.
IV. Mammals also do not have glutamate-gated chloride channels, so a wide margin of safety of macrolide parasiticides exists in host animals relative to the target.
V. Dogs deficient in P-glycoprotein (from MDR1 mutation, classically in herding breeds) are uniquely susceptible to macrolide toxicosis because of the inability to pump these drugs out of the brain.
VI. Once in the brain, macrolides potentiate the release of GABA and bind to its receptors.

Clinical Signs

I. Signs occur within several hours of ingestion and include depression, mydriasis, blindness (often reversible with time), tremors, ataxia, respiratory depression, hypothermia, bradycardia, coma, and death.
II. Severe CNS depression and seizures may also occur.
III. Depending on the degree of toxicosis, signs may persist for weeks because of enterohepatic recirculation.

Diagnosis

I. History of exposure, consistent clinical signs, and breed predisposition help make the diagnosis.
II. Drug levels may be determined in serum, liver, adipose tissue, and the brain for confirmation of the toxicosis.
III. Blood levels do not correlate well with clinical toxicosis because the level of the drug in the brain is what determines the extent of the clinical reaction.
IV. A genetic test for the MDR1 gene mutation can be performed on a cheek swab of a suspected P-glycoprotein–deficient dog.
V. Although the genetic test is not diagnostic of an avermectin toxicosis, it provides evidence of the susceptibility of the individual.

Differential Diagnosis

I. Any agent that causes CNS depression: alcohol, ethylene glycol, amitraz, marijuana, benzodiazepines, barbiturates, opiates, phenothiazines
II. Any condition that results in obtundation or severe lethargy: diabetic ketoacidosis, intracranial neoplasia, hypoadrenocorticism, renal failure

Treatment and Monitoring

I. Asymptomatic animal
   A. Decontamination with emesis, followed by activated charcoal with a cathartic is indicated.

TABLE 125-1

Miscellaneous Insecticides and Molluscicides

TOXICANT	SOURCES	ACTION	CLINICAL SIGNS	TREATMENT
Naphthalene	Mothballs: *Miracle, Enoz, Curran Home Guard, Excell* Pesticides: *Bonide Mosquito Beater, Shot Gun, Dr. T's Bat Scat, Detour* Herbicides: *Prestige, Vantage*	Oxidizes hemoglobin to methemoglobin via a 1,2-oxide metabolite that forms epoxides or quinones Results in Heinz body formation and erythrolysis Also directly irritating to GI mucosa	PO: vomiting, diarrhea, abdominal pain, anorexia, pale mucous membranes, tachypnea, dyspnea, tachycardia, exercise intolerance, hemoglobinuria, fever, hepatomegaly, icterus, acute renal failure Inhalation: pulmonary edema, respiratory distress	Asymptomatic animal: decontamination with induction of emesis and administration of activated charcoal Symptomatic animal: antiemetic agents, sucralfate, famotidine; NPO for GI signs; whole blood transfusion, N-acetylcysteine, methylene blue, or ascorbic acid for methemoglobinemia; fluid therapy to protect kidneys; oxygen for inhalation exposure; bicarbonate to alkalinize urine to enhance excretion
Borate	*Borax, Timbor*	Unknown: thought to be secondary to cytotoxic properties	Vomiting most commonly, hypersalivation, retching, depression, abdominal pain, anorexia, diarrhea Less commonly weakness, ataxia, tremors, seizures, renal tubular nephrosis, hepatotoxicosis, metabolic acidosis, coma, death Dermal exposures may result in erythema, desquamation, exfoliation	Asymptomatic animal: decontamination with induction of emesis with large ingestions (>6.51 g/kg PO); activated charcoal no benefit; bathe areas in contact with liquid dishwashing detergent Symptomatic animal: IV fluids, antiemetic agents, GI protectants, electrolyte and glucose supplementation as needed, sodium bicarbonate as needed for acidosis, forced diuresis for 48 hours if kidney function may be compromised, diazepam for seizures
Rotenone	*Derris* and *Lonchocarpus* spp., *Bonide Garden Dust, Hilo Flea Dip, Goodwinol* ointment, *Durakyl Pet Dip, Flys Off Insect Repellant for Dogs, Noxfish, Green Light Rotenone Dust, Otocide, Durvet Earmite Lotion*	Inhibitor of complex I of mitochondrial electron transport in the respiratory chain	Vomiting, tachypnea, muscle tremors, respiratory and CNS depression, seizures, hypoglycemia, respiratory failure, death	Asymptomatic animal: decontamination with induction of of emesis and administration of activated charcoal for oral exposure; bathe with a liquid dishwashing detergent for dermal exposure Symptomatic animal: supportive care including antiemetic agents and GI protectants, IV fluids, diazepam or barbiturates for seizures, supplemental oxygen, endotracheal intubation, dextrose as needed
DEET	*Cutters, Deep Woods Off, 3M Ultrathon, Autan*	Unknown	Dogs and cats: tremors, hyperactivity, hypersalivation, vomiting, ataxia, seizures, death Rabbits and rats: depression, excitation, ataxia, tremors, seizures, coma, death	Asymptomatic animal: decontamination with induction of emesis for a recent and significant oral ingestion if risk of aspiration is outweighed; activated charcoal Symptomatic animal: supportive care including IV fluids to maintain hydration and promote excretion, diazepam or barbiturates for seizures

PO, Per os exposure; *NPO,* nothing by mouth; *CNS,* central nervous system; *GI,* gastrointestinal; *IV,* intravenous; *DEET,* N,N-diethyl-m-toluamide.

B. Because of enterohepatic recirculation, repeated doses of activated charcoal are given (6.6 to 11 mL/kg PO initially, followed by 3.3 to 5.5 mL/kg PO TID for 1 to 2 days).
C. Use caution with cathartic agents because the potential exists for diarrhea and hypernatremia to develop.

II. Symptomatic animal
A. Endotracheal intubation and assisted ventilation may be required in the animal with severe respiratory depression.
B. IV fluid therapy, parenteral nutrition, management of hypothermia, and prevention of decubital ulcers are important supportive measures.
C. If activated charcoal can be safely administered, repeated doses of it are helpful because of the agent's ability to undergo enterohepatic recirculation.
D. Atropine can be used for severe bradycardia.
E. CNS status, cardiovascular status, arterial blood gases, body temperature, and ophthalmic changes are important parameters to continually assess.
F. Signs may persist for weeks; however, with aggressive supportive care, recovery is expected.

MISCELLANEOUS INSECTICIDES AND MOLLUSCICIDES

See Table 125-1.

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CHAPTER 126

Household Hazards

Eric K. Dunayer

ZINC

Sources

I. U.S. pennies minted after 1982 (zinc core with copper cladding)
II. Zinc, brass, or galvanized steel metal hardware
III. Zinc oxide topical ointments

Action

I. Zinc oxide is directly irritating to the gastric mucosa and generally causes mild, self-limiting vomiting.
II. Elemental zinc is released from metallic objects by the action of stomach acid.
III. Zinc causes hemolysis in dogs and cats; the exact mechanism is unknown.

Clinical Signs

I. Vomiting, lethargy, weakness, diarrhea, and abdominal pain are common.
II. Hemoglobinuria, oliguria, anemia, and icterus develop several days after metal ingestion.

Diagnosis

I. Evidence of recent ingestion of pennies or metallic objects
II. Presence of hemolytic anemia or hemoglobinuria
III. Presence of metallic objects in the gastrointestinal (GI) tract on radiographs
IV. Serum zinc levels >10 ppm
    A. Collect in royal blue top tubes.
    B. Rubber stoppers in syringes may falsely elevate zinc levels.

Treatment

I. Blood transfusions for severe anemia
II. IV fluid therapy to protect the kidneys
III. Alkalization of the urine to reduce risk of precipitation of hemoglobin in the renal tubules
IV. Endoscopic or surgical removal of GI metallic objects
V. Chelation therapy not required once objects removed
VI. Symptomatic control of vomiting, especially from zinc oxide ointments

LEAD

Sources

I. Lead paints such as exterior or artist paints
    A. Lead levels in interior paint have been strictly regulated since 1977.
    B. Older homes may still contain lead paint.
II. Lead weights such as fishing sinkers or curtain weights
III. Lead hunting shot
IV. Environmental contamination from lead smelters or discarded auto and marine batteries

Action

I. Lead binds to sulfhydryl groups on proteins and can inhibit numerous enzymes and other cellular functions.
II. Lead inhibits heme synthesis and red blood cell production.
III. Lead competes with calcium and may alter nerve transmission.

Clinical Signs

I. GI signs
    A. Vomiting, diarrhea
    B. Abdominal pain
    C. Anorexia
    D. Weight loss with chronic toxicosis
II. Neurological signs
    A. Ataxia
    B. Tremors, seizures
    C. Behavioral changes

Diagnosis

I. History
    A. Ingestion of paint containing lead or lead paint chips, typically found in old dwellings
    B. Recent or ongoing lead removal projects in the house
    C. Ingestion of lead weights
II. Radiography
    A. Dense metallic objects or radiopaque chips in GI tract
    B. Lead shot in tissues

1. Pellets in tissue are stable.
2. Pellets in acidic environments (joints, abscesses) can release lead.

C. Possible lead lines (dense opacification of the metaphyseal region of long bones) in young, growing animals

III. Clinical laboratory tests
A. Hematological findings
1. Anemia
2. Basophilic stippling
3. Increased number of nucleated red blood cells
B. Blood lead levels
1. Assays are run on whole blood samples.
2. Blood lead levels >0.15 to 0.3 ppm (>15 to 30 μg/dL) indicate significant exposure.
3. Blood lead levels >0.35 ppm (>35 μg/dL) are diagnostic for lead poisoning.
4. Animals with compatible clinical signs and blood lead levels of >0.15 ppm (>15 μg/dL) should be treated.

Treatment and Monitoring

I. Prevent further absorption from GI tract.
A. Emesis if ingestion recent
B. Activated charcoal not effective
C. Enemas
D. High fiber or increased dietary bulk to decrease transit time
E. Surgical or endoscopic removal of GI or selected soft tissue metallic objects

II. Control seizures and neurological signs (see Chapter 22).

III. Chelation therapy binds lead for renal excretion.
A. Chelators can be nephrotoxic.
1. Ensure adequate hydration.
2. Monitor renal parameters during treatment.
B. Most should not be used until the GI tract is free of lead (succimer is an exception).
C. They may also bind essential minerals.
D. Calcium disodium ethylenediamine tetraacetic acid (EDTA) is effective in most cases.
1. Dosage is 100 mg/kg/day for 2 to 5 days SC divided into four treatments per day and given in a 10 mg/mL solution of 5% dextrose in water (D5W).
2. Do not exceed 2 g/day in dogs.
3. Dogs with initial blood lead levels >100 μg/dL may require two courses of therapy, separated by 7 to 10 days.
4. Cats have an increased risk of nephrotoxicity.
5. Side effects and disadvantages are as follows:
a. Painful injections
b. Removes lead from bones, so treatment may initially increase blood lead levels and worsen clinical signs
c. Cannot be administered until the GI tract is free of lead materials; requires hospitalization because of QID treatments
6. Do not use sodium EDTA because it may cause hypocalcemia.
E. D-Penicillamine *(Cuprimine)* may be used in animals that are not vomiting.
1. Dosage in dogs is 30 to 50 mg/kg/day PO divided QID for 7 days on, 7 days off, 7 days on.
2. Dosage in cats is 125 mg PO BID for 5 days.
3. Vomiting is common, so consider diphenhydramine 2 mg/kg PO or dramamine 2 to 4 mg/kg PO 30 minutes before penicillamine.
F. Succimer *(Chemet)* may be used in most animals.
1. Dosage in dogs: 10 mg/kg PO TID for 10 days
2. Dosage in cats: 10 mg/kg PO TID for 5 days followed by 10 mg/kg PO or rectally BID for 10 days
3. Given rectally if animal is seizuring or unable to swallow
4. Advantages over other chelators
a. Low nephrotoxicity
b. Does not chelate essential minerals such as zinc, copper, or iron
c. Reduced incidence of vomiting
d. Can be used if lead is still present in the GI tract

IV. Additional care may be needed for the animal and the environment.
A. Identify and remove lead source to prevent further exposure.
B. Recheck blood lead levels 2 weeks after treatment and repeat chelation if needed (blood lead values ≥40 μg/dL).
C. People in the house, especially children, may need to be tested for lead exposure.

CORROSIVES

Sources

I. Acids
A. Toilet bowl cleaners
B. Antirust compounds
C. Metal-etching chemicals

II. Alkalis
A. Drain openers: potassium or sodium hydroxide, lye
B. Automatic dishwasher detergents
C. Alkaline batteries
D. Chlorine bleaches

III. Cationic detergents
A. Germicidal detergents such as quaternary ammonium compounds
B. Fabric softeners
C. Liquid simmering potpourri

Action

I. Acids
A. They produce localized coagulation necrosis of tissues.
B. Immediate pain on contact may limit further exposure.

II. Alkalis
A. They penetrate tissues and produce localized liquefactive necrosis.
B. Little pain on contact may lead to greater exposure.

III. Cationic detergents
A. They may produce both local and systemic effects.

B. Concentrations of 1% to 7.5% may be irritating; concentrations >7.5% are corrosive.
C. Cats may show significant tissue injury with concentrations <2%.
D. Systemically, cationic detergents appear to block ganglionic function and can cause muscular paralysis.

Clinical Signs

I. Local ulcerative and/or necrotic injury: mouth, esophagus, stomach, cornea, and/or skin
II. Vomiting, drooling, anorexia, depression, vocalization
III. Central nervous system (CNS) depression with cationic detergents

Diagnosis

I. Evidence of recent ingestion or exposure to agent
II. Presence of typical burnlike injuries

Treatment and Monitoring

I. Decontamination is essential.
A. Emesis, gastric lavage, and activated charcoal are contraindicated.
B. Do not attempt to neutralize acids or alkalis because of potential generation of heat from the neutralization process.
C. Dilution with milk and/or water may be done for recent oral exposure.
D. Copious flushing of eyes or skin with water or saline is indicated for ocular or dermal exposure.
II. Monitor tissues for signs of irritation or necrosis.
III. The following may help oral exposures:
A. Sucralfate 25 to 40 mg/kg PO BID to TID (liquid or slurried tablets) to coat and protect GI tract injuries
B. Pain control with injectable opioids
1. Butorphanol 0.2 mg/kg IV, IM, SC TID to QID
2. Buprenorphine 0.01 mg/kg IV, IM, SC BID to QID
C. Broad-spectrum antibiotic agents for secondary oral infection
1. Amoxicillin 10 mg/kg IM, SC, PO BID
2. Cefadroxil 20 mg/kg PO BID
3. Metronidazole 25 mg/kg BID PO or 10 to 15 mg/kg IV BID
D. Fluid support with balanced electrolyte solutions (*Normosol-R*, lactated Ringer solution)
E. Feeding tube insertion (gastrotomy tube) for nutritional support
F. Monitoring for esophageal stricture
1. Signs may not appear for several weeks.
2. Use of short-acting corticosteroid medications to prevent esophageal scarring is controversial.

METHYLXANTHINES

Sources

I. Caffeine
A. Coffee
1. Coffee beans contain about 1% to 2% w/w dry weight caffeine.
2. Brewed coffee may contain 8 to 30 mg/oz caffeine.
B. Tea
1. Dry tea contains 3% to 4% w/w dry weight caffeine.
2. Brewed tea contains 1.8 to 10 mg/oz caffeine.
II. Chocolate
A. Derived from the cocoa bean
B. Contains combination of caffeine and theobromine (Table 126-1)
C. Found in candies, baked goods, cocoa, baker's chocolate, and cocoa bean mulch

TABLE 126-1

Methylxanthine Content of Various Chocolates

COMPOUND	THEOBROMINE (mg/oz)	CAFFEINE (mg/oz)
White chocolate	0.25	0.85
Milk chocolate	58.0	6.0
Semisweet chocolate chips	138.0	22.0
Baker's chocolate (unsweetened)	393.0	47.0
Dry cocoa powder	737.0	70.0

Action

I. Methylxanthine agents antagonize adenosine receptors.
II. Calculate methylxanthine dose based on combined caffeine and theobromine in products; see Table 126-1 for typical amounts in chocolates.
III. GI upset occurs with ingestion of 20 mg/kg of methylxanthines PO.
IV. Cardiac stimulation occurs with ingestion of 40 to 50 mg/kg PO.
V. CNS stimulation occurs with ingestion of 60 mg/kg PO.
VI. Minimum lethal dose is 100 mg/kg PO.

Clinical Signs

I. Polydipsia
II. Vomiting, diarrhea
III. Tachycardia
IV. CNS stimulation: agitation, tremors, seizures

Diagnosis

I. Evidence of recent ingestion of agent
II. Presence of agent in vomitus
III. Appropriate clinical signs

Treatment and Monitoring

I. Decontamination is indicated.
A. Emesis
1. Chocolate may form a large ball in the stomach.
2. Emesis may be useful even 6 to 8 hours after ingestion if animal is still asymptomatic.
B. Activated charcoal
1. Theobromine has a longer half-life in dogs (17.5 hours) than caffeine (4.5 hours) because of enterohepatic recirculation.

2. Multiple doses of activated charcoal (every 3 to 4 hours) may disrupt this recirculation.

II. Manage vomiting with antiemetic agents.
   A. Metoclopramide 0.2 to 0.4 mg/kg SC, IM TID to QID or 1 to 2 mg/kg/day IV as constant rate infusion (CRI)
   B. Chlorpromazine 0.5 mg/kg IV, IM, SC TID to QID

III. Control cardiac signs.
   A. Tachycardia can be controlled with propranolol 0.02 to 0.06 mg/kg IV.
   B. Ventricular tachycardia in dogs may be controlled with lidocaine 1 to 2 mg/kg IV bolus, followed by 60 to 90 μg/kg/min CRI.

IV. Control agitation, tremors, and/or seizures.
   A. Diazepam 0.5 to 2.0 mg/kg IV
   B. Methocarbamol 50 to 220 mg IV slowly
   C. Phenobarbital 2 to 6 mg/kg IV

V. Fluid diuresis promotes excretion.

VI. Caffeine can be reabsorbed through the bladder wall.
   A. Encourage frequent voiding.
   B. Insert urinary catheter to keep the bladder empty.

VII. Because of the high fat content of many chocolate products, monitor for pancreatitis.

GRAPES AND RAISINS

Sources

I. Commercially sold grapes and raisins
II. Pulp from wine pressings
III. Backyard vines

Action

I. Grapes and raisin ingestion can cause acute tubular necrosis with acute renal failure in dogs and possibly cats.
II. Toxic mechanism is unknown.

Clinical Signs

I. Vomiting (usually within 6 hours of ingestion)
II. Diarrhea
III. Lethargy
IV. Polydipsia, polyuria
V. Oliguria or anuria (may develop in 48 to 72 hours)

Diagnosis

I. Evidence of recent ingestion of grapes or raisins
II. Presence of grapes or raisins in vomitus or stool
III. Elevated blood urea nitrogen (BUN), creatinine, phosphorus
   A. Values may start to increase 24 to 36 hours postingestion.
   B. Creatinine level may be disproportionately elevated compared with BUN.
IV. Renal tubular casts in urine sediment

Treatment

I. Emesis and activated charcoal are indicated within 4 hours of ingestion if spontaneous vomiting is not present.
II. Fluid diuresis (IV administration of balanced electrolyte fluids at twice maintenance) is done for at least 48 hours.
III. Prognosis varies.
   A. Good with early intervention in asymptomatic animals
   B. Guarded if oliguria and anuria occurs
      1. Renal function may return to normal in days to weeks.
      2. Chronic renal failure may be a sequela.
      3. Peritoneal dialysis or hemodialysis may be useful until renal function improves.

ADHESIVES

Sources

I. Commercially available glues
II. Cyanoacrylate-based "super" glues
III. Isocyanate-based polyurethane glues
   A. *Gorilla Glue*
   B. *Elmer's Probond Polyurethane Ultimate Glue*

Action

I. Super glues can instantly glue skin, eyelids, and lips together.
   A. They may cause local tissue burns from release of heat during the polymerization process.
   B. These glues polymerize rapidly, so systemic toxicity from ingredients is unlikely.
II. Polyurethane glues contain isocyanate monomers that polymerize to polyurethane, forming a large gastric foreign body.

Clinical Signs

I. Super glues
   A. Inability to open mouth or eyelids
   B. Localized irritation
II. Polyurethane glues
   A. Vomiting
   B. Anorexia
   C. ± Firm abdominal mass

Diagnosis

I. Evidence of recent ingestion of product
II. Polyurethane glues
   A. Radiographic presence of large, granular gastric foreign body
   B. Full stomach in a chronically vomiting animal

Treatment

I. Super glues
   A. Do not force glued skin or eyelids apart.
   B. Allow glue around gums and teeth to wear away from abrasion.
   C. Allow eyelids and skin to separate on their own.
II. Polyurethane glues
   A. Do not induce emesis, as it may result in an expanding esophageal mass.

B. Activated charcoal, food, and other diluents are contraindicated because they may accelerate the polymerization process.
C. Gastrotomy may be needed to remove the foreign body.
D. GI protectants such as sucralfate (0.5 to 1 g PO TID in dogs) may be helpful.

MACADAMIA NUTS

Sources

I. Macadamia nuts are harvested from the *Macadamia integrifolia* tree.
II. They are sold as nuts or in baked goods.

Action

I. Mechanism of action has not been determined.
II. Doses >2.4 g/kg PO may cause symptoms in dogs.

Clinical Signs

I. Vomiting, anorexia
II. Weakness, pelvic limb ataxia
III. Tremors
IV. Mild hyperthermia

Diagnosis

I. Evidence of recent ingestion of the nuts
II. Presence of macadamia nuts in vomitus or stool

Treatment

I. Emesis is induced within 4 hours of ingestion if animal is not already spontaneously vomiting.
II. Give repeated doses of activated charcoal (1 g/kg PO followed by 0.5 g/kg TID).
III. Most cases recover without specific treatment.
IV. Signs usually appear within 12 hours of ingestion.
V. Signs may take 12 to 48 hours to resolve.
VI. Severe cases may require the following:
A. Control tremors with methocarbamol 50 to 200 mg/kg IV slowly.
B. Cold-water enemas may help recovery by decreasing transit time.
C. Prognosis is usually excellent.
VII. Because of the high fat content of macadamia nuts, monitor for pancreatitis.

HOPS

Sources

I. Derived from the *Humulus lupulus* plant
II. Used for brewing beer

Action

I. Ingestion of hops by dogs can lead to a malignant hyperthermia-like syndrome.
II. No toxicity has been reported in cats.
III. Mechanism of action is unknown.

Clinical Signs

I. Vomiting
II. Restlessness
III. Abdominal pain
IV. Panting
V. Hyperthermia: may exceed 41.7° C (107° F)
VI. Rapid onset and progression of signs: usually within 3 to 6 hours of ingestion

Diagnosis

I. Evidence of recent ingestion of hops
II. Presence of hyperthermia without other obvious causes (e.g., heatstroke)

Treatment

I. Emesis and activated charcoal are indicated early.
II. Fluid therapy may be needed for cardiovascular support.
III. Manage hyperthermia.
A. External cooling with cold-water baths
B. Dantrolene sodium
1. Skeletal muscle relaxant
2. Dosage: 2 to 3 mg/kg IV or 3.5 mg/kg PO, followed by 3.5 mg/kg PO BID for 3 days
IV. Prognosis is guarded with severe, prolonged hyperthermia.

BREAD DOUGH

Sources

I. Raw yeast dough
II. Examples: bread or pizza dough
III. Usually occurs in dogs

Action

I. Dough expands from carbon dioxide accumulation and causes gastric distension.
A. Pressure necrosis of gastric mucosa
B. Compromise of caudal venous return to heart
II. Yeast releases ethanol during fermentation.
A. CNS depression
B. Acidosis from ethanol breakdown products

Clinical Signs

I. Nonproductive vomiting, retching
II. Gastric distention
III. Ataxia
IV. CNS depression, collapse, coma

Diagnosis

I. Evidence of recent ingestion of uncooked dough
II. Abdominal distention
III. Radiographic evidence of soft tissue density (foreign body) in the stomach

Treatment

I. Emesis early
A. Consider if ingestion was within 1 to 2 hours.
B. Do not induce emesis if CNS signs are present.

II. Intravenous fluid therapy for cardiovascular support and acidosis
III. Cold-water lavage
  A. To remove dough
  B. To inhibit ethanol production
IV. Correction of any acid-base imbalances
V. Possible gastrotomy to remove mass of dough

GLOW JEWELRY

Sources

I. Glow-in-the-dark necklaces, bracelets, and light sticks
II. Common around holidays such as Halloween and Independence Day
III. Often sold at fairs and carnivals

Action

I. Products contain dibutyl phthalate.
II. Dibutyl phthalate has a wide margin of safety (rat oral LD_{50} >8 g/kg).
III. Signs arise from the extremely unpleasant taste of dibutyl phthalate, which causes a repugnant reaction in the animal.

Clinical Signs

I. Profuse salivation
II. Vomiting
III. Agitation or aggression
IV. Cats more likely to show signs than dogs
V. Generally occur immediately after exposure

Diagnosis

I. Evidence of ingestion of the agent
II. Liquid on fur that glows in the dark

Treatment

I. Gently rinse the mouth or offer the animal an oral treat, such as milk, tuna juice, or canned cat food.
II. Remove any agent from the fur to prevent reexposure; placing the animal in a darkened room aids with identification and removal of the agent.
III. Signs may resolve quickly even without treatment.

XYLITOL

Sources

I. A five-carbon sugar alcohol used as a sugar substitute
II. Sugar-free gums, candies, or mints
III. Low-carbohydrate baked goods
IV. Toothpastes, mouthwashes
V. Granular powder used for sweetening baked goods, drinks, cereals

Action

I. In dogs, xylitol causes release of large amounts of insulin with resultant hypoglycemia.
II. Hepatic metabolism of xylitol may cause depletion of adenosine triphosphate (ATP) and hepatic necrosis.
III. As little as 0.15 g/kg PO of xylitol may cause hypoglycemia.

Clinical Signs

I. Vomiting
II. Weakness progressing to ataxia, collapse, and seizures
III. Hypoglycemia
  A. May develop in <30 minutes.
  B. With some gums, onset of hypoglycemia may be delayed up to 12 hours.
  C. Hypoglycemia may persist for 24 to 36 hours.
  D. Some dogs may become hyperglycemic secondary to glycogenolysis by the liver (which develops to compensate for hypoglycemia).
IV. Hypokalemia
V. Possible acute hepatic failure and necrosis in 24 to 72 hours
  A. Elevated alanine aminotransferase, aspartate aminotransferase, serum alkaline phosphatase
  B. Hyperbilirubinemia
  C. Coagulopathy
  D. May occur without initial signs of hypoglycemia

Diagnosis

I. Evidence of recent ingestion of agent
II. Progressive weakness, ataxia, seizures
III. Hypoglycemia
IV. Hypokalemia
V. Elevated liver enzymes

Treatment and Monitoring

I. Emesis is indicated in asymptomatic animals with recent ingestion.
II. Activated charcoal is of limited use.
III. Monitor blood glucose levels.
IV. Supplemental IV dextrose (bolus of 25% dextrose at 2 mL/kg IV, followed by D5W 1 to 2 mL/kg/hr IV) is often required.
V. Supplement with potassium if hypokalemia is severe (<2.5 mmol/L).
VI. Hepatic failure is treated similarly to other causes (see Chapter 37).
  A. Liver protectants such as S-adenosylmethionine *(Denosyl)* 20 mg/kg PO SID may be helpful.
  B. Plasma may be given for a coagulopathy (see Chapters 68 and 71).
VII. Prognosis is variable.
  A. Good for hypoglycemia
  B. Guarded if liver failure develops

PAINTBALLS

Sources

I. Marble-sized paint-filled balls used for warlike games
II. Labeled as nontoxic

Action

I. They contain osmotically active agents such as sorbitol, polyethylene glycol (PEG), and glycerol that can draw water into the GI tract and cause a relative hypernatremia.
II. Low-molecular weight PEGs can be absorbed and cause direct CNS depression and acidosis.

Clinical Signs

I. Vomiting
II. Ataxia
III. Tremors, seizures
IV. Hypernatremia

Diagnosis

I. Evidence of recent ingestion of paintballs
II. Paint in vomitus or on fur
III. Hypernatremia

Treatment and Monitoring

I. Emesis may be induced in asymptomatic animals.
II. Consider gastric lavage for large ingestions, especially if CNS depression is present.
III. Do not give activated charcoal because it can exacerbate the hypernatremia.
IV. Institute low-sodium IV fluid diuresis (D5W, 0.45% sodium chloride and 2.5% dextrose) to lower blood sodium levels.
V. Plain-water enemas (3 to 5 mL/kg) are given to provide free water to lower blood sodium levels and are repeated as needed.
VI. Monitor serum sodium levels.
VII. Prognosis is good with prompt control of clinical signs.

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CHAPTER 127

Human Medications

Charlotte Means

IRON

Sources

I. Iron is an essential mineral.
II. Iron is found in vitamin supplements, generally as a ferric (Fe^{3+}) or ferrous (Fe^{2+}) salt.
III. Children's vitamins are frequently flavored and palatable.
IV. Other sources include the following:
  A. Injectable iron (iron dextran)
  B. Fertilizers
  C. Snail and slug bait
  D. Instant hand warmers
  E. Birth control pills

Action

I. Iron has a direct corrosive effect on the gastrointestinal (GI) tract.
II. It is metabolized in the stomach and mucosal cells to the Fe^{3+} form and transported to the blood where iron binds to transferrin.
III. When transferrin is saturated, free iron (serum iron) is released in the circulation.
IV. Free iron increases lipid peroxidation, which damages mitochondria, microsomes, and organelles in the brain, heart, and liver.
V. Vitamin C enhances the absorption of iron.
VI. In dogs, oral doses of elemental iron <20 mg/kg are nontoxic, 20 to 60 mg/kg are mild to moderately toxic, >60 mg/kg are seriously toxic, and 100 to 200 mg/kg are potentially lethal.

Clinical Signs

I. Iron toxicosis occurs in four stages.
II. Stage 1 occurs within the first 6 hours.
  A. During this stage the direct corrosive effect on the gut causes vomiting and diarrhea, possibly hemorrhagic.
  B. In mild to moderate cases, clinical signs may not progress beyond stage 1.
III. In stage 2 the animal appears to stabilize while the reticuloendothelial system takes up iron.
IV. In stage 3 (12 to 96 hours after the overdose) severe to life-threatening signs develop.
  A. Recurrence of GI signs: frequently hemorrhagic
  B. Metabolic acidosis
  C. Hepatic necrosis, hypoglycemia
  D. Coagulopathies
  E. Hypotension, shock
  F. Cardiovascular collapse, death
V. Stage 4 develops 2 to 6 weeks postingestion when healing GI ulcers cause scarring and stricture formation.

Diagnosis

I. Iron is absorbed erratically.
II. Submit samples to measure serum iron (SI) and total iron-binding capacity (TIBC) at 3 to 4 and 8 to 10 hours postingestion to human hospital laboratories.
III. If SI > TIBC, then the animal is at risk for toxicity.
IV. Radiographs of the abdomen may be helpful to verify ingestion.
  A. Negative findings on radiographs are meaningless.
  B. If iron tablets are present, then radiodense outlines of the tablets may be seen.

Differential Diagnosis

I. Other causes of hemorrhagic gastroenteritis or hepatic necrosis
II. Other toxicities
  A. Sago palm
  B. Castor beans
  C. Mushrooms
  D. Arsenic
  E. Bacterial, viral gastroenteritis

Treatment and Monitoring

I. Decontamination
  A. Induce emesis within 2 hours of ingestion in asymptomatic animals.
  B. Gastric lavage is indicated for massive ingestions.
  C. Magnesium hydroxide 30 to 90 mg/kg PO, repeated in 6 hours may complex with iron, resulting in decreased absorption.
  D. Activated charcoal does not adsorb iron well.
II. Symptomatic care
  A. IV fluids: rate and type dependent on maintenance and replacement needs
  B. GI protectants: sucralfate 0.5 to 1.0 g/25 kg PO TID in dogs and 0.25 g PO TID in cats
  C. Monitoring of electrolytes and serum biochemistries
III. Chelation therapy

A. Give deferoxamine *(Desferal)* at 40 mg/kg IM TID to QID.
B. Deferoxamine turns the urine a salmon-pink color.
C. Continue until the urine is normal in color.

ACETAMINOPHEN

Sources

I. Acetaminophen is a synthetic, nonopiate derivative of p-aminophenol.
II. It is also known as APAP, paracetamol *(Panadol),* and nonaspirin pain reliever.
III. More than 200 prescription and nonprescription formulations exist, and it may be found in combination with antihistamines, decongestants, opiates, or other agents.
IV. It is used to treat mild to moderate pain and fever.

Action

I. It is rapidly absorbed from the GI tract, but absorption can be delayed by other drugs and high carbohydrate foods that prolong gastric emptying.
II. It is metabolized in the liver by glucuronidation, glutathione conjugation, or sulfation.
A. Cats are deficient in glucuronyl transferase.
B. The metabolite N-acetyl-p-benzoquinone (NAPQI) is toxic because it damages hepatic cells and red blood cells.
III. Depletion of glutathione stores allows NAPQI to bind to hepatic cell membranes.
IV. NAPQI binds to sulfhydryl groups on cell membranes causing hepatic cell necrosis.
V. If glutathione is present, then NAPQI can be neutralized.
VI. NAPQI also oxidizes Fe^{2+} to Fe^{3+}, resulting in methemoglobinemia.
VII. Oxidation of hemoglobin forms disulfide bonds that precipitate hemoglobin and form Heinz bodies.
VIII. Toxic doses are as follows:
A. Dogs
1. Hepatoxicity: 100 mg/kg
2. Potential for methemoglobinemia: 200 mg/kg
3. Potential for keratoconjuctivitis sicca (KCS): therapeutic doses
4. Therapeutic dose in dogs: 10 mg/kg PO BID
5. Trigger dose for decontamination: 50 mg/kg PO
B. Cats
1. Never use in cats.
2. Cats may develop toxicity with doses of 10 mg/kg (Aaronson and Drobatz, 1996).

Clinical Signs

I. Methemoglobinemia 2 to 4 hours postexposure in cats
II. Heinz bodies and anemia
III. Hypersalivation, edema of face and feet (more common in cats)
IV. Vomiting
V. Icterus
VI. Tachycardia, tachypnea
VII. Cyanosis, purplish-brown color to mucous membranes
VIII. Hematuria, hemoglobinuria
IX. Acute hepatic necrosis (more common in dogs)
X. KCS (more common in toy breed dogs)
XI. Acute renal failure

Diagnosis

I. History of exposure to agent
II. Measurement of acetaminophen plasma levels 4 hours postexposure
A. Most human hospitals can run this assay.
B. If acetaminophen is present in the plasma, then exposure is confirmed.
III. Elevated liver enzymes
IV. Methemoglobinemia
V. Heinz bodies on peripheral blood smears
VI. Central lobular necrosis of the liver on histopathology

Differential Diagnosis

I. Methemoglobinemia: naphthalene, local anesthetic agents, oxidant drugs (phenazopyridine [*Pyridium*]), chlorates, phenols, onions or garlic (*Allium* spp.)
II. Hepatotoxicity: iron, mycotoxins, mushrooms, phosphorus (P), carbon tetrachloride, phenolics, nitrosamines, thiacetarsamide, pyrrolizidine alkaloid plants, blue-green algae

Treatment and Monitoring

I. Decontamination
A. Emesis within 1 hour of exposure
B. Activated charcoal 1 to 2 g/kg PO; repeated in 6 to 8 hours
II. Oxygen therapy for dyspnea or cyanosis
III. Whole-blood transfusion for significant anemia
IV. N-acetylcysteine (*Mucomyst* PO, *Acetadote* IV) to supplement glutathione
A. Loading dose is 140 to 280 mg/kg PO, IV.
B. Then give 70 mg/kg PO, IV QID for 7 to 17 treatments.
V. S-adenosyl-methionine (SAMe) 18 mg/kg PO for 1 to 3 months to increase hepatic glutathione levels
VI. Ascorbic acid 30 mg/kg PO BID to QID to reduce methemoglobin to hemoglobin
VII. Cimetidine 5 to 10 mg/kg PO TID to QID to reduce metabolism of acetaminophen
VIII. IV fluid therapy
IX. Contraindicated drugs: corticosteroids, antihistamines
X. Monitoring
A. Methemoglobinemia: drop blood on white filter paper and compare color to normal animal's blood
B. Heinz bodies on peripheral blood smears
C. Packed cell volume
1. Ingestion of 60 mg/kg PO in cats can produce 21.7% methemoglobinemia within 4 hours.
2. If anemia has not developed by 72 hours, then it is unlikely.
D. Liver and renal function tests
E. Schirmer tear test: baseline and 72 hours later
XI. Prognosis
A. Prognosis is guarded to poor if severe methemoglobinemia, anemia, or hepatic damage occur.

B. In most other cases, prognosis is good with prompt treatment.

ASPIRIN AND OTHER SALICYLATES

Sources

I. Salicylates are analgesics with antipyretic and antiinflammatory actions.
II. Aspirin (acetylsalicylic acid [ASA]) is the salicylate ester of acetic acid.
III. Many brands and generic forms are available, some in combination with other products.
IV. Bismuth salicylate is found in several brands of antidiarrheals *(Pepto-Bismol, Kaopectate)*.
V. Salicylates are found in liniments, creams, and lotions (e.g., sunblock).
VI. Methyl salicylate is found in many plants and some foods (e.g., apples, blackberries).

Action

I. Salicylates decrease prostaglandin and thromboxane synthesis by inhibiting cyclooxygenase (COX).
II. They also inhibit platelet function.
III. Mitochondrial oxidative phosphorylation is uncoupled, resulting in hyperglycemia and hyperthermia.
IV. Salicylates stimulate the central nervous system (CNS) respiratory center in the medulla.
V. Metabolic acidosis occurs from increased production of organic acids.
VI. Gastric ulceration is a common side effect.
VII. Toxic doses are as follows:
  A. Dogs
    1. With doses <150 mg/kg, signs are generally mild and can be managed by the owner at home.
    2. Ingestion of 150 to 300 mg/kg requires decontamination and medical management.
    3. Doses >300 mg/kg generally require hospitalization.
    4. Therapeutic dose is 10 to 20 mg/kg PO BID.
  B. Cats
    1. Clinical signs are possible at doses above the therapeutic range.
    2. Therapeutic dose is 6 to 10 mg/kg PO QOD.

Clinical Signs

I. Hyperthermia (body temperature >39° C [102.5° F])
II. Tachypnea initially, respiratory depression as signs progress
III. Vomiting ± blood
IV. GI ulceration
V. Metabolic acidosis
VI. Prolonged bleeding times
VII. Hepatic necrosis
VIII. Seizures, coma

Diagnosis

I. History of exposure to salicylate-containing products
II. Compatible clinical signs
III. Metabolic acidosis and increased anion gap (see Chapter 2)
IV. Serum or urine salicylate levels to confirm exposure

Differential Diagnosis

I. Acetaminophen or other nonsteroidal antiinflammatory drugs (NSAIDs)
II. Toxic mushroom ingestion: *Agaricus* spp., *Albatrellus* spp., *Boletus* spp., *Laetiporus* spp.
III. Blue-green algae ingestion
IV. Iron toxicity
V. Hepatotoxic mushroom ingestion: *Amanita* spp., *Galerina* spp., *Lepiota* spp.
VI. Other causes of acute gastritis or hemorrhagic gastritis (see Chapter 31)
VII. Other causes of metabolic acidosis

Treatment and Monitoring

I. Decontamination
  A. Induce emesis in asymptomatic animals, within 2 hours of exposure.
  B. Give activated charcoal 1 to 2 g/kg PO, repeat in 6 to 8 hours.
  C. Peritoneal dialysis can be considered for massive (>300 mg/kg) doses.
II. GI protectants
  A. Dogs: misoprostol 1 to 3 µg/kg PO TID to QID
  B. Sucralfate
    1. Dog: 0.5 to 1 g/25 kg PO BID to TID
    2. Cat: 250 to 500 mg PO BID to TID
  C. Famotidine
    1. Dog: 0.5 to 1 mg/kg PO SID to BID
    2. Cat: 0.5 mg/kg PO SID to BID
III. Urine alkalinization
  A. Give sodium bicarbonate at 10 to 90 g/day PO.
  B. The goal is a urine pH of 7.0.
  C. Do not attempt if acid-base status cannot be monitored.
IV. IV fluid for maintenance and replacement needs
V. Assisted ventilation if comatose
VI. Management of seizures: see Chapter 22
VII. Whole-blood transfusions for severe bleeding
VIII. Cool-water baths or enemas for severe hyperthermia: see Chapter 135
IX. Monitoring
  A. Liver enzymes
  B. Acid-base status: blood gases
  C. Electrolytes: during severe vomiting or diarrhea
  D. Urine pH
  E. Coagulation profile: platelet count, prothrombin time

NONSTEROIDAL ANTIINFLAMMATORY DRUGS

Sources

I. NSAIDs are analgesic, antipyretic, and antiinflammatory drugs.

II. They comprise both over-the-counter and prescription drugs.
III. In general, NSAIDs have a narrow margin of safety in dogs and cats.
IV. Approved NSAIDs in dogs include the following:
  A. Carprofen *(Rimadyl)* 2.2 mg/kg PO BID
  B. Meloxicam *(Metacam)* 0.2 mg/kg PO, SC loading dose, then 0.1 mg/kg PO SID for maintenance
  C. Deracoxib *(Deramaxx)* 1 to 2 mg/kg PO SID
  D. Tepoxalin *(Zubrin)* 10 to 20 mg/kg PO loading dose, then 10 mg/kg PO SID for maintenance
  E. Etodolac *(EtoGesic)* 10 to 15 mg/kg PO SID
  F. Ketoprofen *(Anafen)* 2 mg/kg PO loading dose, then 1 mg/kg PO SID for 4 days
V. Piroxicam 0.3 mg/kg PO SID is not approved but is frequently used in dogs.
VI. A limited number of NSAIDs are approved for cats in United States.
  A. Meloxicam *(Metacam)* 0.3 mg/kg SC once
  B. No approved oral NSAIDs

Action

I. NSAIDs reduce prostaglandin synthesis by inhibiting cyclooxygenase (COX-1, COX-2).
II. NSAIDs cause a decrease in GI cytoprotective effects that allows gastric ulcers to form (with potential for hemorrhage or perforation), which is predominately a COX-1 effect.
III. Renal blood flow is decreased; mechanisms regulating filtration and urine output are altered (predominately COX-1 effects).
IV. Idiopathic hepatopathy may occur from interaction of reactive glucuronide metabolites with plasma and hepatocellular proteins, as well as from an immune-mediated attack on the proteins.
V. Toxic oral doses are as follows:
  A. Ibuprofen in dogs
    1. Gastric ulcers: 50 mg/kg
    2. Acute renal failure (ARF) and gastric ulcers: 125 mg/kg
    3. Seizures, ataxia, ARF, GI ulcers: 400 mg/kg
    4. Potentially lethal: 600 mg/kg
  B. Naproxen in dogs
    1. Ulcerative gastritis: 5 mg/kg for 7 days
    2. ARF: 25 mg/kg
  C. Piroxicam in dogs: GI ulcers and ARF with 1 mg/kg
  D. Indomethacin in dogs: gastric ulcers at 2 mg/kg
  E. Carprofen
    1. Dogs: GI ulcers with 20 mg/kg, ARF with 40 mg/kg
    2. Cats: GI ulcers with 4 mg/kg, ARF with 8 mg/kg
  F. Minimum toxic doses not established in small animals for most NSAIDs
  G. Hepatopathy: idiosyncratic, not dose-related

Clinical Signs

I. GI signs
  A. Lethargy, anorexia
  B. Vomiting ± blood, diarrhea, abdominal pain, melena
  C. Acute collapse and sudden death with perforating GI ulcers
II. Renal signs
  A. Polyuria, polydipsia
  B. Isosthenuria, oliguria, anuria
III. CNS signs: ataxia, seizures, coma
IV. Hepatobiliary signs: lethargy, anorexia, vomiting, diarrhea, icterus
V. Death

Diagnosis

I. History of exposure to agent
II. Abnormalities in total protein, liver enzymes, renal function tests
III. Urinalysis: hematuria, pyuria, proteinuria, isosthenuria
IV. Endoscopy to verify GI ulcers
V. Histopathology
  A. GI tract: ulcers, inflammation, hemorrhage
  B. Kidneys: renal tubular or papillary necrosis, interstitial nephritis
  C. Liver
    1. Multifocal to bridging hepatocellular degeneration and necrosis
    2. Periportal inflammation, bridging fibrosis, biliary hyperplasia, bile retention

Differential Diagnosis

I. Acetaminophen or salicylates
II. Ingestion of toxic (GI, hepatic) mushrooms
III. Iron toxicity
IV. Other causes of acute gastritis or hemorrhagic gastroenteritis (see Chapter 31)
V. Ingestion of lilies
VI. Ingestion of grapes or raisins
VII. Ingestion of arsenic
VIII. Other causes of acute renal failure

Treatment and Monitoring

I. Decontamination
  A. Induce emesis for recent ingestions in asymptomatic animals.
  B. Give activated charcoal 1 to 2 g/kg PO, and repeat in 6 to 8 hours.
II. GI protectants
  A. Dogs: misoprostol 1 to 3 µg/kg PO TID to QID
  B. Sucralfate
    1. Dogs: 0.5 to 1.0 g/25 kg PO BID to TID
    2. Cats: 250 to 500 mg PO BID to TID
  C. Famotidine
    1. Dogs: 0.5 to 1.0 mg/kg PO SID to BID
    2. Cats: 0.5 mg/kg PO SID to BID
  D. Omeprazole
    1. Dogs: 0.5 to 1.0 mg/kg PO SID
    2. Cats: 0.7 mg/kg PO SID
III. Fluid therapy
  A. Institute diuresis for a minimum of 48 hours.
  B. Fluid choice depends on the timing of treatment and electrolyte status (see ARF in Chapter 48).

IV. Monitoring
  A. Complete blood count (CBC): baseline, repeated if melena and hematochezia present
  B. Biochemistry panel: baseline, repeated at 48 and 72 hours
  C. Urinalysis: baseline, repeated in 72 hours after fluids stopped

HYPOGLYCEMIC AGENTS

Sources

I. Three major classes of hypoglycemic agents exist.
  A. Sulfonylurea agents
    1. Acetohexamide *(Dimelor)*
    2. Chlorpropamide *(Diabinase)*
    3. Glimepiride *(Amaryl, Avandaryl)*
    4. Glipizide *(Glucotrol)*
    5. Glyburide *(Diabeta)*
    6. Glibenclamide *(Glyben);* also called *glibenzyclamide*
    7. Tolazamide *(Ronase)*
    8. Tolbutamide *(Orinase, Mobenol)*
  B. Thiazolidinedione agents
    1. Troglitazone *(Rezulin)*
    2. Pioglitazone *(Actos, Actoplus Met)*
    3. Rosiglitazone *(Avandia, Avandamet)*
  C. Biguanide hypoglycemic agents: metformin *(Glucophage, Glucovance, Actoplus, Avandamet)*
II. These products are used therapeutically to control hyperglycemia in noninsulin-dependent human diabetics patients.

Action

I. Sulfonylurea agents stimulate insulin production by the beta cells of the pancreas.
II. Thiazolidinedione agents increase sensitivity to insulin as peroxisome proliferator-activated receptor (PPAR)-gamma agonists.
  A. These drugs only work in the presence of insulin.
  B. Activation of PPAR receptors increases the movement of glucose into tissues and decreases hepatic glucose output.
III. Biguanide increases metabolism of glucose to lactate in the intestines and reduces hepatic gluconeogenesis.
IV. Sulfonylurea agents have a narrow margin of safety.
  A. Hypoglycemia can be seen even with therapeutic doses.
  B. Therapeutic doses are as follows:
    1. Glipizide in cats: 0.25 to 0.5 mg/kg PO BID
    2. Glyburide in cats: 0.625 mg/day PO
    3. Chlorpropamide in cats and dogs: 10 to 40 mg/kg/day PO
  C. Glipizide 0.1 mg/kg PO has caused hypoglycemia in dogs.
V. Thiazolidinedione agents have a fairly wide margin of safety, and no minimum toxic doses have been established in dogs and cats.
VI. With biguanide agents, GI signs can be seen with doses as low as 33 mg/kg PO in dogs, and metabolic acidosis may occur with large ingestions.

Clinical Signs

I. Sulfonylurea and thiazolidinedione agents
  A. Depression, weakness
  B. Anorexia
  C. Behavioral changes: confusion, disorientation
  D. Tremors and seizures from hypoglycemia
II. Biguanide agents
  A. Vomiting, diarrhea
  B. Lactic acidosis: weakness, abdominal pain, Kussmaul breathing
  C. Hypoglycemia: rare finding

Diagnosis

I. History of exposure to agents
II. Suspicious clinical signs
III. Sulfonylurea agents detected in plasma or urine

Differential Diagnosis

I. Sulfonylurea and thiazolidinedione agents: insulin overdose, insulinoma, hunting dog (exercise-related) hypoglycemia, primary hypoglycemia
II. Biguanide agents: GI irritants; diabetic ketoacidosis; uremic acidosis; toxicity associated with ingestion of aspirin, methanol, ethanol, ethylene glycol, isoniazid

Treatment and Monitoring

I. Sulfonylurea and thiazolidinedione agents
  A. Induce emesis in asymptomatic animals if ingestion occurred <30 minutes ago.
  B. Give activated charcoal 1 to 2 g/kg PO if <2 hours after exposure.
  C. Monitor blood glucose every 3 hours for 24 hours, then periodically for 72 hours, especially if chlorpropamide was ingested.
  D. Obtain baseline electrolytes.
    1. Chlorpropamide can cause hyponatremia.
    2. Repeat electrolytes in symptomatic animals.
  E. Feed frequent small meals.
  F. If hypoglycemia develops, then give 1 to 2 mL/kg of 25% dextrose IV and continue a 2.5% to 5% dextrose infusion IV until glucose returns to normal.
  G. Control tremors and seizures (see Chapter 22).
  H. Signs generally resolve within 48 hours.
II. Biguanide agents
  A. Induce vomiting if within 3 hours of exposure.
  B. Give activated charcoal 1 to 2 g/kg PO if within 6 hours of exposure.
  C. Food in the stomach decreases absorption of biguanide agents, so feed the animal.
  D. Control vomiting (as needed) in dogs with metoclopramide 0.2 to 0.4 mg/kg SC, IM TID or chlorpromazine 0.25 to 0.5 mg/kg SC, IM BID to TID.
  E. Begin IV therapy.
  F. Monitor blood gases for 48 hours if severe vomiting, diarrhea, or other clinical signs are present.
  G. Monitor electrolytes as needed.
  H. Continue treatment until clinical signs resolve, which is usually within 48 hours.

CALCIPOTRIENE

Sources

I. Synthetic Vitamin D_3 derivatives contain calcipotriene *(Dovonex),* calcipotriol *(Calcijex),* or calcitriol *(Rocaltrol).*
II. Topical agents (e.g., calcipotriene, calcipotriol) are used to treat psoriasis in humans.
III. Calcitriol is an adjunctive treatment for chronic renal disease and hypoparathyroidism in dogs and cats.
IV. Calcipotriene ointments are formulated in μg/g of product.
  A. Calcipotriene: 0.005% cream, ointment or scalp solution (50 μg/g)
  B. Tacalcitol: 0.0002% to 0.0004% ointment (2 to 4 μg/g)
V. Calcitriol is dosed in nanograms (2.5 to 3.5 ng/kg PO SID in dogs and cats).
  A. *Rocaltrol:* 0.25 and 0.5 μg capsules; 1 μg/mL in 15 mL bottles
  B. *Calcijex:* 1 μg/mL, 2 μg/mL in 1-mL ampules (injectable)

Action

I. Parathyroid hormone synthesis and secretion are suppressed.
II. Osteocalcin secretion in bone cells is stimulated.
III. Calcium (Ca) absorption is enhanced from the gut, and resorption of Ca from bones and kidneys is increased.
IV. Net result is a hypercalcemia and hyperphosphatemia.
V. ARF and soft tissue mineralization account for the clinical signs.
VI. Margin of safety is very narrow, and therapeutic doses of calcitriol have caused hypercalcemia.
VII. Any ingestion of calcipotriene or calcitriol warrants decontamination and monitoring.
VIII. Clinical signs have occurred with ingestion of calcipotriene at 10 μg/kg, and doses of 36 μg/kg have caused death.

Clinical Signs

I. Vomiting, anorexia, lethargy, depression
II. Polyuria, oliguria, anuria
III. Cardiac arrhythmias or sudden death from mineralization cardiac tissue

Diagnosis

I. History of exposure to agent
II. Compatible clinical signs
III. Supportive laboratory findings
  A. Hypercalcemia, hyperphosphatemia
  B. Elevated blood urea nitrogen (BUN), creatinine
  C. Hyposthenuria
IV. Radiography or ultrasonography: soft tissue mineralization in the kidneys and heart
V. Assays for vitamin D_3 (test for cholecalciferol rodenticides): do not detect calcipotriene in blood or tissues

Differential Diagnosis

I. Cholecalciferol rodenticide toxicity: see Chapter 124
II. Vitamin-D toxicosis
III. Hyperparathyroidism: see Chapter 43
IV. Hypercalcemia of malignancy: see Chapter 73

Treatment and Monitoring

I. Decontamination
  A. Induce emesis if <4 hours postingestion.
  B. Repeated doses of activated charcoal 1 to 2 g/kg PO TID are given for 24 hours.
II. Initial monitoring
  A. Obtain a biochemistry profile.
    1. If Ca, P, BUN, and creatinine are initially normal, then repeat the profile SID for 4 days.
    2. P tends to increase before Ca.
  B. If Ca, P, BUN, and creatinine are elevated, then begin therapy for hypercalcemia.
  C. Monitor Ca × P product; with values >60, potential exists for soft tissue mineralization.
III. Management of hypercalcemia
  A. Fluid diuresis at twice the maintenance rate using 0.9% saline IV
  B. Furosemide 2.5 to 4.5 mg/kg PO, SC, IM TID to QID
  C. Dexamethasone or prednisone 0.25 mg/kg PO, SC QID
IV. Specific antidotes
  A. Pamidronate *(Aredia)* 1.3 to 2.0 mg/kg is diluted in 0.9% saline and administered IV over a 2-hour period; this drug is preferred over salmon calcitonin.
  B. Calcitonin *(Calcimar)* 4 to 7 IU/kg SC TID may be tried.
  C. Pamidronate and calcitonin cannot be used concurrently because of the increased risk of soft tissue mineralization.
V. Aluminum hydroxide *(Amphojel)* 60 mg/kg PO TID for hyperphosphatemia
VI. After stabilization of Ca levels
  A. Wean off IV fluids while monitoring Ca, P, BUN, and creatinine SID.
  B. If BUN and creatinine remain elevated, then continue diuresis.
  C. If Ca starts to rise, then continue IV fluids and consider a second dose of pamidronate (usually within 5 to 7 days of the first dose).
  D. Gradually decrease furosemide and dexamethasone as long as animal remains asymptomatic.
  E. Monitor appetite.
  F. Monitor Ca and P SID for 5 to 7 days after values return to normal, then two to three times weekly for 2 weeks, then at 1 month postexposure.

5-FLUOROURACIL

Sources

I. Antimetabolite used to treat solar keratitis, skin cancers, and plantar warts in humans
II. Available as a cream, topical solution, or injectable
III. The most common brands
  A. *Efudex:* 5% cream or 2% solution
  B. *Fluoroplex:* 1% cream or solution

Action

I. 5-Fluorouracil destroys rapidly dividing cells.
II. It is converted to fluorocitrate, which inhibits the Krebs cycle, resulting in seizures.
III. Bone marrow stem cells can be destroyed, most likely by the metabolite FdUMP.
IV. It has a narrow margin of safety, so treat all ingestions seriously.
  A. Minimum lethal dose in dogs is 20 mg/kg PO.
  B. Trigger dose for decontamination and treatment is 8.6 mg/kg PO.

Clinical Signs

I. Dogs and cats appear to be more sensitive to the development of CNS signs (seizures, tremors) than humans.
II. Other signs listed in decreasing frequency include the following:
  A. Vomiting ± blood
  B. Lethargy
  C. Death
  D. Cardiac arrhythmias
  E. Respiratory distress
  F. Hypersalivation
  G. Cardiac arrhythmias
  H. Ataxia
  I. Disorientation
  J. Diarrhea ± blood
  K. Bone marrow suppression: if survives acute stages

Diagnosis

I. History of exposure to the agent
II. Suspicious clinical signs
III. No specific lesions or laboratory abnormalities
IV. Definitive diagnosis: difficult without history of ingestion

Differential Diagnosis

I. Other causes of hemorrhagic vomiting or seizures
II. Other toxicoses
  A. Metaldehyde
  B. Fluoroacetate
  C. Zinc phosphide
  D. Other antimetabolite agents: methotrexate, hydroxyurea, 6-mercaptopurine

Treatment and Monitoring

I. Induce emesis and give activated charcoal in asymptomatic animals, if the ingestion was within 1 hour.
II. Start GI protectants.
  A. Sucralfate
    1. Dogs: 0.5 to 1.0 g/25 kg PO BID to TID
    2. Cats: 250 to 500 mg PO BID to TID
  B. Dogs: misoprostol 1 to 3 µg/kg PO TID
  C. Dogs: metoclopramide 0.1 to 0.3 mg/kg IV for severe vomiting, but controversial because can cause additional neurologic signs
  D. Dogs: ondansetron 0.11 mg/kg IV slowly BID to QID for severe vomiting
III. Control seizures and tremors.
  A. Diazepam rarely effective
  B. Phenobarbital 3 to 30 mg/kg IV slowly
  C. Propofol 4 to 6 mg/kg IV or as continuous rate infusion at 0.1 to 0.6 mg/kg/min IV
  D. Inhalant anesthetic agents
IV. Supportive care
  A. IV fluid crystalloid therapy
  B. Thermoregulation for hyperthermia from prolonged seizures
  C. Butorphanol 0.2 to 0.4 mg/kg every 2 to 5 hours SC, IM, IV for pain
  D. Antibiotics for secondary infections
V. Filgrastim *(Neupogen)* 4 to 6 µg/kg SC SID for ≤5 days for bone marrow suppression
VI. Monitoring
  A. Obtain a baseline CBC and biochemistry profile.
  B. Repeat biochemistries SID until clinical signs resolve.
  C. Repeat CBC every 24 to 72 hours for 2 weeks.
VII. Prognosis guarded to poor if clinical signs develop

SKELETAL MUSCLE RELAXANTS

Sources

I. Numerous skeletal muscle relaxants exist, with a variety of actions and range of toxicities.
II. Baclofen *(Lioresal)* is one of the most common muscle relaxants encountered.
III. Baclofen is prescribed for the treatment of spasticity in humans with multiple sclerosis, spinal disorders, Huntington's chorea, and Parkinson's disease.

Action

I. Baclofen mimics gamma-aminobutyric acid (GABA) within the spinal cord and blocks excitatory responses to sensory input.
II. Overall effect is a flaccid paralysis of skeletal muscles.
III. It has a narrow margin of safety in most species.
  A. Clinical signs occur with ingestions as low as 1.3 mg/kg PO in dogs.
  B. Death may occur with ingestions of 8 to 16 mg/kg PO in dogs.

Clinical Signs

I. Vomiting, hypersalivation
II. Vocalizing, seizures, ataxia
III. Coma, depression
IV. Hypothermia
V. Cardiac arrhythmias
VI. Respiratory depression, apnea

Diagnosis

I. History of exposure to agent
II. Suspicious clinical signs
III. Baclofen detected in urine and serum

Differential Diagnosis

I. Barbiturates
II. Other skeletal muscle relaxants

III. Opioids
IV. Benzodiazepines
V. Botulism
VI. Ivermectin toxicosis
VII. Ionophores: monensin, lasalocid, salinomycin, narasin
VIII. Tick paralysis

Treatment and Monitoring

I. Decontamination is performed under veterinary supervision because of the potential for rapid onset of signs.
   A. Onset of action is possible 30 minutes postingestion or may be delayed for several hours.
   B. Induce emesis only with very recent ingestions in asymptomatic animals.
   C. Give activated charcoal 1 to 2 g/kg PO once; repeated doses are not beneficial.
II. Control seizures with diazepam 0.5 to 1.0 mg/kg IV slowly (see Chapter 22).
III. Maintain respiration; positive-pressure ventilation may be needed for several days in severe cases.
IV. Institute supportive care.
   A. Comatose or recumbent animals can become hypothermic.
   B. IV fluid diuresis enhances excretion of baclofen and helps maintain blood pressure.
   C. Cyproheptadine 1.1 mg/kg PO or rectally TID can be used in vocalizing dogs.
V. Clinical signs may require 3 to 4 days of treatment.
VI. Monitor serum glucose, liver enzymes, and electrolytes SID in animals with significant clinical signs.
VII. Monitor electrocardiograms and respirations until clinical signs resolve.
VIII. Prognosis is generally good if adequate ventilatory support is provided.
IX. Prognosis is guarded for animals with seizures.

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CHAPTER 128

Outdoor Hazards

Sharon M. Gwaltney-Brant

ANTIFREEZE

Sources

I. Antifreeze is most commonly formulated from ethylene glycol (EG), propylene glycol (PG), or methanol.
   A. EG is also present in brake fluid, photographic developing fluid, windshield deicer, ink, paint, industrial solvent and wood stains.
   B. PG is also found in a variety of food and pharmaceutical preparations, hydraulic fluid, cosmetics, and industrial solvents.
   C. Methanol is present in windshield washer fluid, as well as gasoline antifreezes.
II. Other ingredients that may be found in antifreezes include diethylene glycol, dipotassium phosphate, corrosion inhibitors, silicates, antifoaming agents, surfactants, dyes, and fragrances, but these compounds are generally present in low concentrations, are of relatively low toxicity, and are not clinically significant.

Action

I. EG, methanol, and PG produce inebriation and narcosis from the alcohol parent compound and aldehyde metabolic products.
II. EG, methanol, and PG are further metabolized to glycolic acid, formic acid, and lactic acid, respectively, which contribute to metabolic acidosis.
III. EG is further metabolized to oxalic acid, which binds with serum calcium to form calcium oxalate crystals in the kidney.
   A. Hypocalcemia and renal insufficiency result from the formation of calcium oxalate crystals.
   B. Rarely, calcium oxalate crystals may precipitate within the meningeal vessels of the central nervous system (CNS), resulting in profound and permanent CNS derangement.
IV. In cats, PG induces Heinz-body anemia by an unknown mechanism.

Clinical Signs

I. Signs from ingestion of EG, methanol, and PG occur within 40 to 60 minutes of exposure and include CNS depression, ataxia, vomiting, polyuria, and behavior changes (inebriation).
II. Ingestion of large amounts may cause severe CNS depression, coma, seizures, hypothermia, and severe acidosis.
III. Death is possible from hypoglycemia, respiratory depression, or aspiration.
IV. Signs generally improve over approximately 12 hours.
   A. With methanol and PG exposure, full recovery occurs in most cases.
   B. With EG, dogs may appear to have recovered for a short while.
   C. With EG, cats usually remain depressed.
V. With EG, severe acidosis occurs 4 to 6 hours after ingestion and results in tachypnea, vomiting, hypothermia, miosis, and profound depression.
   A. Cardiac arrhythmias, muscle fasciculations, and coma may develop.
   B. With EG, oliguric renal failure develops 12 to 36 hours after ingestion.
   C. Anorexia, vomiting, hypersalivation, lethargy, oral ulceration, oliguria, and anuria may occur.

Diagnosis

I. History of exposure to product
II. Consistent clinical signs
III. Ethylene glycol
   A. Ethylene glycol test
      1. Commercial kits detect levels ≥50 mg/dL and are reliable for dogs.
         a. Cats can develop toxicosis at <50 mg/dL, so false negatives are possible.
         b. False positives can occur if formaldehyde, metaldehyde, propylene glycol, glycerol, or diethylene glycol are present in the blood.
         c. Some commercial activated charcoal preparations contain PG or glycerol and cause false-positive results.
         d. Some injectable drugs (diazepam) contain PG.
         e. Methanol, ethanol, isopropanol, and fomepizole do not cause false positives.
      2. Laboratories in human hospitals can often run quantitative tests for EG on an urgent basis.
         a. These tests are specific for EG and there are no false positives if PG, metaldehyde, etc. are present.
         b. For dogs, levels >50 mg/dL are significant.
         c. For cats, any detectable level is significant.

B. Clinical laboratory results
   1. Early (within 12 hours) in clinical course
      a. Increased serum osmolality, metabolic acidosis, and decreased plasma bicarbonate may be found.
      b. Anion gap is high by 3 hours after ingestion, peaks at 6 hours, and remains increased for up to 48 hours.
      c. Hyperkalemia may be associated with acidosis.
      d. Hypocalcemia may be detected.
      e. Urine is usually isosthenuric.
      f. Calcium oxalate crystalluria occurs within 3 hours in cats and 4 to 6 hours in dogs.
      g. Absence of crystalluria does not rule out EG exposure.
   2. Late (24 to 72 hours) in clinical course
      a. Increased serum blood urea nitrogen (BUN) and serum creatinine occur.
      b. In cats, BUN and creatinine become elevated as early as 12 hours.
      c. Hyperkalemia may be associated with renal insufficiency.

C. Fluorescence testing
   1. Some antifreezes contain sodium fluorescein, which fluoresces if EG is present in vomitus or urine.
   2. Absence of fluorescence in urine or vomitus does not rule out the possibility of exposure.

D. Ultrasonography of the kidneys
   1. A "halo sign," an increase in cortical and medullar echogenicity with hypoechoic corticomedullary and central medullary regions, is highly suggestive of EG toxicosis.
   2. The presence of a halo sign indicates the presence of calcium oxalate crystals and warrants a grave prognosis.

E. Histopathology of kidneys
   1. Renal tubular degeneration and necrosis associated with calcium oxalate crystals
   2. Possible identification of calcium oxalate crystals under polarized light

IV. Propylene glycol
   A. Increased serum osmolality can occur with intravenously administered PG.
   B. No specific confirmatory tests are available that will provide timely results.

V. Methanol: serum methanol levels measured by some human hospitals

Differential Diagnosis

I. CNS effects of early methanol, PG, EG
   A. Other alcohol ingestion: ethanol, dipropylene glycol
   B. Marijuana toxicosis
   C. Ivermectin toxicosis
   D. Psychogenic drugs: tranquilizers, sedatives, antidepressants, etc.

II. Increased anion gap in EG: diabetic ketoacidosis, lactic acidosis (PG toxicosis)

III. Increased osmolality in EG: alcohol toxicosis

IV. Acute renal failure in EG
   A. Leptospirosis
   B. Nonsteroidal antiinflammatory drug toxicosis
   C. Grape or raisin toxicosis
   D. Lily toxicosis (cats)
   E. Cholecalciferol toxicosis
   F. Aminoglycoside toxicosis
   G. Hemolytic uremic syndrome

Treatment and Monitoring

I. Prevention of absorption
   A. Because of the rapid absorption and onset of signs following methanol, EG, and PG ingestion, oral decontamination must be done soon after exposure (within 20 to 40 minutes).
   B. Emesis may be induced in animals without severe neurologic signs.
   C. Apomorphine must be used with care as it may enhance CNS depression.
   D. Activated charcoal binds poorly with EG, methanol, and PG, and the risks of aspiration of charcoal may outweigh its benefits in this instance.

II. Management of alcohol toxicosis (inebriation, acidosis)
   A. Fluid diuresis with IV crystalloid solutions at two to three times maintenance promotes excretion of the parent alcohol.
   B. Acid-base and electrolyte abnormalities are corrected as needed.
      1. Sodium bicarbonate is administered according to the base deficit of the animal.
      2. For EG, correction of hypocalcemia with calcium gluconate or calcium chloride is indicated.
   C. Hypothermia or hyperthermia is managed as needed.
   D. For profoundly comatose animals, yohimbine 0.1 mg/kg IV has been successfully used as a general CNS stimulant.
   E. Monitor respiration, body temperature, heart rate and rhythm, hydration, and urine production carefully.
   F. For PG and methanol, general supportive care usually results in full recovery, with no residual adverse effects.

III. Prevention of calcium oxalate formation and renal failure in EG intoxication.
   A. Goal is to inhibit the metabolism of EG to its toxic metabolites, allowing excretion of the parent compound in urine via fluid diuresis.
   B. Dogs may be given fomepizole *(Antizol-Vet)* 20 mg/kg IV as a loading dose, followed by 15 mg/kg IV 12 and 24 hours later, and 5 mg/kg IV at 36 hours.
      1. Fomepizole inhibits alcohol dehydrogenase, reducing the amount of EG that is metabolized.
      2. Fomepizole is the treatment of choice for EG toxicosis in dogs.
   C. If fomepizole is unavailable, ethanol may be given to dogs, as described for the cat.
   D. Experimental studies have indicated there is a narrow window of opportunity (3 to 4 hours after ingestion) to successfully treat cats that have been exposed to EG.
      1. Ethanol (grade alcohol)

a. Constant rate infusion (CRI) is preferred over IV boluses to avoid fluctuations in CNS depression and acidosis.
b. Give 30% ethanol 1.3 mL/kg IV as a loading dose, followed by 0.42 mL/kg/hr IV as a CRI for 48 hours.
c. Boluses of 20% ethanol 5.5 mL/kg IV every 4 hours for five treatments, then QID for 4 treatments may also be used.
d. Ethanol contributes to acidosis, so monitor blood gases closely and use bicarbonate to manage any base deficits.
e. Ethanol competes with EG as a substrate for alcohol dehydrogenase, so it slows the metabolism of EG.

2. Fomepizole
a. Fomepizole is not approved for use in cats.
b. Give a loading dose of 125 mg/kg IV, followed by 31.25 mg/kg IV at 12, 24, and 36 hours.
c. All cats given lethal doses of EG and treated with fomepizole survived, compared with one third of cats treated with boluses of ethanol (Thrall et al., 2006).
d. One fomepizole-treated cat developed acute renal failure that was successfully treated with prolonged IV therapy (Thrall et al., 2006).

IV. Management of acute renal failure (see also Chapter 48)
A. Start IV fluid diuresis with crystalloid solutions at two times maintenance, or as needed to maintain hydration.
B. Antiemetics such as metoclopramide may be helpful.
1. Dogs: 0.1 to 0.4 mg/kg PO, SC, IM QID or 1 to 2 mg/kg/day IV as a CRI
2. Cats: 0.2 to 0.4 mg/kg PO, SC TID to QID or 1 to 2 mg/kg/day IV as a CRI
C. Consider diuresis with mannitol 0.25 to 0.5 g/kg IV over 15 to 20 minutes every 4 to 6 hours.
D. Peritoneal dialysis or hemodialysis has been used successfully in EG-intoxicated cats and dogs.
E. Renal transplantation may be considered in severe cases of chronic renal failure in stabilized animals.

HERBICIDES

Sources

I. Herbicides are commonly used for lawn care and agricultural purposes.
A. Agricultural formulations are more concentrated than residential products.
B. Table 128-1 summarizes several of the most commonly used herbicides in the United States.
II. With many of the modern herbicides, the solvents and surfactants in the products may account for most of their toxicity when compared with the active ingredients.

Action

I. Mechanisms vary with the specific herbicides (see Table 128-1).
II. The majority of the signs are secondary to the gastrointestinal (GI) irritation caused by the inert ingredients ("carriers").
III. Once liquid herbicides have dried on the plant, the likelihood of significant exposure to the animal is minimized, as most modern herbicides are internalized and translocated to plant roots.
IV. Paraquat is a vesicant that causes corrosive injury to alimentary tissues, skin, and corneas.
A. GI hemorrhage and perforation are possible.
B. Paraquat is readily absorbed, distributes widely in the body, and concentrates in the lung.
C. Paraquat undergoes cyclic oxidation-reduction reactions, resulting in the formation of oxygen-derived free radicals.
1. The high oxygen content of the lung provides ample substrate for free radical production.
2. Lipid peroxidation, inactivation of enzymes, DNA injury and damage to cell membranes result in cell necrosis, inflammation, and eventual fibrosis.
3. Regeneration of paraquat during the oxidation-reduction cycles results in further free-radical production.
4. Treatment with pure oxygen provides more fuel for the development of free radicals and accelerates the process.
D. Renal and hepatic injury develops from free-radical production in these tissues.

Clinical Signs

I. Expected clinical signs after exposure to major herbicides are summarized in Table 128-1.
II. Most signs are mild and self-limiting, and systemic toxicosis is not usually expected.
III. Paraquat may cause oral, esophageal, GI, dermal, or ocular irritation or ulceration.
A. Vomiting, diarrhea, abdominal pain
B. Polyuria, dehydration, azotemia in 48 to 72 hours as renal failure develops
C. Dyspnea from pulmonary edema (early) and pulmonary fibrosis (late), possibly leading to death
D. More insidious onset of pulmonary dysfunction with low levels of exposure

Diagnosis

I. History of exposure
II. Clinical signs, especially progressive pulmonary dysfunction
III. Measurement of plasma paraquat concentrations
IV. Measurement of urine paraquat levels up to 48 hours after ingestion
V. Necropsy samples
A. Histopathologic examination of the lungs reveals necrosis and fibrosis.
B. Lung, liver, and kidney can be analyzed for the presence of paraquat.

TABLE 128-1

Toxicological Features of Commonly Used Herbicides

HERBICIDE	USAGE	TOXICITY	MECHANISM OF ACTION	CLINICAL EFFECTS
2,4-D (2-chloro-4-phenoxyacetic acid) MCPA (4-chloro-2-methylphenoxyacetic acid) MCPP (2-methyl-4-chlorophenoxypropanoic acid)	Broadleaf herbicides Used on lawns and commercial properties 2,4-D is the most commonly used herbicide in United States Residues on treated grass: 25-75 ppm; rapidly dissipate after several days MCPA and MCPP are rarely used alone and are often combined with 2,4-D.	Severe toxicosis is unlikely from dilute products applied for residential use Rare systemic toxicities are related to ingestion of concentrates by dogs Dogs are more susceptible owing to poor excretion of organic acids No observable effects occurred from 2,4-D at oral doses of 1-20 mg/kg in dogs or from MCPA 1 mg/kg, and 6 ppm in diet for 1 year	Direct GI irritation Decreased chloride conductance in myocytes	Small exposures: vomiting Larger exposures: vomiting, diarrhea Massive exposures (rare): depression, ataxia, skeletal muscle rigidity (myotonia), mild tremors, spasticity, opisthotonos, anorexia, alimentary tract ulcers (may be related to carriers) CNS depression and coma in lethal exposures (very rare)
Glyphosate (N-[phosphonomethyl] glycine)	Nonselective herbicide Second most widely used herbicide in the United States Residues on grass following application = 1-100 ppm	Very wide margin of safety in animals Toxicity is related to surfactant carriers that can comprise up to 15% of formulated products.	Direct GI irritation from surfactants	Hypersalivation, vomiting, diarrhea, anorexia, lethargy Fluid and electrolyte abnormalities with protracted vomiting and/or diarrhea
Diquat (1,1′-ethylene-4,4′bipyridylium dibromide)	Dipyridyl herbicide related to paraquat Nonselective desiccant herbicide	Poor absorption No sequestration in lungs (unlike paraquat) Low concentrations in formulated products Systemic toxicosis unlikely	Can form free radicals and cause tissue necrosis Target organs are GI tract, liver, kidneys. GI irritation from carriers possible	Hypersalivation, vomiting, diarrhea, anorexia, lethargy Fluid and electrolyte abnormalities with protracted vomiting and/or diarrhea Massive exposures (very rare): corrosive oral injury, myocardial necrosis, seizures, coma, renal injury, hepatic injury
Dicamba (3,6-dichloro-2-methoxybenzoic acid)	Post-emergent broadleaf herbicide Often used in combination with other herbicides, such as 2,4-D and MCPP	Very low toxicity in mammals No observable effects at 50 ppm in daily diet for 2 years (dogs)	GI irritation from surfactant carriers	Hypersalivation, vomiting, diarrhea, anorexia, lethargy Fluid and electrolyte abnormalities with protracted vomiting and/or diarrhea
Pendimethalin (N-[1-ethylpropyl]-3,4-dimethyl-2,6-dinitrobenzeneamine) Prodiamine (2,6-dinitroaniline)	Most widely used pre-emergent herbicide in residential areas	Very low toxicity in mammals No observable effects at 2.5 mg/kg/day for 2 years (dogs)	GI irritation from surfactant carriers Pendimethalin: dye can stain hair coats	Hypersalivation, vomiting, diarrhea, anorexia, lethargy Fluid and electrolyte abnormalities with protracted vomiting and/or diarrhea Orange-yellow discoloration of haircoats Prodiamine: similar to pendimethalin but less likely to stain haircoats

GI, Gastrointestinal; *CNS*, central nervous system.

Differential Diagnosis

I. Paraquat
   A. Other causes of GI injury: other corrosives (alkalis, acids, etc.), uremic stomatitis, thallium toxicosis
   B. Other causes of renal failure
II. For 2,4-D in dogs, other causes of myositis, myopathy: myasthenia gravis, macadamia nut toxicosis, sewage-sludge fertilizer *(Milorganite)* exposure, etc.
III. Other herbicides: other causes of GI upset

Treatment and Monitoring

I. Paraquat
   A. Aggressive treatment is required as quickly as possible after exposure.
   B. Decontamination is undertaken.
      1. Because of its corrosive nature, induction of emesis is not recommended.
      2. Gastric lavage is performed under anesthesia, using a cuffed endotracheal tube.
      3. Activated charcoal is effective at adsorbing paraquat.
      4. Bathe off dermal exposures with liquid dishwashing detergent.
   C. IV fluids are used for general support, and forced diuresis with IV crystalloids and furosemide (2 mg/kg IV) may enhance elimination.
   D. Charcoal hemoperfusion using a Hemocol cartridge (113 to 156 mL/min IV) improves the chance of survival.
   E. GI protectants are indicated in most cases.
      1. Slurries of sucralfate 0.25 to 1 g PO TID (dogs)
      2. Famotidine 10 to 20 mg PO SID (or other acid reducers)
   F. Supportive care is required.
      1. Oxygen supplementation is contraindicated, as it hastens pulmonary injury.
      2. Pain medication may be required.
         a. Buprenorphine
            (1) Dogs: 0.005 to 0.02 mg/kg IM, IV, SC BID to QID
            (2) Cats: 0.005 to 0.01 mg/kg IM, IV, SC BID to QID
         b. Fentanyl patch
            (1) Dogs <10 kg, cats: 25 µg/hr
            (2) Dogs 10 to 20 kg: 50 µg/hr
            (3) Dogs 20 to 30 kg: 75 µg/hr
            (4) Dogs >30 kg: 100 µg/hr
      3. Manage renal insufficiency.
      4. Institute topical management of dermal or ocular injury.
   G. Monitor cardiovascular function, serum renal and hepatic values, hematologic parameters, and acid-base status.
II. Myotonia from 2,4-D
   A. Forced alkaline diuresis with sodium bicarbonate (1 to 2 mEq/kg) per liter of crystalloid solutions may enhance elimination (Osweiler, 1996).
   B. Most cases resolve within 24 hours with no residual effects.
III. GI upset from most herbicides
   A. Most cases are self-limiting and resolve without specific treatment.
   B. Withholding food and water for a few hours is often helpful.
   C. For protracted vomiting, antiemetics (chlorpromazine 0.5 mg/kg IV, IM, SC TID to QID) may be used.
IV. Dermal decontamination
   A. Wash with liquid dishwashing detergent.
   B. For haircoats stained from pendimethalin, use waterless hand cleaners (e.g., *GOJO*) on affected area, followed by shampoo and rinse.

HYDROCARBONS

Sources

I. Hydrocarbons encompass a huge array of vastly different products, ranging from those of high volatility (gasoline) to those of very low volatility (waxes).
II. The relative toxicity of hydrocarbons is related to their volatility, with toxicity increasing as the agent becomes more volatile.
   A. Low-volatility hydrocarbons (waxes, petroleum jelly, mineral oil, etc.) are of very low toxicity.
   B. High-volatility hydrocarbons (e.g., propane, gasoline, kerosene, diesel oil) have more potential to cause toxicity.
   C. Recently, some shoe and boot waterproofing sprays containing a variety of hydrocarbons, including hexane, have caused acute respiratory distress syndrome in pets.
III. Hydrocarbon products are found in motor vehicle fuels, as lubricants, and as solvents for paints, pesticides, and medications.
IV. Exposure of pets to hydrocarbons frequently occurs in or around the garage area.

Action

I. Hydrocarbons are irritants, and the primary toxic effect is irritation.
II. Contact of highly volatile hydrocarbons with the skin of dogs and cats may result in dissolution of dermal lipids, localized dermatitis, and chemical burns.
III. Ingestion of highly volatile hydrocarbons frequently results in immediate vomiting.
IV. The primary life-threatening effect from hydrocarbons is aspiration pneumonia, particularly with hydrocarbons of high volatility (gasoline, kerosene, lighter fluid).
V. Inhalation of highly volatile hydrocarbon fumes can result in CNS depression from a direct physicochemical interaction with neuronal membranes.
VI. Renal and hepatic injury after hydrocarbon exposure is rare and may arise from formation of toxic metabolites.
VII. Some hydrocarbons can sensitize the myocardium to endogenous catecholamines, resulting in arrhythmias.

Clinical Signs

I. Signs of oral irritation: hypersalivation, pawing at muzzle
II. Vomiting, retching

III. Gagging, coughing, dyspnea, and cyanosis if aspiration has occurred
IV. Acute respiratory distress within minutes after exposure to aerosolized waterproofing sprays for boots and shoes
V. Abdominal pain, diarrhea
   A. Ingestion of heavier oils (e.g., lamp oil, motor oil) may be followed by oily diarrhea within a few hours and is often associated with fecal incontinence.
   B. Cramping from rapid movement of oily compounds through the GI tract may manifest as abdominal pain.
VI. CNS depression, ataxia, behavioral changes after exposure to high concentrations of highly volatile hydrocarbon fumes
   A. Signs occur within minutes of exposure and resemble ethanol intoxication.
   B. Cardiac arrhythmias may also occur.
VII. Local erythema, irritation or ulceration at the site of dermal exposure

Diagnosis

I. History of exposure
II. Characteristic hydrocarbon odor to vomitus, breath, skin
III. Mixing vomitus with water: hydrocarbons floating to the surface
IV. Radiography of lungs
   A. May reveal fine perihilar densities and extensive infiltrates in ventral lung fields
   B. May have delayed onset up to 12 hours
   C. Progression of radiographic abnormalities during first 3 to 4 days, then gradual clearing

Differential Diagnosis

I. Respiratory signs: other causes of pneumonia and pneumonitis (e.g., infectious, toxic)
II. GI signs: other causes of GI irritation (e.g., infectious, dietary indiscretion)
III. Dermal signs: other chemical burns, dermatitis, demodicosis, etc.

Treatment

I. Therapy for aspiration
   A. Supplemental oxygen, mechanical ventilation
      1. Positive-pressure ventilation must be used with care because of the potential for pneumomediastinum and pneumothorax.
      2. Closed ventilation systems must be purged frequently, as the lungs are a primary route of hydrocarbon elimination.
   B. Cage rest
   C. Prophylactic antibiotics controversial
   D. Corticosteroids contraindicated
II. Decontamination
   A. Because of the risk of aspiration, decontamination of oral hydrocarbon exposure by induction of emesis is contraindicated.
   B. If gastric decontamination is necessary, gastric lavage may be performed.
   C. Bathing with warm water and a liquid dishwashing detergent are helpful for dermal exposures.
   D. Institute topical treatment of chemical burns (see Chapter 134).

TREMOROGENIC MYCOTOXINS

Sources

I. Several hundred toxins produced by several *Penicillium* spp. have been identified.
II. Penitrem A and roquefortine are the mycotoxins most commonly associated with toxicosis in pets (notably dogs).
III. Ingestion of moldy foods, compost, carcasses, and other decaying organic material is the most common source of exposure.

Action

I. The exact mechanism is unknown.
II. It is thought to involve inhibition of inhibitory CNS neurotransmitters, particularly glycine.

Clinical Signs

I. Signs begin within 30 minutes to several hours of ingestion.
II. Early signs include restlessness, hypersalivation, panting, and mild to moderate muscle tremors.
III. Later signs include severe tremors, hyperesthesia, seizures, hyperthermia, dehydration, metabolic acidosis, rhabdomyolysis, coma, and death.

Diagnosis

I. History of potential exposure is helpful.
II. Compatible clinical signs are supportive.
III. Analysis of suspect feed, gastric contents, and vomitus can confirm presence of penitrem A or roquefortine.
IV. Turnaround time limits usefulness of these analyses in acute situations.

Differential Diagnosis

I. Strychnine
II. Metaldehyde
III. Methylxanthines
IV. Anticholinesterase insecticides
V. Pyrethroids
VI. Organochlorine insecticides
VII. Nicotine
VIII. *Brunsfelsia* spp.: yesterday-today-tomorrow plant, lady of the night plant, kiss-me-quick plant

Treatment

I. Control tremor and seizures.
   A. Diazepam 0.5 to 2 mg/kg IV to effect for seizures and hyperesthesia
   B. Methocarbamol 50 to 220 mg/kg IV slowly (maximum 330 mg/kg/day) for tremors
   C. Phenobarbital 3 mg/kg IV to effect, if unresponsive to diazepam and methocarbamol
II. Minimize intake.
   A. Emesis in asymptomatic animals

B. Sedation/anesthesia and gastric lavage in symptomatic animals
C. Activated charcoal with a cathartic

III. Provide supportive care.
A. Intravenous fluid therapy with crystalloids
B. Management of hyperthermia as needed
C. Correction of electrolyte and acid-base disorders, as needed

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CHAPTER 129

Illicit Human Drugs

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DEPRESSANTS

Barbiturates

Sources

I. Sources include the following:
   A. Amobarbital *(Amytal),* aprobarbital *(Alurate)*
   B. Butabarbital *(Busodium, Butalan, Butisol)*
   C. Mephobarbital *(Mebaral)*
   D. Pentobarbital *(Nembutal),* phenobarbital *(Solfoton, Luminal, Barbita)*
   E. Secobarbital *(Seconal)*
II. They are classified by their onset and duration of action.
   A. Short-acting drugs (pentobarbital, secobarbital) have an onset of 10 to 15 minutes and a duration of 3 to 4 hours.
   B. Intermediate-acting drugs (amobarbital, aprobarbital, butabarbital) have an onset of 45 to 60 minutes and a duration of 6 to 8 hours.
   C. Long-acting drugs (mephobarbital, phenobarbital) have an onset of 1 hour and a duration of 10 to 12 hours.
III. Forms include capsules, tablets, liquid, and suppositories.
IV. Street names are barbs, downers, red devils, goof balls, yellow jackets, block busters, pinks, reds and blues, and Christmas trees.
V. Secondary toxicosis can occur via ingestion of the carcass of an animal euthanized with pentobarbital.

Action

I. The principal effect of barbiturates is depression of the central nervous system (CNS) through interference with impulses to the cerebral cortex.
   A. Activation of inhibitory gamma-aminobutyric acid (GABA) receptors
   B. Inhibition of the excitatory glutamate receptors
II. The oral median lethal dose (LD_{50}) for phenobarbital in dogs is 150 mg/kg.
III. The minimum oral lethal dose of phenobarbital in cats is 125 mg/kg.
IV. Coma can occur with doses of 50 to 100 mg/kg PO (long-acting barbiturates).
V. These drugs may interact with other drugs.
   A. Accelerate clearance of certain drugs by increasing cytochrome p450 levels
   B. Additive effect with other compounds causing sedation
   C. Potentiate respiratory depression from tricyclic antidepressants
   D. Prolong effects of monoamine oxidase (MAO) inhibitors

Clinical Signs

I. Common signs: CNS depression, ataxia, incoordination, weakness, disorientation, dilated pupils
II. Possible signs with severe intoxication: respiratory depression, recumbency, coma, hypothermia, death
III. Excitement in some animals
IV. Tachycardia or bradycardia
V. Possible hepatotoxicity with chronic ingestion

Diagnosis

I. History of exposure and compatible clinical signs
II. Barbiturates detected in stomach contents, blood, urine, or feces

Differential Diagnosis

I. Other CNS depressants: alcohols (ethanol, methanol), opioids, benzodiazepines, phenothiazines, marijuana, ethylene glycol, muscle relaxants (baclofen), avermectins (especially ivermectin), amitraz
II. Other systemic conditions: hypoglycemia, hypotension

Treatment and Monitoring

I. Induce emesis if exposure was recent and the animal is asymptomatic.
II. Gastric lavage can be considered if emesis is contraindicated and the dose is >50 mg/kg.
III. Activated charcoal can decrease the duration of clinical effects.
   A. Repeated doses of activated charcoal (1 to 2 g/kg PO BID to TID) with a cathartic must be administered carefully to prevent aspiration.
   B. Magnesium-containing cathartics are avoided because excess magnesium may be absorbed.
IV. IV fluids are given for hypotension, and positive-pressure ventilation or oxygen supplementation may be need for respiratory abnormalities.
V. Alkaline diuresis may promote elimination in the urine (only recommended for long-acting barbiturates).

VI. Monitor liver enzymes with chronic ingestions or in animals with pre-existing hepatic dysfunction.
VII. Prognosis is good in acute ingestions if adequate cardiovascular and ventilatory support is provided.

Benzodiazepines

Sources

I. Benzodiazepines are prescription antianxiety, anticonvulsant, sedative drugs that are Schedule IV controlled substances.
II. Most have an "-azepam" or "-zolam" suffix.
   A. Examples: lorazepam *(Ativan),* clorazepate *(Tranxene),* prazepam *(Centrax),* clonazepam *(Klonopin),* flurazepam *(Dalmane),* triazolam *(Halcion),* chlordiazepoxide *(Librium),* halazepam *(Paxipam),* temazepam *(Restoril),* oxazepam *(Serax),* diazepam *(Valium),* alprazolam *(Xanax)*
   B. Flunitrazepam *(Rohypnol):* frequently used as a "date-rape" drug; not legal in the United States
III. Street names include downers, V *(Valium),* rophies, roofies, roach, and rope *(Rohypnol).*

Action

I. They bind to benzodiazepine receptors in the CNS, kidneys, liver, heart, and lungs, with potentiation of the GABA response.
II. They are rapidly and well absorbed orally.
III. These drugs are metabolized in the liver, conjugated with glucuronide, and eliminated in urine.
   A. In dogs, diazepam has a half-life of 2.4 hours, and its active metabolite (nordiazepam) has a half-life of 2.85 hours.
   B. In cats, the half-life of diazepam is 5.46 hours and of nordiazepam it is 21.3 hours.
IV. A wide margin of safety exists between symptomatic and lethal doses.

Clinical Signs

I. Low doses: ataxia, CNS depression
II. High doses: tremors, seizures
III. Possible hypothermia
IV. Vocalization, anxiety, excitation possible at therapeutic dosages

Diagnosis

I. Suspicious history and clinical signs
II. Benzodiazepines (or metabolites) identified in urine or blood

Differential Diagnosis

I. Other CNS depressants: alcohols (ethanol, methanol), opioids, barbiturates, phenothiazines, marijuana; ethylene glycol, muscle relaxants (e.g., baclofen), avermectins (especially ivermectin), amitraz
II. Other systemic conditions: hypoglycemia, hypotension

Treatment

I. Ingestion of low doses (<20 mg/kg diazepam PO in a healthy dog) requires monitoring and protection of the animal from injury (e.g., falling down stairs, off furniture).
II. Decontamination may be effective, especially with large exposures.
III. Low doses of acepromazine may effectively calm animals exhibiting excitation.
IV. Flumazenil *(Romazicon)* is an antidote (competitive blocker) that can be administered if signs are severe.
   A. Dose is 0.1 mg/kg IV in dogs and cats.
   B. Use with care in animals that are prone to seizures, because it may exacerbate seizures.
V. Institute symptomatic and supportive care for cardiovascular abnormalities, hypothermia, etc.

Gamma Hydroxybutyrate

Sources

I. Gamma hydroxybutyrate (GHB) is a naturally occurring CNS depressant that is structurally related to GABA and was developed as an anesthetic agent.
II. Sodium oxybate *(Xyrem)* has limited legal use in the United States as a sleep aid.
III. It is produced as clear liquid, white powder, tablet, and capsule.
IV. GHB may be illicitly manufactured from gamma-butyrolactone (GBL) and 1,4-butanediol (BD); the latter is found in acetone-free nail polish remover, paint strippers, and adhesives.
V. Street names include G, grievous bodily harm, Georgia home boy, liquid ecstasy, liquid x, scoop, and goop.

Action

I. Structurally related to GABA
   A. Acts as an inhibitory neurotransmitter on dopaminergic neurons
   B. Reduces dopaminergic activity
   C. Stimulates dopamine production
II. Rapidly absorbed
   A. Onset of signs is within 10 to 30 minutes.
   B. Signs may last 6 to 12 hours.
III. GBL and BD are both metabolized to GHB (in humans).
IV. Animal poisonings are not commonly reported.

Clinical Signs

I. Vomiting
II. Muscle weakness, depression
III. Bradycardia, respiratory depression

Diagnosis

History of exposure and compatible clinical signs

Differential Diagnosis

I. Other CNS depressants: see discussion under Barbiturates
II. Other systemic conditions: hypoglycemia, hypotension

Treatment

I. Emesis is not recommended owing to the rapid onset of signs and the risk of aspiration.
II. Activated charcoal (1 to 2 g/kg PO) may be beneficial.
III. Atropine (0.02 to 0.04 mg/kg IV, IM, SC) is indicated for bradycardia.
IV. Some animals may require ventilatory support.

Marijuana *(Cannabis sativa)*

Sources

I. The entire plant is toxic and generally available in three forms.
   A. Dried herb: composed of top leaves and buds
   B. Resin (hash or hashish): extracted from the buds and flower heads
   C. Sticky liquid (hash oil): prepared from the resin
II. Cannabinoids, such as dronabinol *(Marinol)* and nabilone *(Cesamet)* are prescribed in humans as antiemetics for chemotherapy patients and to decrease intraocular pressure with glaucoma.
III. Marijuana extract *(Sativex)* is used to treat multiple sclerosis in Europe and Canada.
IV. Street names include hemp, pot, grass, Mary Jane, sinsemilla, hash, hashish (may contain other drugs), Bhang, Ganja, charas, Thai stick, reefer, and wacky-backy.

Action

I. Δ-9-Tetrahydro-cannabinol (THC) is considered the primary toxic resin, although other compounds are present.
II. THC activates cannabinoid receptors in the cerebrum and causes the brain to misinterpret nerve impulses from the different sense organs.
III. THC interacts with neurotransmitters and neuromodulators to stimulate dopamine release and enhances GABA turnover.
IV. THC is metabolized by the liver, excreted in bile, and enterohepatic recirculation occurs.
V. Because it is lipid soluble, it has a long half-life.
VI. Behavioral effects are seen with THC doses of approximately 3 mg/kg PO in dogs.
VII. Lethal dose has not been established; dosages of 3 to 9 g/kg PO have not been lethal in dogs.

Clinical Signs

I. THC has biphasic clinical signs, with euphoria followed by depression.
II. Signs include nervousness and disorientation progressing to depression that may last for 18 to 72 hours.
III. Mydriasis, nystagmus, ataxia, and recumbency have been described.
IV. Vomiting, diarrhea, tremors, and respiratory difficulty can occur.
V. Usually bradycardia occurs, although occasionally tachycardia develops.
VI. Hypothermia may also occur.
VII. Exposure is rarely fatal, although death is possible in severe cases.

Diagnosis

I. History of exposure and compatible clinical signs are suggestive.
II. Marijuana may be identified in urine, but time from ingestion, concurrent water consumption, and the amount ingested can complicate the diagnosis.

Differential Diagnosis

I. Other CNS depressants: see discussion under Barbiturates
II. Other systemic conditions: hypoglycemia, hypotension

Treatment and Monitoring

I. Decontamination (emesis, activated charcoal) is indicated, especially with large exposures.
   A. Effectiveness of emesis may be limited owing to the antiemetic properties of cannabis.
   B. Repeated doses of activated charcoal (cathartic with first dose) can hasten recovery time.
      1. Give an initial loading dose of 1 to 2 g/kg followed by 0.5 to 1.0 g/kg PO TID for 24 hours in symptomatic animals.
      2. Use caution with administration to recumbent animals because of the risk of aspiration.
II. With ingestion of low doses, protect the animal from injury (e.g., falling down stairs, off furniture).
III. Diazepam may be effective in animals with excitation.
IV. In nearly all cases, effects wear off with little or no permanent damage.

OPIOIDS

Sources

I. Opioids are CNS drugs originally derived from the poppy plant *(Papaver somniferum)*.
II. They are classified by their activity at different opioid receptors.
   A. Agonists: apomorphine, hydromorphone, codeine, meperidine, fentanyl, methadone, morphine, oxycodone, hydrocodone, oxymorphone
   B. Partial agonists: buprenorphine, butorphanol
   C. Antagonists: naloxone, naltrexone
III. Street names include the following:
   A. Morphine: M, morph, Miss Emma
   B. Heroin: smack, skag, hammer, H, horse, rock, white, slow, Harry cone, China white
   C. Codeine: T-threes, schoolboy
   D. Methadone: dollies
   E. Hydromorphone: dillies

Action

I. Opioid receptors are present in the CNS, gastrointestinal (GI) tract, heart, kidneys, vas deferens, pancreas, fat cells, lymphocytes, and adrenal glands.
II. The mu receptor is the most important therapeutic opioid receptor.
   A. Mu_1 is associated with analgesia.
   B. Mu_2 is associated with respiratory depression.

III. Opioids are well absorbed from the GI tract.
IV. Peak plasma levels depend on the individual compound, but in general are as follows:
  A. When given IV: 5 minutes
  B. When given IM: 10 minutes
  C. When taken PO: 1 to 2 hours
V. They are metabolized in the liver, undergo enterohepatic recirculation, and are conjugated with glucuronic acid (which may account for the sensitivity of cats to them).
VI. Toxic doses are as follows:
  A. Morphine
    1. Minimum lethal doses: 210 mg/kg SC (dogs) and 40 mg/kg SC (cats)
    2. LD_{50} in dogs: 133 mg/kg IV
  B. Heroin minimum lethal doses: 25 mg/kg SC (dogs) and 20 mg/kg PO (cats)
  C. Codeine LD_{50} in dogs: 69 mg/kg IV

Clinical Signs

I. Common signs: vomiting, hypersalivation, ataxia, depression, miosis
II. Bradycardia or tachycardia
III. Severe cases: respiratory depression, hypothermia, tremors, seizures, coma
IV. Possible vocalizing
V. Excitation in some cats

Diagnosis

I. History of exposure and compatible clinical signs are suggestive.
II. If no improvement occurs after one or two doses of naloxone, reconsider the diagnosis.
III. Morphine can be detected in urine and serum.

Differential Diagnosis

I. Other CNS depressants: see section on Barbiturates
II. Other systemic conditions: hypoglycemia, hypotension

Treatment and Monitoring

I. Decontamination (emesis, activated charcoal) is indicated, especially with large exposures.
  A. Avoid apomorphine because it is an opioid.
  B. Give activated charcoal at 1 to 2 g/kg PO followed by repeated doses of activated charcoal at half the original dose BID to TID.
  C. Administer a cathartic with the first dose.
II. Antidote is naloxone 0.1 to 0.2 mg/kg IV, repeated as needed (short half-life).
III. Respiratory and cardiac function must be closely monitored.
  A. Assess blood gas status.
  B. Noncardiogenic pulmonary edema is possible.
  C. IV fluids are given for hypotension, and ventilatory support may be needed.
IV. Prognosis is good if respiratory and cardiovascular systems are adequately supported, but guarded in animals with seizures.

HALLUCINOGENS

Sources

I. Lysergic acid diethylamide (LSD)
  A. Forms include tablets, thin gelatin squares, impregnated paper, and sugar cubes.
  B. LSD is found naturally in morning glory seeds (e.g., *Ipomoea violacea*, *Rivea corymbosa*).
  C. Street names include acid, boomers, yellow sunshines, microdots, dots, cube, sugar cube, window pane (thin gelatin squares), and blotter acid.
  D. Toxicosis in animals is not commonly reported.
II. Psilocybin mushrooms
  A. They include mushrooms in the genera *Psilocybe*, *Panaeolus*, *Gymnopilus*, *Conocybe*, and some *Stropharia* spp.
  B. Hallucinogenic mushrooms can be found fresh, dried, brewed in tea, packaged in capsules, and added to cigarettes or marijuana.
  C. Frequently, they are covered in chocolate, and signs seen in animals are most likely from the mushrooms, not the chocolate.
  D. Street names include shrooms, magic mushrooms, and caps.
III. Phencyclidine (PCP)
  A. It is a dissociative anesthetic.
  B. Although it comes as a white crystalline powder (capsules, tablets), its most common form is a liquid.
  C. Cigarettes, marijuana joints, parsley, mint leaf, and basil are often dipped in liquid PCP.
  D. Street names include angel dust, boat, love boat, hog, embalming fluid (mixed with ether, formaldehyde, and methanol), rocket fuel, dummy dust, peace, supergrass, and zombie.
  E. Marijuana joints dipped in liquid PCP have been called wet-stick, amp, wet, sherm, and happy stick.
  F. Toxicosis in animals is not commonly reported.

Action

I. LSD affects multiple sites in the CNS, such as serotonin receptors (where it can be both stimulatory and inhibitory), and it is rapidly metabolized.
II. Psilocybin is the most common active agent in hallucinogenic mushrooms.
  A. Psilocybin is metabolized to psilocin, a hallucinogen that is structurally similar to serotonin.
  B. The hallucinogenic content of individual mushrooms varies widely; a dried mushroom contains about 0.2% to 0.4% psilocybin.
  C. Clinical signs are usually seen within 20 to 60 minutes after ingestion, although they can be delayed up to 3 hours.
  D. Effects usually last 2 to 4 hours, although there are reports of effects lasting 15 hours.
III. PCP is poorly absorbed from the stomach, but well absorbed in the relatively alkaline environment of the intestines.
  A. Absorbed PCP can be secreted into the stomach and reabsorbed in the intestines.

B. PCP has multiple effects on many neurotransmitters.
   1. GABA inhibition
   2. Anticholinergic and sympathomimetic effects
   3. Alpha-adrenergic stimulation
   4. Binds to opiate receptors

C. It is extensively metabolized in the liver in dogs, and doses of 2.5 to 10 mg/kg PO can result in clinical signs.

D. PCP is predominately excreted unchanged in the urine of cats, and clinical signs are seen at dosages of 1.2 to 12 mg/kg PO.

Clinical Signs

I. Signs vary greatly.
II. Disorientation, ataxia, tachycardia, apprehension, hyperesthesia, hypertension, and tremors are possible.
III. With psilocybin mushrooms, vomiting, vocalization, mydriasis, and hyperactivity have been reported in dogs.
IV. PCP exposure may also result in coma, seizures, hypotension or hypertension, and muscular rigidity.
V. Dogs may exhibit grimacing, jaw snapping, and blank stares with PCP.

Diagnosis

I. Known exposure with compatible clinical signs is suggestive.
II. Assays are difficult because of rapid metabolism of these agents.
   A. LSD may be detected in urine, serum, and feces.
   B. PCP may be detected in urine.

Differential Diagnosis

I. Other illicit substances: both stimulants and depressants
II. Other substances that increase serotonin: antidepressants, selective serotonin reuptake inhibitors, MAO inhibitors, 5-hydroxytryptophan, L-tryptophan, tricyclic antidepressants, avermectins, ketamine

Treatment

I. It depends on the clinical signs.
II. Decontamination (emesis, activated charcoal) is effective with psilocybin exposure, and activated charcoal may reduce GI recirculation of PCP.
III. LSD is rapidly metabolized, so most exposures are self-limiting and decontamination is not beneficial.
IV. Fluid therapy may enhance elimination of PCP in the cat.
V. Sensory stimulation should be minimized.
VI. Cyproheptadine (a serotonin blocker) at 1.1 mg/kg PO or rectally may be effective for psilocybin exposure.
VII. Diazepam has been recommended for signs of apprehension and aggression.
   A. Acepromazine is avoided with PCP exposures, as it may exacerbate anticholinergic effects and produce hypotension.
   B. Acepromazine may be used for treating psilocybin toxicosis.
VIII. In severely affected animals, barbiturates or general anesthesia may be needed.

STIMULANTS

Amphetamines

Sources

I. Methamphetamine or methylamphetamine *(Methedrine, Desoxyn)*
II. Dexamphetamine or dextroamphetamine *(Dexedrine)*
III. Amphetamine *(Benzedrine, Adderall)*
IV. 3,4-methylenedioxymethamphetamine (Ecstasy, MDMA): sometimes classified as a hallucinogen, although structurally related to amphetamine
V. Methylphenidate *(Ritalin),* ephedrine
VI. Street names: speed, bennies, meth, crank, crystal, chalk, snow seals (cocaine and amphetamine), b-bombs, aimies (amphetamine and amyl nitrite), ice

Action

I. Cause release of catecholamines from adrenergic nerve endings and act as dopamine excitatory receptor agonist
II. Potential for CNS stimulation: methamphetamine > dexamphetamine > amphetamine
III. Secondary effects on the serotonergic system: serotonin release with MDMA
IV. Inhibit MAO
V. Rapidly absorbed, onset delayed with sustained release preparations
VI. Highly lipophilic, cross the blood brain barrier
VII. Metabolized in the liver, excreted in urine
VIII. Half-life in dogs: 6.3 hours with urine pH of 7.5, 3.67 hours with urine pH of 5.96
IX. Oral LD_{50} in dogs
   A. Amphetamine sulfate: 20 to 27 mg/kg PO
   B. Methamphetamine hydrochloride: 9 to 11 mg/kg PO
X. Possible signs in dogs at therapeutic doses (unpublished ASPCA Poison Control Center data, 2006)
XI. Signs with doses of methylphenidate and *Adderall* <1 mg/kg PO
XII. Death with doses of approximately 3 mg/kg PO

Clinical Signs

I. Hyperexcitability and agitation occur within 1 to 2 hours of ingestion.
II. Dilated pupils, tachycardia, cardiac arrhythmias, hypertension, panting, or hyperpnea may be seen.
III. Tremors and shaking, hyperactive reflexes, and seizures (closely resembling tetanic seizures of strychnine poisoning) may occur.
IV. Hyperthermia can be a problem.

Diagnosis

I. History of exposure and clinical signs
II. Agents detected in urine, blood, or saliva

Differential Diagnosis

I. Cocaine, methylxanthines: theobromine, caffeine
II. Metaldehyde, tremorogenic mycotoxins, pseudoephedrine

III. Herbal preparations: ma huang, ephedra, guarana
IV. Strychnine, tricyclic antidepressants, 5-fluoruracil

Treatment and Monitoring

I. Decontamination (emesis, activated charcoal with cathartic) is indicated.
II. Sedate dogs with acepromazine 0.05 mg/kg IM, SC, IV (with caution) or chlorpromazine 0.10 to 0.18 mg/kg IV (Catravas et al., 1977).
   A. Phenobarbital, pentobarbital, or other barbiturates can also be used.
   B. Diazepam is not recommended, as it can cause excitation in some animals.
III. Cyproheptadine 1.1 mg/kg PO or rectally may be effective in dogs to control serotonin syndrome signs (e.g., hyperthermia) when other treatments are not effective.
IV. IV fluids promote elimination and maintain renal function.
V. Acidification of the urine with ammonium chloride or ascorbic acid (to pH of 4.5 to 5.5) can enhance urinary excretion, but it is contraindicated when renal function is compromised from severe myoglobinuria.
VI. Monitor for severe CNS effects, hyperthermia, and cardiac arrhythmias.
VII. Monitor acid/base status if acidification of urine is undertaken.
VIII. Monitor renal function, especially if myoglobinuria or acidosis is present.

Cocaine

Sources

I. Cocaine is a CNS stimulant derived from the coca plant (*Erythroxylum* spp.).
II. It is a Schedule II drug and is medically used as a topical, local anesthetic in people.
III. In general, it is found in two forms.
   A. Hydrochloride salt: powdered, soluble form
   B. "Free-base": not neutralized by an acid; often smoked
IV. Crack cocaine is made from cocaine powder and is 75% to 90% pure cocaine (1 g powder forms about 0.89 g crack cocaine)
V. Street names include all-American drug, beam, big C, blow, Carrie Nation, coke, girl, her, lady, leaf, nose candy, snow, snowbirds, stardust, white (generally for powder), basa, crack, electric kool-aid, flake, rock (crack cocaine), banano, bazooka, and tio (marijuana or tobacco cigarettes laced with cocaine).

Action

I. Cocaine blocks the reuptake of serotonin and norepinephrine at receptor sites.
II. Cocaine is well absorbed from all mucosal surfaces.
III. It is metabolized in the liver and excreted in the urine.
IV. The LD_{50} for pure cocaine in the dog is 13 mg/kg IV.
V. The lowest published subcutaneous lethal dose in the dog is 3.5 mg/kg SC and the cat is 16 mg/kg SC (Volmer, 2006).
VI. The lowest published lethal IV dose in the cat is 7.5 mg/kg.

Clinical Signs

I. Signs are similar to amphetamines but tend to be shorter acting.
II. The potential exists for significant cardiovascular (especially hypertension, arrhythmias) and CNS effects.
III. Aggression, excitation, hyperesthesia, and seizures have all been described.

Diagnosis

I. History of exposure
II. Cocaine detected in serum, stomach contents, or urine

Differential Diagnosis

I. Amphetamines, methylxanthines: chocolate, caffeine
II. Metaldehyde, tremorogenic mycotoxins, pseudoephedrine
III. Herbal preparations: ma huang, ephedra, guarana
IV. Strychnine, tricyclic antidepressants, 5-fluorouracil

Treatment

I. Because of rapid onset of signs, induce emesis cautiously.
II. Activated charcoal 1 to 2 g/kg PO may be beneficial.
III. Tremors and seizures are controlled with diazepam, chlorpromazine, or barbiturates, as needed.
IV. Severe tachyarrhythmias are treated with propranolol 0.02 mg/kg IV, slowly.
V. Institute IV fluid therapy to support cardiovascular function and promote excretion.
VI. Hyperthermia may be a problem and is treated appropriately (see Chapter 135).

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CHAPTER 130

Herbal Toxicities

Charlotte Means

EPHEDRINE AND PSEUDOEPHEDRINE

Sources

I. *Ephedra sinica* (common names: ma huang, yellow horse, sea grape) contains sympathomimetic alkaloids, ephedrine, and pseudoephedrine.
II. *Sida cordifolia* (common name: Indian common mallow) contains sympathomimetic alkaloids, ephedrine, and pseudoephedrine.
III. *Citrus aurantium* (common name: bitter orange) contains synephrine.
IV. They are used as decongestants and for weight loss.
V. They are used illicitly as herbal ecstasy or as precursors for methamphetamine.

Action

I. They are rapidly absorbed.
II. α-Adrenergic and β-adrenergic receptors are stimulated, which release endogenous catecholamines that affect the brain and heart.
III. Catecholamines cause peripheral vasoconstriction and cardiac stimulation.
IV. Pseudoephedrine causes bronchodilation.
V. They are metabolized in the liver and excreted in the urine.
VI. Toxic doses are as follows:
    A. Clinical signs occur at 5 to 6 mg/kg.
    B. Death is possible with doses of 10 to 12 mg/kg.
    C. Toxicity increases with ingestion of other sympathomimetics (phenylpropanolamine) or methylxanthines.
    D. Drug interactions occur with nonsteroidal antiinflammatory drugs (NSAIDs), monoamine oxidase (MAO) inhibitors, digitalis, and tricyclic antidepressants.

Clinical Signs

I. Initial signs include agitation, restlessness, pacing, and vocalization.
II. Hallucinogenic behavior is possible.
III. Head bobbing has been associated with higher mortality.
IV. Tachycardia and hypertension are typical.
V. Bradycardia and hypertension are also possible.
VI. Tremors and seizures are frequent findings.
VII. Serotonin syndrome, which is characterized by hyperthermia, abdominal pain, vocalizing, and central nervous system (CNS) signs, may be seen.
    A. Serotonin syndrome is the overstimulation of serotonin receptors in the gastrointestinal tract, and CNS, cardiovascular, and respiratory systems.
    B. Sympathomimetics and amphetamines increase the release of stored serotonin.
VIII. Death generally results from cardiovascular collapse.

Diagnosis

I. History of exposure to agent
II. Compatible clinical signs
III. Laboratory tests: possible hypokalemia, hyperglycemia
IV. Pseudoephedrine detected in plasma and urine

Differential Diagnosis

I. Pharmaceuticals containing pseudoephedrine, phenylpropanolamine, or other sympathomimetics or amphetamines
II. Illicit drugs: cocaine, amphetamines
III. Methylxanthines: chocolate, tea, coffee, theophylline, aminophylline
IV. Tremorogenic mycotoxins
V. Insecticides: pyrethroids, organophosphorus and organochlorine agents
VI. Lead poisoning
VII. Other causes of seizure disorders: see Chapter 22

Treatment and Monitoring

I. Institute decontamination.
    A. Induce emesis with hydrogen peroxide (0.5 mL/kg PO; maximum 45 mL) or apomorphine (0.04 mg/kg SC or ocularly) for recent (<30 minutes) ingestions.
    B. Give activated charcoal 1 to 2 g/kg PO.
II. Administer a phenothiazine for agitation, restlessness.
    A. Acepromazine 0.05 to 1 mg/kg IV, IM, SC, as needed
    B. Chlorpromazine 0.5 to 1 mg/kg IV, IM, as needed
III. Cyproheptadine is used to treat serotonin syndrome.
    A. Dogs: 1.1 mg/kg PO QID, if needed
    B. Cats: 2 mg for cats PO QID, if needed
    C. Alternate route: tablets dissolved in saline and given rectally in symptomatic animals or with recent activated charcoal administration
IV. Propranolol (0.02 to 0.06 mg/kg IV slowly) is used to treat tachycardia, and it is also a serotonin antagonist.
V. Phenobarbital (3 mg/kg IV to effect) is used to control tremors and seizures.

VI. Urine acidification hastens elimination.
   A. Attempt only if blood gases can be monitored.
   B. Administer ammonium chloride 50 mg/kg PO QID.
   C. Alternatively, ascorbic acid 20 to 30 mg/kg PO, IM, IV TID can be tried.
VII. Fluid therapy is cautiously instituted to maintain renal function, and possibly increase elimination, but monitor closely for pulmonary edema or fluid overload.
VIII. Diazepam is contraindicated because of the possibility of paradoxical responses (e.g., increased vocalization, head bobbing, CNS excitation, death).
IX. Monitoring parameters include the following:
   A. Blood pressure
   B. Heart rate and rhythm
   C. Routine biochemistries, especially potassium and glucose
X. Signs generally resolve within 72 hours with appropriate treatment.

GUARANA

Sources

I. *Paullinia cupana* seeds contain 3% to 5% caffeine.
II. It is used for weight loss and as an herbal "no doze" stimulant.
III. It is also used as a caffeine source by the soft drink industry.

Action

I. It is well absorbed orally; the plasma half-life ($T_{1/2}$) is 4.5 hours in dogs.
II. Adenosine receptors are inhibited, which causes CNS excitation, vasoconstriction, and tachycardia.
III. Phosphodiesterase is inhibited, resulting in increased levels of cyclic adenosine monophosphate (AMP), which stimulates catecholamine release.
IV. Free calcium is released in muscle cells, which increases cardiac and skeletal muscle contractility.
V. It is metabolized in the liver and undergoes enterohepatic recirculation.
VI. It is excreted in urine.
VII. The LD_{50} of caffeine in dogs is 100 to 200 mg/kg PO, and 80 to 150 mg/kg PO in cats.
VIII. Mild signs occur with doses between 15 and 30 mg/kg PO, moderate signs with doses between 30 and 40 mg/kg PO, and serious signs with doses >40 mg/kg PO.
IX. Combination products containing ma huang increase the toxicity.
   A. Minimum toxic dose: 4.4 mg/kg guarana and 1.3 mg/kg ma huang.
   B. Minimum lethal dose: 19.1 mg/kg guarana and 5.8 mg/kg ma huang.

Clinical Signs

I. Initial signs: vomiting, polyuria, polydipsia, hyperactivity
II. Muscle tremors, ataxia
III. Cardiac arrhythmias
IV. Seizures
V. Death

Diagnosis

I. History of exposure to agent
II. Compatible clinical signs
III. Caffeine detected in stomach contents, serum, or urine

Differential Diagnosis

I. Methylxanthines: chocolate, coffee, tea, theophylline, aminophylline
II. Amphetamines, other pharmaceutical stimulants
III. Strychnine
IV. Insecticides: pyrethroids, organochlorines, carbamates, organophosphorous insecticides
V. Metaldehyde

Treatment and Monitoring

I. Decontamination
   A. Induce emesis in asymptomatic animals within 2 hours of exposure.
   B. Give activated charcoal 1 to 2 g/kg PO; repeat in 4 to 6 hours.
II. Treatment of muscle tremors and seizures (dogs and cats)
   A. Diazepam: 0.5 to 1.0 mg/kg IV
   B. Phenobarbital: 3 to 6 mg/kg IM, IV
III. Fluid diuresis until resolution of clinical signs
   A. Insert a urinary catheter in dogs or walk frequently.
   B. Methylxanthines can be reabsorbed through the bladder wall.
IV. Correction of cardiac arrhythmias
   A. Beta blockers are given for tachycardia.
      1. Metoprolol is preferred because it does not slow renal excretion of methylxanthines.
      2. Dose for metoprolol or propranolol is 0.02 to 0.06 mg/kg IV slowly in dogs and cats.
   B. Premature ventricular contractions are treated with lidocaine in dogs at 1 to 2 mg/kg IV bolus, followed by a constant rate infusion of 25 to 80 μg/kg/minute IV. (Avoid lidocaine in cats.)
   C. Bradycardia is treated with atropine at 0.02 mg/kg IV, IM, as needed.
V. Monitoring
   A. Monitor heart rate and rhythm.
   B. Obtain a baseline complete blood count (CBC) and electrolytes, and repeat electrolytes in 8 to 12 hours in animals with seizures or tremors.
   C. Clinical signs usually resolve within 48 hours with appropriate treatment.

SAINT JOHN'S WORT

Sources

I. *Hypericum perforatum* has the common names of St. John's Wort, rosin rose, and Klamath weed.
II. In the United States, it grows naturally in the Pacific Northwest and is considered a weed.

III. It contains the anthraquinone derivatives hypericin and pseudohypericin.
IV. It is commonly manufactured as a 300-mg standardized capsule.
V. It is used to treat depression.

Action

I. St. John's wort inhibits serotonin uptake and MAO activity.
II. It alters biogenic amine synthesis of neurotransmitters, including norepinephrine, histamine, and serotonin.
III. Toxicity is enhanced if other MAO inhibitors or other selective serotonin reuptake inhibitors (SSRIs) are ingested concurrently.
IV. A minimum toxic dose has not been established in small animals.

Clinical Signs

I. Depression
II. Vomiting, diarrhea
III. Serotonin syndrome with large ingestions: vocalizing, hyperthermia, tremors
IV. Seizures

Diagnosis

I. History of exposure to agent
II. Compatible clinical signs
III. Elevated liver enzymes

Differential Diagnosis

I. SSRI medications: fluoxetine, fluvoxamine, paroxetine, sertraline
II. MAO inhibitors: selegiline, phenelzine, nialamide

Treatment and Monitoring

I. Institute decontamination.
  A. Induce emesis in asymptomatic animals if a large or unknown amount of product was ingested.
  B. Give one dose of activated charcoal 1 to 2 g/kg PO to animals that have ingested large quantities.
II. Manage vomiting and diarrhea.
  A. Give nothing PO for 8 to 12 hours.
  B. Start sucralfate as a gastric protectant.
    1. Dog: 0.5 to 1 g/25 kg PO BID to TID
    2. Cat: 250 to 500 mg PO BID to TID
  C. Administer an antiemetic (metoclopramide, chlorpromazine) if necessary, but it is rarely needed.
  D. Once vomiting has stopped, start a bland diet.
III. Control tremors or seizures with diazepam 0.5 to 1 mg/kg IV.
IV. If serotonin syndrome is noted, give cyproheptadine 1.1 mg/kg for dogs or 2 to 4 mg for cats PO, or dissolve tablet in saline and give rectally.
V. Hepatic support is rarely needed.
  A. If liver disease is present, start S-adenosyl-L-methionine *(Denosyl)* at 18 mg/kg PO in dogs and cats.
  B. A low-protein diet and supplementation of B vitamins are beneficial for dogs.
VI. Monitoring is as follows:
  A. Mild gastrointestinal signs generally resolve within 24 hours.
  B. Baseline liver enzyme levels are obtained if the animal has ingested a large amount or has preexisting liver disease, and are repeated every few days if abnormal.

ECHINACEA

Sources

I. *Echinacea purpurea* is also known as *purple coneflower* and *scurvy root.*
II. The plant is native to the United States.
III. It contains essential oils and glycol-proteins, aklomide, and flavonoids.
IV. It is generally used as an immune stimulant and has a wide margin of safety.

Action

I. Immune function is enhanced by stimulation of phagocytosis, increased cellular respiration, and increased leucocyte mobility.
II. Cell-mediated immunity is enhanced with a single dose but suppressed with long-term usage.
III. Arabinogalactan, an active component of *E. purpurea*, has been given to mice at 4 g/kg in acute toxicity trials, without adverse effects.

Clinical Signs

I. Ingestion of a small amount does not usually produce clinical signs.
II. Vomiting and diarrhea are the most common signs.
III. Because the whole plant is used in commercial preparations, allergic or anaphylactic reactions are possible.

Diagnosis

I. History of exposure to agent
II. Compatible clinical signs

Differential Diagnosis

I. Other causes of mild gastroenteritis
II. Allergic reactions from other etiologies

Treatment

I. Ingestion of small amounts does not require medical intervention.
II. Induce emesis for a large ingestion.
III. Gastrointestinal signs are generally self-limiting.

VALERIAN

Sources

I. *Valerian officinalis* is also known as *all-heal, vandal root,* and *heliotrope.*
II. It contains volatile oils, alkaloids, and valepotriates.
III. The root is the only part of the plant used, and it is used as a sedative and sleeping aid.

Action

I. Some studies indicate that valerian inhibits gamma-aminobutyric acid (GABA) transaminase.
II. GABA-inhibitory effects are increased and lead to sedation.
III. Valerian has a wide margin of safety, with doses of >1 g/kg in mice producing only mild sedative effects.

Clinical Signs

I. Lethargy
II. Ataxia
III. CNS depression
IV. Respiratory depression

Diagnosis

I. History of exposure to agent
II. Compatible clinical signs

Differential Diagnosis

I. Benzodiazepine sedatives: diazepam, alprazolam, clonazepam, lorazepam
II. Nonbenzodiazepine hypnotics: zolpidem, zaleplon

Treatment and Monitoring

I. Small ingestions do not require treatment.
II. Sedative effects are short-lived.
    A. Confine the animal if it is ataxic to prevent injury.
    B. Monitor mental status and respirations.
III. Large, recent (within 2 hours) ingestions can be managed by induction of emesis and administration of activated charcoal.

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CHAPTER 131

Toxic Plants

Valentina Merola

GASTROINTESTINAL IRRITANTS

Sources

I. Poinsettia (*Euphorbia* spp.)
II. Aloe *(Aloe vera)*
III. Crocus (*Crocus* spp.)
IV. Gladiola (*Gladiolus* spp.)
V. Hyacinth (*Hyacinthus* spp.)
VI. Iris (*Iris* spp.)
VII. Buttercup (*Ranunculus* spp.)
VIII. Insoluble oxalate containing plants
  A. Philodendron (*Philodendron* spp.)
  B. Caladium, elephant's ear (*Caladium* spp.)
  C. Jack in the pulpit *(Arisaema triphyllum)*
  D. Dumb cane (*Diffenbachia* spp.)
  E. Pothos (*Epipremnum* spp.)
  F. Peace lily (*Spathiphyllum* spp.)
  G. Calla lily (*Zantedeschia* spp.)

Action

I. Insoluble oxalate plants contain sharp crystals of calcium oxalate; during ingestion the crystals are expelled from the cell, penetrate tissues, and cause oral or gastrointestinal (GI) pain and inflammation.
II. Other plants contain a variety of toxic agents that cause GI irritation.

Clinical Signs

I. Vomiting, diarrhea, drooling, anorexia, and dehydration may all be seen.
II. Rarely, with calcium oxalate-containing plants, pharyngeal swelling and dyspnea may be seen.

Diagnosis

I. No specific laboratory findings are expected.
II. Diagnosis is based primarily on history and clinical signs.

Treatment

I. In recent exposures, emesis may be induced and activated charcoal administered at 1 to 2 g/kg PO.
II. Treatment is primarily symptomatic and supportive with fluid therapy, GI protectants, and antiemetics if needed.
III. With insoluble oxalate-containing plants, dairy products (yogurt or cottage cheese) may be given to help relieve discomfort caused by the crystals.
IV. Animals with severe pharyngeal swelling may require oxygen and close monitoring.

GASTROINTESTINAL SIGNS AND OTHER SERIOUS EFFECTS

Sources

I. Cyclamen (*Cyclamen* spp.)
II. Daffodil (*Narcissus* spp.)
III. Tulip (*Tulipa* spp.)
IV. Holly (*Ilex* spp.)
V. Ivy *(Hedera helix)*

Clinical Signs

I. In most exposures, signs are primarily GI (e.g., vomiting, diarrhea, drooling, anorexia).
II. In rare cases involving exposure to bulbs (for those plants that have bulbs) or with ingestion of large quantities, more serious and rarely fatal signs may occur.
  A. Cyclamen very rarely causes hemolysis, cardiac arrhythmias, and seizures (Burrows and Tyrl, 2001).
  B. Daffodils rarely cause central nervous system (CNS) depression, seizures, and cardiac dysfunction.
  C. Tulips can rarely increase the heart and respiratory rate.
  D. Holly and ivy can cause CNS depression.

Treatment

I. Induce emesis and give activated charcoal at 1 to 2 g/kg PO.
II. In general, further treatment is symptomatic and supportive.

CARDIOTOXIC PLANTS

Sources

I. Plants containing grayanotoxins
  A. Kalmia (*Kalmia* spp.)
  B. Rhododendron, azalea (*Rhododendron* spp.)
  C. Pieris (*Pieris* spp.)
II. Yew (*Taxus* spp.)
III. Plants containing cardiac glycosides
  A. Lily of the valley *(Convallaria majalis)*
  B. Foxglove *(Digitalis purpurea)*
  C. Oleander *(Nerium oleander)*

Action

I. Grayanotoxins bind to sodium channels and slow their opening and closing, leading to decreased cardiac conduction.
II. Yew contains taxine, which decreases cardiac conduction and contractility.
III. Cardiac glycosides inhibit the myocardial membrane sodium-potassium-ATPase pump, which leads to increased intracellular calcium and cardiac conduction deficits.

Clinical Signs

I. Vomiting and anorexia are common, and diarrhea is occasionally seen.
II. Weakness and ataxia may be noted.
III. Hypotension and many types of cardiac arrhythmias may occur.
IV. Dyspnea and pale mucous membranes are common findings.
V. In cases involving yew and oleander, sudden death often occurs.

Diagnosis

I. Diagnosis is based on history and clinical signs.
II. Animals exposed to cardiac glycosides may be hyperkalemic.
III. Urine and feces can be tested for grayanotoxins and for some of the cardiac glycosides.

Treatment and Monitoring

I. For recent exposures, induce emesis and administer activated charcoal at 1 to 2 g/kg PO.
II. Fluid therapy is started, and close monitoring of potassium and other electrolytes is performed.
III. Cardiac arrhythmias are treated as needed
IV. Digoxin immune Fab *(Digibind)* can bind to many of the cardiac glycosides and inactivate them, with 1 to 2 vials administered IV for most cardiac glycoside plant exposures.
V. Monitor heart rate, blood pressure, and electrocardiography.

ERYTHROCYTE TOXINS

Sources and Action

I. Onions, chives, and garlic (*Allium* spp.)
II. These plants contain a group of N-propyl disulfides that cause oxidative damage to red blood cells.

Clinical Signs

I. Initially, vomiting and diarrhea
II. Depression, anorexia, and weakness
III. Tachypnea, dyspnea, and tachycardia
IV. Heinz-body hemolytic anemia, hemoglobinemia, hemoglobinuria, and possibly methemoglobinemia

Diagnosis

I. History of ingestion or evidence of plant material in vomitus
II. Anemia and decreased numbers of red blood cells
III. Heinz bodies and evidence of regeneration on blood smears (reticulocytes, basophilic stippling, polychromasia)

Treatment and Monitoring

I. Induce emesis and administer activated charcoal at 1 to 2 g/kg PO for recent ingestions.
II. Monitor for red blood cell changes and clinical signs over the next few days.
III. Administer oxygen, whole blood, or purified hemoglobin as needed (see Chapter 71).
IV. Intravenous fluid therapy may be needed to maintain cardiovascular support and renal function.

NEPHROTOXIC PLANTS

Sources

I. Plants containing soluble salts of oxalic acid
  A. Rhubarb (*Rheum* spp.)
  B. Shamrock, wood sorrel (*Oxalis* spp.)
  C. Dock, sorrel (*Rumex* spp.)
II. Plants containing unknown toxic principles
  A. Grapes/raisins (*Vitus* spp.)
  B. Lilies (*Lilium* spp.)
  C. Day lilies (*Hemerocallis* spp.)

Action

I. Oxalic acid is absorbed systemically and chelates calcium.
II. In the renal tubules, calcium oxalate crystals can precipitate and cause tubular blockage and vascular stasis.
III. The mechanism of renal damage is not known with grape and lily intoxication.
IV. Lilies only appear to cause problems in cats.
V. Grapes only appear to cause problems in dogs.

Clinical Signs

I. Vomiting, diarrhea, and anorexia are commonly seen.
II. Acute renal failure with depression, dehydration, polydipsia, oliguria, polyuria, or anuria may be noted.

Diagnosis

I. Increased blood urea nitrogen (BUN), creatinine, and phosphorus are likely.
II. In cases involving oxalic acid–containing plants, hypocalcemia is expected.
III. In cases involving grapes, hypercalcemia is common, along with an elevation of the calcium × phosphorus product, so the potential for tissue mineralization exists.

Treatment and Monitoring

I. In recent exposures, induce emesis and administer activated charcoal at 1 to 2 g/kg PO.
II. Obtain baseline laboratory tests, and closely monitor chemistries and electrolytes.
III. Intravenous fluid diuresis is instituted for at least 48 hours to protect renal function and prevent tubular obstruction.
IV. Calcium supplementation may be needed in cases involving oxalate-containing plants.

V. Phosphorus binders (aluminum hydroxide) are given as needed (see Chapter 48).
VI. GI protectants and antiemetics are indicated if signs warrant them.
  A. Metoclopramide to control vomiting: 0.2 to 0.4 mg/kg TID, PO, or SC in dogs and cats
  B. Sucralfate for uremic gastritis: 0.5 to 1.0 g PO TID in dogs and 0.25 to 0.5 g PO TID in cats
  C. H_2 antagonist famotidine: 0.5 mg/kg PO SID to BID in dogs and cats
VII. Animals with renal damage may recover some function with aggressive therapy, but the potential exists for long-term, residual renal damage.

HEPATOTOXIC PLANTS

Sources and Action

I. Sago palm (*Cycas* spp.)
II. Contain at least two types of toxins in all parts of the plant, with highest concentrations in the nut
  A. Glycosides of methylazoxymethanol (cycasin and macrozamin)
    1. GI irritation
    2. Hepatic necrosis
    3. Alkylate deoxyribonucleic acid (DNA): mutagenic, teratogenic, and carcinogenic
  B. L-Beta-*N*-methylamino-L-alanine (L-BMAA): a neurotoxic amino acid

Clinical Signs

I. Moderate to severe GI signs: vomiting, diarrhea (often with blood), dehydration
II. CNS signs: depression, ataxia, seizures, coma
III. Hepatic necrosis: icterus, secondary coagulopathy
IV. Death

Diagnosis

I. Increased liver enzymes: alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, bilirubin
II. Possible increase in BUN
III. Increased activated partial thromboplastin time, partial thromboplastin time, activated clotting time

Treatment and Monitoring

I. Induce emesis and administer activated charcoal at 1 to 2 g/kg PO for recent exposure.
II. Institute supportive and symptomatic care.
  A. GI protectants
    1. Sucralfate for uremic gastritis: 0.5 to 1.0 g PO TID in dogs and 0.25 to 0.5 g PO TID in cats
    2. Famotidine: 0.5 mg/kg PO SID to BID in dogs and cats
    3. Metoclopramide to control vomiting: 0.2 to 0.4 mg/kg TID, PO, SC in dogs and cats
  B. SAMe as a hepatoprotectant at 20 mg/kg PO SID
  C. Whole blood transfusion as needed (see Chapter 71)
III. After recovery from acute signs, liver damage may be a lifelong complication.

INTERFERENCE WITH CELLULAR DIVISION

Sources

I. Castor bean, precatory bean *(Ricinus communis, Abrus precatorius)*
II. Autumn crocus *(Colchicum autumnale)*
III. Glory lily *(Gloriosa superba)*
IV. Mayapple *(Podophyllum peltatum)*

Action

I. Castor and precatory bean contain lectins that inhibit protein synthesis and cause cell death.
II. Autumn crocus, glory lily, and mayapple all contain toxic agents that disrupt normal microtubule function during cell division.

Clinical Signs

I. Severe GI irritation: vomiting and diarrhea that may be bloody
II. Dehydration
III. Possible bone marrow suppression
IV. Death
V. Castor bean: also renal and hepatic damage, ataxia, tremors, seizures

Diagnosis

I. Diagnosis is usually based on history and clinical signs.
II. Anemia and leukopenia may be seen after acute exposure.

Treatment and Monitoring

I. For recent exposures, induce emesis and administer activated charcoal at 1 to 2 g/kg PO.
II. Start aggressive IV fluid therapy.
III. Antiemetics and GI protectants are indicated (see under Gastrointestinal Irritants).
IV. Monitor complete blood counts.
  A. Myelosuppression can occur within a few weeks of exposure.
  B. Consider erythropoietin for anemia at 100 IU/kg SC three times weekly for dogs and cats.
  C. Consider filgrastim for leukopenia at 1 to 5 µg/kg SC SID for dogs and cats.

SOLANACEOUS PLANTS

Sources

I. Nightshades, potato (*Solanum* spp.)
II. Jimsonweed (*Datura* spp.)
III. Tomato *(Lycopersicon lycopersicum)*
IV. Belladonna *(Atropa belladonna)*

Action

I. These plants contain a mixture of tropane alkaloids and glycoalkaloids that have anticholinergic effects.
II. They also cause a variety of effects on the CNS and GI tract.

Clinical Signs

I. Signs variable and sometimes confusing
II. CNS signs: disorientation, hallucinations, sedation, weakness
III. GI signs
  A. Vomiting, drooling
  B. Diarrhea, cramping
  C. Possible dry mucous membranes or GI atony
IV. Cardiovascular abnormalities
  A. Bradycardia or tachycardia
  B. Hypotension or hypertension
V. Mydriasis possible

Diagnosis

I. A history of ingestion is often needed.
II. Diagnosis may be based on suspicious clinical signs because laboratory findings are nonspecific.

Treatment

I. Initially, decontamination is done by inducing emesis and administering activated charcoal at 1 to 2 g/kg PO.
II. Additional treatment is symptomatic and supportive.

CENTRAL NERVOUS SYSTEM TOXICANTS

See Table 131-1.

OTHER MISC PLANTS

See Table 131-2.

TABLE 131-1

Plants Affecting the Central Nervous System

PLANT	CLINICAL SIGNS	TREATMENT
Macadamia nuts *(Macadamia integrifolia)*	Weakness, depression, ataxia, tremors, hyperthermia Signs are generally self-limiting	Decontamination and supportive care
Yesterday, today, and tomorrow plant (*Brunfelsia* spp.)	Tremors, seizures, vomiting, diarrhea, death	Decontamination and supportive care Control seizures
Chinaberry *(Melia azedarach)*	Vomiting, drooling, diarrhea, ataxia, seizures, death	Decontamination and supportive care Control seizures
Bleeding-heart (*Dicentra* spp.)	Vomiting, ataxia, tremors, rarely seizures It is rare that enough is ingested to cause problems	Decontamination and supportive care

TABLE 131-2

Miscellaneous Toxic Plants

PLANT	CLINICAL SIGNS	TREATMENT
Avocado *(Persea americana)*	Noninfectious mastitis, agalactia in large animals and rabbits Cardiac arrhythmias, pulmonary edema, dyspnea, death in rabbits, birds, and goats Foreign body obstruction from the pit	Decontamination and supportive care
Hops *(Humulus lupulus)*	Malignant hyperthermia in dogs within 3 hours High body temperature, tachycardia, tachypnea, agitation	Decontamination and supportive care Dantrolene for malignant hyperthermia at 2 to 5 mg/kg IV once in dogs
Cyanogenic glycoside containing plants: plum, peach, cherry, apricot (*Prunus* spp.)	Whole pits are unlikely to be a problem Chewed pits can release cyanide Dyspnea, cyanosis, weakness, seizures, coma, death	Decontaminate if asymptomatic It is very rare to require or have the antidote available Sodium nitrite can be given at 16 mg/kg IV, followed by sodium thiosulfate 30 to 40 mg/kg IV The *treatment* can be life-threatening if animal has not been poisoned with cyanide

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CHAPTER 132

Shock

Marie E. Kerl

Definition

Shock refers to the catastrophic failure of oxygen delivery to cells resulting in disordered cellular metabolism.

Causes

I. Classifications schemes are frequently applied to identify causes of shock; however, schemes vary, and an animal can have more than one cause simultaneously.
II. Hypovolemic shock occurs from low, ineffective circulating volume.
  A. Hemorrhage: external or internal
  B. Marked gastrointestinal (GI) losses from vomiting or diarrhea
  C. Renal losses from excessive diuresis
  D. Vascular losses from hypoalbuminemia and poor oncotic pressure
  E. Relative loss from sequestration of fluid volume (e.g., gastric torsion)
III. Cardiogenic shock occurs from inhibition of cardiac output.
  A. Impaired forward flow
    1. Dilated cardiomyopathy
    2. Valvular insufficiency
    3. Valvular stenosis
    4. Cardiac arrhythmias
    5. Myocardial depression from drugs or illness
  B. Impaired filling
    1. Hypertrophic cardiomyopathy
    2. Pericardial effusion/tamponade
    3. Severe pulmonary thromboembolism
IV. Distributive shock occurs from loss of vascular tone or peripheral resistance from anaphylaxis, septicemia, or heat stroke.

Pathophysiology

I. As shock ensues, compensatory mechanisms are triggered (early stage).
  A. Baroreceptors in carotid body and aortic arch are activated by actual (hypovolemic shock) or perceived (cardiogenic or distributive shock) loss of volume, with triggering of compensatory mechanisms, such as tachycardia, to improve cardiac output and peripheral vasoconstriction to normalize blood pressure.
  B. Declines in renal blood flow, glomerular filtration, and renal tubular flow cause activation of the renin-angiotensin-aldosterone system, which results in sodium retention.
  C. Hyperosmolarity and hypovolemia cause hypothalamic stimulation and release of antidiuretic hormone (ADH), resulting in free water uptake and vasoconstriction.
II. With no resolution of the inciting cause, these compensatory mechanisms fail to normalize heart rate, blood pressure, and cardiac output (middle stage).
III. With continued shock, compensatory mechanisms fail and the condition deteriorates (late stage).
IV. Upon decompensation, a systemic inflammatory response syndrome is triggered, and multiorgan dysfunction syndrome can occur.

Clinical Signs

I. Initiation of compensatory mechanisms coincides with early shock.
  A. Clinical signs are minimal.
  B. Mild tachycardia can occur.
II. Middle-stage shock is associated with tachycardia, prolonged capillary refill time, pallor, and weak pulses.
  A. Distributive shock in dogs can result in hyperemic mucous membranes.
  B. Cats commonly develop bradycardia and hypothermia with distributive shock.
III. Late-stage shock is associated with bradycardia, weakness, severe hypotension, marked pallor, hypothermia, and mental dullness or stupor.

Diagnosis

I. Historical findings
   A. Reduced fluid intake from lack of access or nausea
   B. Increased fluid loss from GI, urinary, dermal, or internal losses
   C. Evidence of infection, inflammation, trauma, cardiac disease
   D. Recent exposure to unusual environmental extremes
   E. Recent vaccinations or drugs

II. Physical examination findings
   A. Mental dullness
   B. Pallor or hyperemic mucous membranes
   C. Prolonged capillary refill time
   D. Poor pulse quality: dorsal pedal pulses lost at mean arterial pressure of 60 mm Hg
   E. Tachycardia or bradycardia
   F. Hypothermia or hyperthermia
   G. Evidence of hemorrhage, fluid loss, underlying disease

III. Clinicopathologic findings
   A. Hematocrit may be low with blood loss or elevated with hemoconcentration.
   B. Total protein is low with blood loss or proteinaceous fluid loss (GI), and high with dehydration or nonproteinaceous fluid loss.
   C. With acute blood loss, a decline in total protein precedes the decline in hematocrit.
   D. Leukocytosis or leukopenia can occur with septicemia.
   E. Mild to moderate thrombocytopenia can occur from hemorrhage or with disseminated intravascular coagulopathy (DIC).
   F. Prolonged coagulation times occur with DIC or indicate a cause of the hemorrhaging.
   G. In early septic shock, hypoglycemia is more common than hyperglycemia.
   H. Serum biochemistries may reveal increased alanine aminotransferase, alkaline phosphatase, total bilirubin, prerenal or renal azotemia.
   I. Blood gas analysis can indicate metabolic acidosis from poor tissue perfusion.
   J. Systemic blood pressure (BP) is frequently low (systolic BP <80 mm Hg).
   K. Serum lactate levels are elevated (>2.5 mmol/L) with poor tissue perfusion in shock, and failure of lactate to normalize (<2.5 mmol/L) with appropriate restoration of circulatory volume indicates ongoing anaerobic metabolism.

Differential Diagnosis

I. Tachycardia, bradycardia, pulse quality abnormalities
   A. Cardiac arrhythmias
   B. Myocardial failure

II. Pallor
   A. Anemia
   B. Peripheral vasoconstriction

III. Altered mentation, weakness
   A. Central or peripheral nervous system diseases
   B. Hypoglycemia
   C. Hepatic encephalopathy

Treatment

I. Supplemental oxygen therapy
   A. Provide emergency oxygen therapy on arrival to increase tissue oxygen delivery.
   B. With severe anemia, increasing the concentration of inspired oxygen does not significantly improve tissue oxygenation, as most of the oxygen delivery occurs from hemoglobin-bound oxygen.
   C. Deliver oxygen by mask or nasal cannulation.
   D. Recommended nasal cannula flow rates are 50 to 100 mL/kg/min (Dunphy et al., 2002).
   E. Oxygen cages are impractical for the animal in shock because they render the animal relatively inaccessible.

II. Fluid resuscitation
   A. Large-bore, peripheral catheters (cephalic, lateral, or medial saphenous) allow for rapid intravenous (IV) fluid administration to treat shock.
   B. With severe hypovolemia, peripheral vessel collapse may necessitate a vascular cutdown or fluid delivery via intraosseous catheterization or a central line.
   C. Administer a balanced, isotonic crystalloid solution, such as lactated Ringer or *Normosol-R* solution, for initial treatment of hypovolemic or distributive shock.
   D. Avoid rapid fluid administration with cardiogenic shock.
   E. Approximate starting doses for fluids are 60 to 90 mL/kg IV for dogs and 40 to 60 mL/kg IV for cats; however, each animal should be resuscitated with the fluid volume needed to normalize clinical parameters.
   F. Recommended fluid dosage ranges approximate one blood volume for dogs and cats, respectively.
   G. Initiate IV fluid therapy and monitor heart rate, blood pressure, peripheral pulse quality, mucous membrane color, and mental status approximately every 5 to 10 minutes.
      1. Mean arterial pressures >80 mm Hg or systolic pressures >100 to 120 mm Hg maximize tissue oxygen delivery.
      2. When clinical parameters improve, discontinue shock (high-volume) fluid resuscitation, and continue with calculated fluid needs for maintenance, dehydration, and ongoing loss.
   H. Colloid-containing fluids can be used with or instead of crystalloids.
      1. Colloids are indicated for animals with hypoproteinemia.
      2. Consider colloids in animals with normal hydration status before onset of shock, as colloids maintain vascular volume for a longer period than do isotonic crystalloids.
         a. Approximately 60% to 70% of isotonic crystalloids translocate to the interstitial space within an hour of administration.
         b. Half-life of the synthetic colloids commonly used (hetastarch, dextran-70) is 25 hours.
      3. Colloids can be used for shock refractory to isotonic crystalloid administration.

4. Approximate starting doses of hetastarch or dextran-containing fluid is 10 to 20 mL/kg IV in dogs and 5 to 10 mL/kg IV in cats, while concurrently monitoring the same resuscitative parameters mentioned above.

III. Sodium bicarbonate
   A. Administer bicarbonate following fluid resuscitation if metabolic acidosis persists (pH <7.1, base deficit >11).
   B. Bicarbonate deficit is calculated as (0.3) × (body weight in kg) × (base deficit).
   C. Administer half the deficit slowly IV over 4 to 6 hours and repeat blood gasses before further administration.

IV. Hemorrhage
   A. Apply pressure to external wounds or compression bandages to the abdomen on initial presentation.
   B. Monitor animal carefully for respiratory compromise if abdominal compression is instituted.
   C. Emergency surgery is indicated if hemorrhage does not respond to emergency control measures.
   D. Evaluation of coagulation status is imperative before surgical intervention.

V. Dilated cardiomyopathy
   A. Avoid resuscitative fluid administration.
   B. Administer positive inotropic support (Boag and Hughes, 2005).
      1. Dobutamine
         a. Dog: 5 to 10 µg/kg/min IV constant rate infusion (CRI)
         b. Cat: 1 to 2 µg/kg/min IV CRI
      2. Dopamine: 5 to 10 µg/kg/min IV CRI

VI. Pericardial effusion: immediate pericardiocentesis to resolve tamponade

VII. Septic shock
   A. Institute broad-spectrum antibiotics.
   B. Choose antibiotics that cover gram-positive and gram-negative bacteria.
   C. Coverage for anaerobic bacteria (metronidazole, ampicillin) may also be indicated.

VIII. Shock refractory to fluid resuscitation
   A. Consider administration of positive inotropes or vasopressors.
   B. Vasopressors include dopamine, norepinephrine, or aqueous vasopressin.
   C. Vasopressor therapy causes peripheral vasoconstriction, which diminishes peripheral tissue oxygen delivery.

Monitoring of Animal

I. Monitoring frequency is tailored to each animal according to the particular situation.

II. The following parameters can be evaluated every 2 to 12 hours:
   A. Blood pressure, pulse quality
   B. Mucous membrane color, capillary refill time
   C. Heart rate and rhythm, electrocardiography
   D. Urine output

III. Respiratory monitoring
   A. Respiratory rate and effort
   B. Arterial oxygen partial pressure (Pao_2) or saturation (SPo_2)
   C. Arterial or venous partial pressure carbon dioxide (Pco_2), end-tidal CO_2
   D. Pulmonary auscultation

IV. Body temperature
   A. Hypothermia indicates poor perfusion.
   B. Fever indicates infection or inflammation.

V. Hematocrit and total protein

VI. Blood glucose

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CHAPTER 133

Electrical Cord and Smoke Inhalation Injuries

Jennifer E. Prittie

ELECTRICAL CORD INJURY

Definition and Causes

I. Electrical shock occurs most frequently when animals chew on live wires of household appliances, and most commonly affects puppies and kittens.
II. Both local and systemic injuries ensue after contact with alternating current.

Pathophysiology

I. Transformation of electrical energy into heat results in coagulation necrosis of tissue proteins at the point of contact, resulting in local thermal injury.
II. Systemic injury results from disruption of the electrophysiologic activity of excitable tissue, with muscle spasms, seizures, loss of consciousness, apnea, and life-threatening cardiac dysrhythmias as reported sequelae.
III. Injury is commonly associated with development of neurogenic (noncardiogenic) pulmonary edema, possibly from transient pulmonary hypertension after centrally mediated vasomotor changes and increased microvascular permeability.
IV. Injury severity is proportional to duration of exposure and intensity of current.

Clinical Signs

I. Local thermal injury
  A. The oral commissures and dorsolateral lingual surfaces are usually affected.
  B. Lesions are well circumscribed, pale, and yellow.
  C. Hypersalivation is common, and animals typically resist examination of the oral cavity because of associated pain.
  D. Oral discomfort may result in inappetence.
II. Systemic manifestations
  A. Neurogenic edema may result in respiratory distress.
    1. Signs include pallor or cyanosis, tachypnea, and dyspnea.
    2. Coughing of blood-tinged pulmonary edema fluid may be observed.
    3. Onset is typically rapid (<4.5 hours) but can be delayed 12 to 24 hours.
  B. Muscle stiffness or generalized seizures may occur during and immediately following electrocution.
  C. Abdominal pain and vomiting may develop.
  D. Cardiopulmonary arrest occurs from respiratory paralysis or ventricular fibrillation.

Diagnosis

I. History
  A. Owners may witness the electrocution or find the cord in the mouth.
  B. Animals may be found collapsed, stiff, seizuring, or dyspneic.
II. Compatible physical findings
  A. Characteristic oral lesions, oral pain, pallor, or cyanosis
  B. Tachypnea, dyspnea, moist cough, and auscultable harsh lung sounds and crackles from pulmonary edema
III. Thoracic radiography
  A. The cardiac silhouette and pulmonary vessels are normal to small.
  B. Neurogenic pulmonary edema is predominantly alveolar and located within the caudodorsal quadrants, but interstitial edema may also be observed.
  C. Distribution is typically bilateral and symmetrical.

Differential Diagnosis

I. Other causes of oral ulceration
  A. Viral infection
  B. Uremic ulcers
  C. Ingestion of a caustic substance
  D. Immune-mediated disease
II. Other causes of neurogenic pulmonary edema
  A. Head trauma
  B. Seizures
  C. Upper airway obstruction
III. Other causes of respiratory distress
  A. Congestive heart failure
  B. Pneumonia
  C. Pulmonary hemorrhage

Treatment

I. Disconnect the electricity and remove the pet from the source of current.
II. Clear the airway of edema, mucus, or vomitus with fingers or a suction catheter.
  A. Animals with altered mentation and diminished airway defenses (decreased gag reflex) require intubation and supplemental oxygen.

B. Mechanical ventilation is indicated for the following:
1. Hypoxemia that persists despite oxygen supplementation
2. Severe hypoventilation
3. Respiratory muscle fatigue

III. Consider oxygen therapy.
A. To ensure adequate tissue oxygenation, maintain arterial hemoglobin (Hb) oxygen saturation (SPo_2) >92%, which corresponds to a partial pressure of oxygen in arterial blood (Pao_2) > 75 mm Hg.
B. Oxygen can be supplied via mask, cage, tent, or nasal cannulation.

IV. Intravenous fluid therapy is based on maintaining adequate systemic perfusion and tissue oxygenation.
A. Crystalloids increase intravascular hydrostatic pressure and decrease intravascular oncotic pressure, possibly promoting pulmonary edema.
B. *Prudent* fluid restriction may be beneficial; however, restriction without maintaining cardiac output and tissue oxygenation should be avoided.
C. With sufficient increase in endothelial permeability, colloids pass through the pulmonary capillary endothelium and are osmotically active in the interstitium to exacerbate pulmonary edema.
D. A test infusion of IV fluids is advisable; if respiratory parameters worsen during administration, and if systemic perfusion is adequate, judicious fluid restriction is recommended.
E. Bolus administration of IV fluids acutely increases pulmonary hydrostatic pressure; constant-rate infusion is preferable.

V. Therapy for pulmonary edema may include the following:
A. Oxygen therapy as needed
B. Diuretic therapy
1. The goal is to decrease pulmonary hydrostatic pressure via reduction in plasma volume, thereby reducing edema formation.
2. Diuretics may be useful in the early stages of noncardiogenic edema formation, when pulmonary hydrostatic pressure may be elevated; however, the use of diuretics remains controversial.
3. Any reduction of cardiac output and tissue oxygenation is detrimental and is to be avoided.
4. Furosemide can be administered once at a dose of 2 to 4 mg/kg IV.
C. Bronchodilators
1. Terbutaline 0.01 mg/kg SC, IM BID to QID
2. Aminophylline
a. Dog: 6 to 10 mg/kg IM, PO TID
b. Cat: 4 to 8 mg/kg IM, PO BID to TID
D. Corticosteroids: no proven benefit, possibly harmful

VI. Oral burns are cleaned with an antiseptic solution BID to TID.
A. Most lesions heal satisfactorily by second intention.
B. Oronasal fistula formation may occur and may require surgical repair.
C. Systemic analgesics are administered as needed.
1. Torbugesic 0.2 to 0.4 mg/kg IV, SC, IM every 4 to 6 hours
2. Hydromorphone 0.05 to 0.1 mg/kg IV, SC, IM QID
3. Buprenorphine 0.01 to 0.02 mg/kg IV BID to QID

Monitoring of Animal

I. Animals are hospitalized for 24 to 48 hours and monitored for delayed-onset respiratory and cardiac symptoms.
II. Respiratory status is monitored by observation of respiratory rate and effort, lung auscultation, and thoracic radiographs.
A. Oxygenation is evaluated by pulse oximetry or arterial blood gas analysis.
B. Ventilatory ability can be monitored by evaluating arterial or venous carbon dioxide.
III. Continuous electrocardiography may be indicated for 24 to 48 hours after electrocution, as the development of ventricular arrhythmias can also be delayed.
IV. Survival rate for animals with neurogenic pulmonary edema secondary to electric shock is 39% to 85% (Drobatz et al., 1995).

SMOKE INHALATION

Definition and Causes

I. Smoke inhalation injury has been most commonly reported following exposure to smoke in residential fires.
II. Direct thermal injury, chemical irritants, and smoke particulates result in respiratory dysfunction and tissue hypoxia.
III. Carbon monoxide (CO) is a colorless, odorless, toxic gas that is a product of incomplete combustion; inhalation of CO exacerbates cellular hypoxia and results in neurologic dysfunction.

Pathophysiology

I. Damage to the respiratory system
A. Heat
1. Thermal injury affects primarily the upper airways (i.e., the supraglottic area and the larynx).
2. Partial or complete upper airway obstruction may occur subsequent to laryngeal inflammation and edema, within several hours of exposure.
B. Vapors
1. Respiratory irritants include sulfur dioxide, chlorine gas, and acrolein.
2. Chemical burns directly damage the respiratory mucosa, and chemicals may incite reflex bronchoconstriction and pulmonary inflammation.
3. Irritants inactivate surfactant, causing atelectasis and decreased compliance.
4. Particulates <5 μm deposit in large and small airways and alveoli, resulting in mucosal irritation and reflex bronchoconstriction.
5. Impaired mucociliary action impedes particulate clearance.

II. Complications
A. Early (0 to 36 hours): acute lung injury
B. Delayed complications

1. Bronchopneumonia (4 to 5 days)
2. Pulmonary fibrosis

C. Carbon monoxide toxicity
1. CO preferentially binds with Hb in place of O_2, forming carboxyhemoglobin (COHb) (Hb affinity for CO is 240 times greater than for O_2).
2. The resultant reduction in arterial O_2 content decreases O_2 delivery to the tissues.
3. Other mechanisms of CO toxicity include the following:
   a. Left shift of the oxyhemoglobin dissociation curve, impairing tissue O_2 release
   b. Decrease in cellular respiration through binding CO to cytochrome P450
   c. Binding to myoglobin with myocardial and skeletal muscle dysfunction

Clinical Signs

I. Manifestations of smoke toxicity include the following:
   A. Ocular abnormalities: corneal ulcers, blepharospasm, conjunctivitis
   B. Cutaneous burns on the face and footpads
   C. Smoky aroma to the animal
   D. Singed hair or soot on the haircoat
II. The major body systems affected include respiratory and central nervous system.
   A. Respiratory signs include nasal discharge, cough, gag, upper airway stridor, open-mouth breathing, tachypnea, and dyspnea.
   B. Neurologic signs include depression, ataxia, loss of consciousness, and coma.
   C. Hypovolemic shock results from respiratory and dermal fluid losses.

Diagnosis

I. History of exposure to household or other fire may be evident.
II. Evaluate for compatible clinical signs, as described above.
III. Additional physical examination findings may be seen.
   A. Cherry red mucous membranes consistent with CO toxicity
   B. Auscultation of harsh lung sounds, crackles or wheezes
IV. Radiographic abnormalities may not be evident for up to 48 hours after exposure.
   A. Alveolar and interstitial infiltrates predominate, with no consistent distribution.
   B. Collapse of the right middle lung lobe may be identified.
V. Documentation of hypoxemia is supportive.
   A. Pulse oximetry is inaccurate in the presence of COHb and overestimates Hb saturation with O_2.
   B. Cooximetry provides a direct measurement of oxy-, carboxy- and methemoglobin, but this technology is not readily available.
   C. Arterial blood gas analysis is unaffected by the presence of COHb.
VI. Measurement of COHb may be helpful.
   A. COHb >15% indicates toxicity.
   B. COHb level roughly correlates with the amount of CO inhaled and with the animal's clinical signs.
VII. Cytological examination of respiratory secretions may reveal the presence of soot, particulate matter, or secondary bacterial infection.
VIII. The results of hemogram and biochemical profile are unremarkable initially, but change with secondary complications.

Differential Diagnosis

I. Other causes of respiratory distress with pulmonary infiltrates: neurogenic edema (upper airway obstruction, electric cord injury, seizures), pneumonia
II. Other causes of oral and facial burns: electrical cord injury, exposure to caustic substances
III. Other causes of altered mentation: seizures (post-ictal), drug or toxin ingestion

Treatment

I. Airway and breathing
   A. Endotracheal intubation or tracheostomy may be indicated for upper airway edema or obstruction, or in cases with altered level of consciousness.
   B. Mechanical ventilation is indicated for respiratory failure.
II. Oxygen therapy
   A. Administer O_2 to any animals showing respiratory or neurologic signs.
   B. Administer high-flow O_2 therapy (80% to 100%) for several hours.
      1. Reduces the half-life of CO
      2. Increases the amount of unbound, dissolved O_2 in the blood
      3. Provided via tight-fitting mask, nasal cannulation, or mechanical ventilation
   C. After 1 to 4 hours of therapy, decrease the inspired concentration of O_2 to 40% to 60% to avoid O_2 toxicity, and attempt to maintain Pao_2 >75 mm Hg.
   D. Hyperbaric oxygen (HBO)
      1. Advocated for CO toxicity, but data are conflicting regarding its benefit
      2. Produces a rapid reduction in COHb levels, faster dissociation of CO from respiratory cytochromes, and decreases oxidative injury
III. Fluid therapy
   A. Intravenous fluids are administered to maintain adequate tissue perfusion and oxygenation, and to avoid drying and thickening of airway secretions.
   B. Overhydration with isotonic crystalloids may exacerbate pulmonary vascular leak and must be avoided.
   C. Burns affecting a large surface area can result in loss of a large quantity of protein-rich fluid; therefore aggressive IV fluid therapy, with the addition of a colloidal solution, may be necessary in burn victims.
IV. Bronchodilators
   A. Terbutaline 0.01 mg/kg SC, IM BID to QID
   B. Aminophylline

1. Dog: 6 to 10 mg/kg IM, PO TID
2. Cat: 4 to 8 mg/kg IM, PO BID to TID

V. Nebulization and coupage every 4 to 6 hours to clear airway secretions
VI. Analgesics
   A. Analgesics are administered if cutaneous burns exist.
   B. Appropriate agents include the following:
      1. Torbugesic 0.2 to 0.4 mg/kg IV, SC, IM every 4 to 6 hours
      2. Hydromorphone 0.05 to 0.1 mg/kg IV, SC, IM QID
      3. Buprenorphine 0.01 to 0.02 mg/kg IV BID to QID
VII. Corticosteroids
   A. Short-acting corticosteroids may be useful for treatment of upper airway edema.
   B. In general, corticosteroids are avoided because of the risk of respiratory and systemic infections.
VIII. Antibiotic therapy
   A. Prophylactic administration of antibiotics is not beneficial and can result in development of resistant infections.
   B. Broad-spectrum systemic antibiotic therapy is instituted after documentation of infection based on culture and sensitivity results.
IX. Monitor corneal ulceration with serial fluorescein staining; treat with topical broad-spectrum antibiotics, and topical atropine as indicated for ciliary spasm.

Monitoring of Animal

I. Respiratory signs may not develop until several hours or days after initial examination, necessitating hospitalization and monitoring for at least 24 to 48 hours.
II. Respiratory rate and effort, arterial blood gas analysis, and serial thoracic radiographs can be used to monitor for respiratory deterioration.
III. CO intoxication can result in a syndrome of delayed neurologic dysfunction, so serial monitoring of mentation, gait, and cranial nerve function is also indicated.
IV. Reported survival rate of dogs and cats following smoke inhalation (without accompanying burns) is 90% (Drobatz et al., 1999).
   A. Animals with concurrent dermal burns may have more severe pulmonary dysfunction.
   B. Respiratory deterioration after hospital admission is associated with a prolonged course of hospitalization and increased mortality in dogs.

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CHAPTER 134

Burns

Rebecca J. Greer | F.A. Mann

Definition and Causes

I. There are three main types of burn injuries (Dhupa, 2002).
   A. With thermal burns, skin comes into contact with a source of heat of sufficient temperature to cause cell injury and death via protein coagulation
   B. With chemical burns, strong acids, bases, or other corrosive substances contact tissue and cause protein and collagen denaturation, generation of thermal energy, coagulation necrosis, and vascular thrombosis
   C. With electrical burns, electric current damages tissue by conversion of electrical energy into heat, and by causing depolarization of nerve/muscle cells (ventricular arrhythmia) (see also Chapter 133)

II. Various causes of burns are summarized in Table 134-1.

Classification

I. The severity of burn injury is determined by evaluating both the degree/depth of injury and the percentage of the total body surface area (TBSA) involved (Fox, 1985).

II. Depth of injury is divided into three categories (Table 134-2).
   A. Epidermal burns (first degree)
      1. Injury is to the outermost epidermis only.
      2. The epidermis is thickened, erythematous or desquamated.
   B. Dermal partial-thickness burns (second degree)
      1. Superficial partial-thickness burns
         a. Epidermis is destroyed but most of the dermis still present.
         b. The tissue has a moist surface, blanches with pressure, is erythematous, has large blebs or bullae, and intact hair follicles.
      2. Deep partial-thickness burns
         a. Dermal destruction occurs, with only the adnexal epithelium remaining in the upper layers of the subcutaneous fat.
         b. Tissue is dry, does not blanch, is dark or yellow-white in color, contains ruptured bullae, and has decreased sensation.
         c. The wound is subject to fluid loss, infection, pain, and can result in metabolic disturbances.
   C. Full-thickness burns (third degree)
      1. Destruction of all layers of skin occurs and may include fat, fascia, muscle and bone.

TABLE 134-1

Types of Burn Injuries

TYPE OF BURN	CLINICAL SIGNS	EXAMPLES
Direct Heat	Tissue damage by direct heat necrosis	*Dry:* heating pads, hot water bottles, heat lamps, radiators, stoves, hot packs, light bulbs, other hot surfaces *Wet:* steam, hot water, hot tar, hot cooking oils, potpourri oils
Flame	Tissue damage by direct heat necrosis	House or barn fires, camp fires, forest fires, malicious burnings
Chemical	Tissue damage via coagulation necrosis, liquefaction necrosis with denaturing of proteins and saponification of fats, and heat necrosis	*Acids:* toilet bowl cleaners, battery acid, metal cleaners, rust removers, concrete cleaners, sulfuric acid *Bases:* bleach, drain cleaners, oven cleaners, ammonias, toilet bowl cleaners, Lysol, potash, pool chlorinating solutions, lime *Oxidizing agents:* bleaches, peroxides, chromates, manganates *Solvents:* phenols, turpentine, paint thinners, gasoline, kerosene, creosols
Electrical	Tissue damage via electron flow depolarizing muscles/nerves, causing abnormal electrical rhythms in heart and brain, with heat and poration damage of cells	*High voltage:* lightning, high-tension power lines *Low voltage:* electrical cord exposure, electrosurgical burns (cautery and grounding plate burns)

TABLE 134-2

Burn Classifications Based on Depth

BURN CLASSIFICATION	USUAL CAUSE	GROSS PATHOLOGY	MICROPATHOLOGY	MAIN SEQUELAE	MEANS OF UNCOMPLICATED HEALING
Epidermal	Radiation (sunburn)	Erythema, small intradermal blebs, desquamation	Partial epithelial destruction	Pain	Spontaneous epithelial regeneration in 5 to 7 days
Partial thickness (dermal), superficial	Scalding, hair dryers, heating pads	Erythema, large blebs or bullae, hair follicles intact	Partial epidermal and dermal destruction	Fluid loss, infection, pain	Spontaneous epithelial regeneration in 7 to 21 days
Partial thickness (dermal), deep	Scalding, flame, heating pads	Dry, does not blanch, insensitive to pinprick, hair follicles intact	Total epidermal and partial dermal destruction	Fluid loss, infection, pain, metabolic disturbances	Spontaneous epithelial regeneration lengthy (≥ 30 days) with scarring
Full thickness	Flame	Charred, blanched, leather-like, hair follicles obliterated	All dermis and epidermis destroyed	Fluid loss, infection, difficult closure, metabolic disturbances	Grafting

Modified from Fox SM: Management of thermal burns—part I. Compend Contin Educ Pract Vet 7:631, 1985; with permission.

2. The tissue appears charred, blanched, and leather-like.
3. Increased permeability of intact deep vessels results in marked edema of the subcutis.
4. The wound is subject to fluid loss and infection, which can result in metabolic disturbances.
5. Skin grafts are required for closure of large wounds.
6. Closure is important and significant; life-threatening systemic effects can occur if large surface areas are involved.

III. No accurate method for estimating TBSA exists in small animals.
   A. The *Rule of Nines* is considered inaccurate in women, infants, and children, making it difficult to apply to animals (Sheridan, 2002).
      1. The head and neck = 9% of TBSA
      2. Each forelimb = 9% of TBSA
      3. Each hind limb = 18% of TBSA
      4. The thorax = 18% of TBSA
      5. The abdomen = 18% of TBSA
   B. Burns affecting >20% TBSA cause interstitial edema in organs as an indirect injury.
      1. The edema can cause significant physiologic abnormalities.
      2. The edema may impair cardiac, respiratory, and immune functions.
   C. Burns affecting >50% TBSA usually have a poor prognosis, but good outcomes were reported in two cases (Fox, 1986; Fox et al., 1988).

Pathophysiology

I. Physiological derangements can be severe in large thermal wounds (Dhupa, 2002; Fox, 1986; Sheridan, 2002).
   A. Degree of systemic involvement is related to both depth of injury and TBSA.
      1. Abnormalities can range from mild electrolyte disturbances to a systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS).
      2. The systemic clinical course changes with time.
   B. Direct thermal injury results in coagulation necrosis of the tissue.

II. Systemic effects may occur in various organs.
   A. Cardiovascular effects
      1. Significant hypovolemia can arise from interstitial edema and evaporation if >20% TBSA is burned.
         a. Vascular leakage develops secondary to release of reactive oxygen species (hydrogen peroxide, hypochlorite ion, hydroxyl radical, superoxide anion) and vasoactive substances from the injured tissue, which results in fluid loss.
         b. The ability to medically manage vascular leakage is currently limited.
         c. Fluid loss is estimated at 1 to 4 mL/kg × %TBSA affected.
      2. Initially, a catecholamine surge results in tachycardia, peripheral vasoconstriction, and hypertension.
      3. Hypovolemia and the generation of myocardial depressant factors decrease cardiac output.
      4. Compensatory mechanisms are overwhelmed by fluid loss, resulting in hypovolemic shock.
      5. Low-voltage electrical injuries may cause fatal ventricular arrhythmias, noncardiogenic pulmonary edema, and death.
      6. The final consequences of cardiovascular failure are decreased tissue perfusion and hypoxemia.

B. Hematological effects
   1. Initial fluid losses can result in hemoconcentration.
   2. Hemolysis may occur as a result of direct thermal injury, passage through damaged vasculature, and disseminated intravascular coagulation (DIC).
   3. Hemolysis occurs even with less severe burns, resulting in hemoglobinuria and anemia.
   4. Platelet consumption contributes to DIC.
   5. Anemia is exacerbated by depressed hematopoiesis, hemolysis, cachexia, and blood loss from removal of eschar and graft harvesting.

C. Respiratory effects
   1. Hot-air inhalation results in mucosal damage, edema, and inactivation of cilia and surfactants.
   2. Inhaled particulate matter and toxins cause direct pulmonary injury, leading to acute lung injury or acute respiratory distress syndrome.
   3. Burns of the thoracic wall and eschar formation cause decreased thoracic compliance and may contribute to hypoventilation.
   4. Electrical injuries may result in noncardiogenic pulmonary edema.

D. Renal effects
   1. Hypovolemia causes decreased renal blood flow and direct renal damage.
   2. Hemoglobinuria and myoglobinuria contribute to acute renal failure.

E. Gastrointestinal effects
   1. Gastrointestinal tract edema results in increased mucosal permeability and compromise of the intestinal barrier, leading to bacterial translocation and endotoxemia.
   2. Gastrointestinal ulceration from compromise of the intestinal barrier may result in blood loss.
   3. Hepatic dysfunction causes hypoglycemia, immunosuppression, and septicemia.

F. Immunological effects
   1. Both the humoral and cell-mediated components of the immune system are affected.
   2. Immunosuppression may occur if >20% TBSA is burned (Sheridan, 2002).
   3. Loss of proteins, such as immunoglobulins, fibronectin, acute phase proteins, and albumin, alters the immune status.
   4. Increased plasma concentrations of cortisol and other "stress" hormones affect both humoral and cell-mediated immunity and may result in immunosuppression.
   5. Inflammatory mediators contribute to SIRS and MODS.

G. Electrolyte disturbances
   1. Hypernatremia or hyponatremia, hyperkalemia or hypokalemia, and acidosis (metabolic, respiratory, or both) can occur and change over time.
   2. Many topical medications placed on wounds draw electrolytes or fluid out of the tissues because of their osmotic effects.
   3. Impaired renal function contributes to altered electrolyte values.

H. Miscellaneous effects
   1. Thermoregulation is impaired by evaporative heat loss from the surface of large wounds.
      a. Initially, hypothermia results from overzealous wound cooling and evaporation of fluids.
      b. Over time, hyperthermia occurs secondary to a hypermetabolic state (Hart et al., 2000).
   2. Affected animals are at increased risk of infection because of gastrointestinal, renal, and hepatic dysfunction, protein catabolism, cytokine release, and immune system dysregulation.
   3. Hypermetabolic states can last for >6 months after injury.
   4. Daily protein loss may exceed 2 g/kg/day and may result in a negative energy balance.

Clinical Signs

I. Thermal burns
   A. Local damage (see Table 134-2)
   B. Systemic effects
      1. Organs other than the skin may manifest abnormalities following deep partial-thickness or full-thickness burns over >20% of TBSA.
      2. Systemic clinical course changes with time.
         a. Immediate effects include hypothermia, electrolyte disturbances, organ edema, cardiovascular compromise, immunosuppression, hemolysis, DIC, decreased urine output, and airway edema.
         b. In the first week, clinical signs can include anemia, DIC, SIRS, early wound infection, and small airway obstruction.
         c. From day 7 to wound closure, clinical signs include hyperthermia, a hypermetabolic state, sepsis, pneumonia, wound demarcation, and healing.

II. Electrical burns (see Chapter 133)

Diagnosis

I. History
   A. Elucidate the events surrounding the burn exposure.
   B. Determine the duration and type of exposure.

II. Physical examination of all body systems
   A. Neurological function
      1. Mentation deteriorates as the animal becomes moribund or receives pain medications, so knowledge of initial mental status is vital to assessment and prediction of return to normal mentation.
      2. Carbon monoxide (CO) intoxication and smoke inhalation causes neurologic signs, such as ataxia, mentation changes, and seizures.
      3. CO can result in neurologic signs days to weeks after discharge from the hospital (Mariani, 2003).
   B. Oropharyngeal structures
      1. Check for inhalation injuries; if noted, treat for smoke inhalation.

a. Look for burns around the mouth and nares or singed facial hair.
b. Look for soot particles in nostrils or pharynx.
2. Laryngeal swelling may necessitate intubation or placement of a tracheostomy tube.

C. Respiratory status
1. Ensure adequate ventilation.
a. Decreased thoracic wall compliance, bronchospasm, upper airway swelling, and lower airway edema may decrease oxygenation of blood, necessitating oxygen supplementation.
b. Assisted ventilation may be needed if hypoxia persists despite oxygen administration.
2. Thoracic radiography helps determine the presence of pulmonary edema and other thoracic trauma.

D. Cardiac changes
1. Monitor blood pressure to assess perfusion parameters.
2. Electrocardiography may be performed to characterize any arrhythmia that is present, especially if there is electrical injury or an auscultable arrhythmia.

E. Abdominal effects
1. Abdominal compliance may be decreased from eschar formation and may alter diaphragm movement and compromise respiration.
2. Gastric ulcers may develop secondary to decreased splanchnic blood flow and mucosal edema.

F. Urogenital changes
1. Swelling may cause a functional urethral obstruction.
2. Consider placement of an indwelling urinary catheter.

G. Changes in extremities
1. Assess large extremity wounds for vascular viability.
2. Evaluate vascular viability via Doppler blood flow, sensation, temperature, and voluntary motion.

III. Supplemental tests
A. Other tests are dependent on the condition of the animal but are recommended if >20% TBSA is affected.
B. Complete blood count (CBC), serum biochemistry profile, and urinalysis detect underlying conditions and provide baseline data.
C. Determine oxygenation and acid-base status via arterial blood gas analysis.

Treatment of Wounds

I. Biological closure of wounds is critical as soon as possible after the injury (Atiyeh et al., 2005; Fox, 1985; Fox,1989; Sheridan, 2002).
A. Wounds change over the first few days.
B. Remove all devitalized material, minimizing damage to viable tissue.

II. Small burns rarely lead to serious sepsis.
A. Allow time for wound evolution to reveal the depth and edges of the wound.
B. Use topical treatments at least once daily to prevent wound infection, decrease vapor loss, prevent desiccation, and control pain.
1. Silver sulfadiazine: painless, broad spectrum, poor eschar penetration, no metabolic effects
2. Silver nitrate: painless, broad spectrum, poor eschar penetration, leaches electrolytes
3. Mafenide acetate: painful, broad spectrum, excellent eschar penetration

III. Large wounds heal faster if surgically closed early (Sheridan, 2002).
A. Remove nonviable material, minimizing damage to viable tissue.
B. It can be difficult to determine margins of viable and nonviable tissue, particularly early in the wound course.
C. Use topical treatments, as described above, for small wounds.
D. Bleeding can be extensive with eschar removal and can be minimized by use of extremity tourniquets, dilute epinephrine injections, reduced operating time, and electrosurgery (Sheridan, 2002).
1. Sterile soaking of wounds helps with eschar removal.
2. Place gauze soaked in warm sterile saline over the wound for several minutes to help soften the eschar.
3. Hydrotherapy can be used to help soften and remove tissue.
4. Small animals can be placed in a clean, disinfected, and newly filled whirlpool tub to enhance softening of the eschar and improve skin circulation.
5. Perform manual removal of obviously devitalized tissue with forceps and scissors (lift and cut away dead tissue).
E. Debriding enzymes can be used to soften and remove eschar.
1. *Collagenase Santyl Ointment* (distributed under license from BioSpecifics by Ross Abbott) is a petroleum-based product for humans that can be placed directly on burns to help liquefy necrotic tissue.
2. G*ranulex V* by Pfizer is approved in animals for the treatment of rope burns.
3. *Debridase* (Mediwound LTD, Yavne, Israel) is a product for humans that has been used in animals (Hebda et al., 1998; Krieger et al., 2005; Rosenberg et al., 2004).
4. Reported use of topically applied enzymatic medications is limited in animals.

IV. Large areas of eschar are surgically removed, leaving viable tissue that bleeds, which is closed or grafted as soon as possible afterward.
A. Autografting is recommended; refer to surgery textbooks for techniques.
B. Use allograft or other temporary wound closure material (see following discussion) if autografting is not possible.
C. Primary grafting can prevent some wound contraction and loss of mobility.
D. Allografts or biological membranes may be used in several settings.

1. To provide temporary physiologic closure of burns while awaiting autografting
2. On donor sites to facilitate pain control and epithelialization from skin edges
3. As a dressing on clean superficial wounds
4. As a test graft over questionable wound beds

E. Multiple biological membranes and xenographs are commercially available.
1. Swine small intestinal submucosa (Cook Biotech Incorporated, West Lafayette, Ind.) is approved for use in animals and can aid wound healing.
2. *Integra* (Integra Life Science, Plainsboro, N.J.) is approved for humans and contains collagen isolated from bovine tissue that facilitates fibrovascular ingrowth from the host and then undergoes biodegradation.
3. *AlloDerm* (LifeCell Corporation, The Woodlands, Tex.) is approved for humans and is manufactured from split-thickness human cadaver skin.
4. Superiority of one xenograft versus another has not been established at this time.

V. Large wounds often become infected in the second week.
A. Systemic prophylactic antibiotics are not recommended because they can predispose the animal to resistant infections.
B. Systemic antibiotics are needed if sepsis or overwhelming wound infection occurs.
C. Obtain a bacterial culture of affected tissue before administering systemic antibiotics.
1. Choose antibiotics based on the culture or the probable agent while the culture is pending.
2. *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and β-hemolytic streptococci are common infectious organisms in burn wounds (Fox, 1985).
3. *Pseudomonas* spp. are the organisms of greatest concern.

VI. Wound protection is important.
A. If possible, bandage wounds with sterile dressings to prevent environmental contamination, desiccation, and to assist with thermoregulation.
B. Use an Elizabethan collar or other method to prevent self-inflicted trauma.

Treatment of Physiologic Abnormalities

I. Severe fluid loss
A. No formula perfectly predicts fluid losses, but the Parkland formula has historically been recommended (Fox, 1985; Sheridan, 2002).
1. Loss for the first 24 hours is body weight (kg) × %TBSA × 4 mL.
2. Replace 50% in the first 8 hours after injury.
3. Replace 25% in the second 8 hours after injury.
4. Replace 25% in the third 8 hours after injury.

B. Colloids improve cardiac output despite increased capillary permeability and may be used when indicated.
1. Administer hetastarch or dextrans at 20 mL/kg/day IV.
2. Concern that colloids add to oncotic leakage from tissues has been neither proven nor refuted.

C. Administer fluids until monitoring parameters are normal.
1. Maintain normal (0 to 5 cm H_2O) or slightly above normal central venous pressure (CVP).
2. Maintain normal urine output (1 to 2 mL/kg/hr).
3. Maintain normal blood pressure (mean arterial pressure of 70 to 110 mm Hg).
4. Normalize capillary refill time (1 to 2 seconds) and clinical assessments of hydration.

D. Blood products may be necessary when severe anemia, hypoproteinemia, or coagulation deficits are present (see Chapter 71).
E. Fluid losses should decrease over the first 48 hours and with wound closure.

II. Airway edema
A. Manually remove debris and dirt from nostrils and oropharynx.
B. Intubation or tracheotomy may be necessary.
C. Oxygenate or ventilate as needed.
D. Bronchodilator therapy may help maintain small airway patency.
E. If pneumonia is present, obtain cultures via transtracheal wash or bronchoalveolar lavage before antibiotic therapy.

III. Hypothermia
A. Evaporative losses from wounds contribute to heat loss.
B. Keep the animal in a warm environment; maintain cage temperature at 80° to 85° F (26.6° to 29.5° C).
C. Body temperature usually normalizes with time and especially after wound closure.
D. Watch for onset of hyperthermia by the second week.

IV. Pain control (Pascoe, 2000; Plumb, 2002)
A. Poor pain control contributes to slowed healing and immunosuppression.
B. Opioids are preferred but may cause respiratory depression.
1. Morphine 0.5 to 2.0 mg/kg IM, SC every 3 to 4 hours, or as a constant rate infusion (CRI) at 0.1 to 1.0 mg/kg/hr, with an IM or SC dose given before starting the infusion
2. Hydromorphone 0.1 to 0.2 mg/kg IM, IV, SC every 4 to 6 hours
3. Fentanyl 2 to 5 μg/kg IV, then as a CRI of 2 to 3 μg/kg/hr

V. Biochemical aberrations
A. Hyponatremia or hypernatremia, hypokalemia or hyperkalemia
1. Supplement as warranted.
2. Severe electrolyte aberrations can cause central nervous system alterations.

B. Hypoglycemia or hyperglycemia
1. Treat with insulin or dextrose as warranted.
2. Maintain normoglycemia to enhance wound healing and immune function.

C. Hemolysis (Norman et al., 2005)

1. Hemoglobinuria and myoglobinuria are often documented, so if present, administer IV fluids to reduce renal damage from these agents.
2. Renal damage can contribute to electrolyte abnormalities.
3. Blood transfusions may be needed to maintain the hematocrit in the low normal range.

D. Hypoproteinemia (Kern et al., 1992)
1. It is consistently documented in all severe burns.
2. Provide oncotic support, nutritional support, and plasma transfusions as warranted.
   a. For colloid oncotic pressures <12 mm Hg or total protein <4 g/dL, give the following:
      (1) Fresh or frozen plasma 10 mL/kg IV over 3 to 6 hours
      (2) Hetastarch or dextrans 20 mL/kg/day IV
      (3) Nutritional support (see below)
   b. For albumin values <1 g/dL and peripheral edema, consider 25% human albumin 2-5 mL/kg slow IV bolus, but be vigilant for signs of anaphylaxis (Mathews and Barry, 2005).
3. Protein loss is reduced once wounds are closed.

E. Other abnormalities
1. Acute renal failure can occur secondary to hypovolemia, shock, sepsis, hemoglobinuria and myoglobinuria (see Chapter 48).
2. Liver insufficiency may occur secondary to edema, splanchnic hypoperfusion, and congestion (see Chapter 37).

VI. Nutritional support

A. Hypermetabolic processes may persist for 6 to 12 months after the burn (Hart et al., 2000).
1. Doubling of cardiac output, doubling of resting metabolic rate, enhanced gluconeogenesis, insulin resistance, and increased protein catabolism are common.
2. A high-calorie, high-protein diet is recommended.

B. Enteric feeding methods are preferred.
1. Enteral feeding keeps enterocytes healthy, decreases bacterial translocation, and minimizes infection rates.
2. Enteral feeding methods include oral intake, as well as nasoesophageal, nasogastric, esophagostomy, gastrostomy, and jejunostomy tube feedings.

C. Vitamin and mineral supplementation is recommended.

D. Parenteral nutrition is required if the enteric route cannot be used.

E. Estimate basal metabolic rate in kilocalories at body weight (kg) × 30 + 70.

Monitoring of Animal

I. Level of monitoring is dependent on severity of the clinical signs.

A. Moribund, critical animals require intensive monitoring.
1. Hematocrit, total solids, blood glucose, CVP, blood pressure every 4 to 6 hours
2. Blood gases, serum electrolytes and biochemistry panel every 12 to 24 hours
3. Physical examination and wound care every 12 to 24 hours
4. CBC and coagulation profiles every 24 to 48 hours
5. Thoracic radiography or other imaging as indicated by clinical signs

B. Stable animals may only require initial diagnostic tests and continued wound care.
1. Initial CBC, serum biochemistry profile with electrolytes, and thoracic radiography
2. Physical examination and wound care every 12 to 24 hours

II. Wound healing can be prolonged (>6 months), and some animals require lengthy hospitalization (Probst et al., 1984).

A. Multiple surgeries may be required.

B. Emotional and financial dedication of the owner is necessary.

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CHAPTER 135

Heat Prostration

Efrat Kelmer | Marie E. Kerl

Definition

I. Heat prostration is a multisystemic disorder that occurs with acute elevations of body temperature >40° to 41°C (104° to 106° F) (Morgan, 1985).
II. Classic or nonexertional heat stroke is exposure to high ambient temperatures that usually occurs in the summer and is precipitated by environmental or medical factors (e.g., confinement in an unventilated vehicle, laryngeal paralysis).
III. Exertional heat stroke occurs when the normal heat dissipation mechanisms cannot keep up with the amount of heat produced by the body, and it usually occurs in spring or early summer before acclimatization occurs.

Causes

I. Decreased ability to dissipate heat
  A. Exogenous factors
    1. Confinement in poorly ventilated space
    2. Lack of acclimatization to a warmer environment
    3. Increased humidity
    4. Water and shade deprivation
  B. Endogenous factors
    1. Obesity
    2. Cardiovascular diseases
    3. Central nervous system diseases
    4. Upper airway obstruction
      a. Laryngeal paralysis
      b. Brachycephalic airway syndrome
      c. Tracheal collapse
      d. Laryngeal or tracheal masses
    5. Previous episode of heat stroke
    6. Physical obstruction to heat exchange (e.g., thick haircoat)
II. Increased heat production
  A. Exogenous
    1. Drugs (data available primarily from humans)
      a. Phenothiazines: chlorpromazine, acepromazine
      b. Antihistamines
      c. Tricyclic antidepressants
      d. Anticholinergics
      e. Amphetamines
      f. Gas inhalants: halothane
    2. Macadamia nuts ingestion (Hansen et al., 2000)
    3. Hops ingestion (Duncan et al., 1997)
  B. Endogenous factors
    1. Prolonged seizure activity
    2. Hormonal hyperthermia: feline hyperthyroidism
    3. Malignant hyperthermia (rare)
    4. Exercise
    5. Eclampsia

Pathophysiology

I. The thermoregulation center, located in the preoptic region of the anterior hypothalamus, maintains the balance between heat production and loss.
  A. The range of temperatures ideal for metabolic activity is narrow.
  B. Body temperatures above this range trigger heat dissipation mechanisms.
  C. Nonpyrogenic hyperthermia (heat stroke) occurs when the body's natural mechanisms for heat dissipation are overwhelmed by elevated environmental temperatures.
II. Four mechanisms of heat exchange exist.
  A. Conduction
    1. Heat is conducted between the body and environmental objects, such as air, water, or a cold floor.
    2. Under normal conditions, conduction represents a small portion of an animal's heat loss.
    3. This mechanism is eliminated when the ambient temperature exceeds the body temperature.
  B. Convection
    1. It is the movement of air or water over the surface of the body.
    2. Under normal conditions, this is the second major source for heat loss.
  C. Radiation
    1. It involves electromagnetic exchange of heat between objects in the environment not in direct contact with the skin.
    2. Relative temperatures determine the direction of heat transfer.
    3. Under normal conditions radiant heat loss is the major source of heat loss.
  D. Evaporation
    1. Evaporation occurs when a liquid is converted to a gas.
    2. A considerable amount of heat is lost during humidification of inspired air with normal breathing.
    3. Panting enhances this mechanism as environmental temperatures increase.

III. Harmful effects of hyperthermia are related to direct thermal injury, high cellular metabolic activity and oxygen consumption, and may affect all body systems (Table 135-1).

Clinical Signs

I. History may include recent exercise, confinement to an unventilated area, prolonged exposure to sunshine without access to water or shade, exposure to certain drugs, as well as collapse or seizure activity.
II. In one study, Belgian malinois, retrievers, and brachycephalic dog breeds were overrepresented, and small dog breeds were underrepresented (Bruchim et al., 2006).
III. The severity of clinical signs is positively correlated to the maximal temperature and duration of exposure.
IV. Clinical signs may vary depending on the intensity and progression.
   A. Panting: most common clinical sign (Drobatz and Macintire, 1996)
   B. Hyperthermia (typical) or hypothermia (rare)
   C. Obtundation, dull mentation, stupor, coma
   D. Cranial nerve deficits, cortical blindness
   E. Ataxia
   F. Dehydration
   G. Tachypnea, respiratory distress
   H. Tachycardia, weak pulses
   I. Tacky, hyperemic, or pale mucous membranes
   J. Hematochezia, hematemesis
   K. Petechiation, ecchymosis
   L. Stridor or stertor with underlying upper airway obstruction
   M. Heart murmur with underlying cardiac disease
   N. Seizures from primary causes or secondary to prolonged hyperthermia

Diagnosis

I. Diagnosis is based on the presence or historical evidence of hyperthermia (body temperature >40° C (104° F), along with compatible history, clinical signs, and predisposing factors.
II. Initial diagnostic tests include the following:

TABLE 135-1

Systemic Effects of Hyperthermia on Various Body Systems

BODY SYSTEM	TIME OF OCCURRENCE	PHYSIOLOGICAL EFFECTS
Cardiovascular	Initial	Increased cardiac output and decreased systemic vascular resistance from peripheral vasodilation
	Late	Decreased cardiac output and circulatory collapse Thermal injury may cause myocardial ischemia and necrosis resulting in supraventricular and ventricular arrhythmias
Pulmonary	Initial	Pulmonary edema from cardiac dysfunction, endothelial damage, and decreased colloid oncotic pressure secondary to hypoalbuminemia
	Late	Acute respiratory distress syndrome
Central nervous	Initial	Decreased cerebral blood flow
	Late	Cerebral edema, cerebral hemorrhage, infarction, cerebellar dysfunction
Renal	Initial	Renal hypoperfusion Thermal injury may result in acute tubular necrosis
	Late	Nephrotoxicity secondary to rhabdomyolysis and hypermyoglobinemia Acute renal failure
Gastrointestinal	Initial	Ischemia leading to compromised mucosa, hematochezia, and hematemesis
	Late	Bacterial translocation, endotoxemia, sepsis
Liver	Initial	Hepatocellular degeneration, cholestasis, centrilobular necrosis Impaired protein synthesis
	Late	Liver failure
Hematologic and coagulation	Initial	Thermal injury may result in destruction of platelets and clotting factors, as well as endothelial damage
	Late	Decreased production of clotting factors owing to impaired hepatic synthesis, endothelial dysfunction, DIC
Musculoskeletal	Initial or late	Myoglobinemia and rhabdomyolysis
Immune	Initial	Inflammation
	Late	Systemic inflammatory response syndrome Immunosuppression secondary to sepsis
Acid-base status	Initial and late	Metabolic acidosis from lactic or uremic acidosis Respiratory alkalosis from hyperventilation

DIC, Disseminated intravascular coagulation.

A. Packed cell volume (PCV), total protein (TP), blood urea nitrogen (BUN), blood glucose, electrolytes, lactate, arterial blood gas analysis, prothrombin time (PT), partial thromboplastin time (PTT), or activated clotting time (ACT)
B. Blood drawn before fluid therapy for complete blood count and a biochemistry panel
C. Urinalysis
D. Indirect blood pressure, pulse oximetry (SpO_2), electrocardiography, colloid osmotic pressure

III. Clinicopathologic findings vary, depending on severity and progression.
A. Hemoconcentration secondary to dehydration
B. Elevated total protein initially, followed by hypoproteinemia
C. Prolonged PT/PTT or ACT
D. Increased BUN and creatinine from prerenal or renal azotemia
E. Decreased blood glucose from increased metabolic demand or sepsis
F. Metabolic acidosis with decreased bicarbonate, most likely from lactic acidosis
G. Respiratory alkalosis with decreased $Paco_2$ secondary to hyperventilation

Differential Diagnosis

Any cause of true fever, such as infection, inflammation, immune-mediated diseases, neoplasia, and paraneoplastic syndromes

Treatment

I. Early and aggressive goal-directed therapy of any potential heat-related injury and proactive management of complications are the keys to a successful outcome.
II. Start initial cooling measures *before* transport of the animal.
A. Wet the animal with cool tap water and use a fan to increase convective heat loss.
B. Avoid ice baths because they are uncomfortable to the animal and they increase metabolic demands from shivering, which increases cellular oxygen consumption.
C. Transport the animal in a well-ventilated vehicle.

III. Institute initial resuscitation measures immediately upon arrival to the hospital.
A. If the animal is hyperthermic, continue cooling methods.
1. In addition, apply ice packs to the jugular vein and inguinal areas.
2. Apply alcohol to the footpads.
3. Terminate cooling once the body temperature reaches 103° F (39.5° C).
B. Initiate oxygen therapy via one of the following methods:
1. Flow-by oxygen is delivered by mask or oxygen tent.
2. Oxygen may also be delivered via nasal tube.
3. If upper airway obstruction is present, consider transtracheal oxygen.
4. Use oxygen cages cautiously, as they can cause overheating.
C. Insert one or two short, large-bore intravenous (IV) peripheral catheters and initiate an isotonic crystalloid solution IV
1. If the animal is in hypovolemic or distributive shock (as determined by tachycardia, weak pulses, tachypnea, hypotension, or decreased mentation), the initial fluid rate is 90 mL/kg IV (dogs) or 60 mL/kg IV (cats) until hemodynamic parameters normalize.
2. If the animal remains hypotensive (systolic blood pressure <80 mm Hg), administer a bolus (5 to 10 mL/kg IV followed by 20 mL/kg/day as a constant rate infusion IV) of a colloid solution (hydroxyethyl starch, dextran 70).
3. If a colloid solution is administered, crystalloid volume may need to be reduced by one third.
4. If hypotension persists despite appropriate fluid resuscitation, consider inotropic therapy (dobutamine 5 to 15 μg/kg/min IV) or vasopressor therapy (dopamine 5 to 15 μg/kg/min IV).
D. If hypoglycemia is present, give 50% dextrose as a bolus (0.5 g/kg IV, diluted 1:1 with sterile water), and supplement dextrose in the IV crystalloid solution.
1. Add 50 mL of 50% dextrose to 1 L crystalloid solution to achieve a final concentration of 2.5% dextrose.
2. Add 100 mL of 50% dextrose to 1 L crystalloid solution to achieve a final concentration of 5% dextrose.
E. Administer diazepam 0.5 mg/kg IV as needed to control seizures.
F. Initiate treatment for life-threatening ventricular arrhythmias.
1. Give dogs lidocaine at 2 mg/kg IV bolus, followed by 50 to 100 μg/kg/min IV as needed.
2. Use lidocaine with extreme caution and in lower doses in cats (0.2 mg/kg IV).
G. Consider giving mannitol 0.5 to 1.5 g/kg IV over 20 minutes for severe neurologic signs suggestive of cerebral edema; mannitol should be avoided in animals that are severely dehydrated.
H. Administer fresh frozen plasma at 10 mL/kg IV over 2 to 4 hours if coagulation tests are prolonged or if there is other evidence suggestive of DIC.

IV. Apply additional treatments and supportive care as indicated.
A. Identify and manage concurrent predisposing conditions associated with heat stroke.
B. Insert a urinary catheter for maintenance of good hygiene and for monitoring of urine output, especially when acute renal failure is suspected.
C. Place a central IV catheter in critically ill animals to facilitate repeated blood sampling and measurement of central venous pressure.
D. Avoid placement of a jugular catheter in animals with severe coagulopathies.
E. Consider broad-spectrum antibiotics, especially if hematemesis and hematochezia are present, or if evidence of sepsis exists (e.g., neutropenia, degenerative left shift, hypoglycemia).

F. Give gastrointestinal protectants, antacids, and antiemetic drugs for nausea, vomiting, or suspected gastrointestinal ulceration.
   1. Sucralfate 0.5 to 1 g PO TID to QID (dogs)
   2. Histamine receptor 2 antagonists (H_2 blockers), such as famotidine 0.5 to 1 mg/kg IV, PO SID to BID, or ranitidine 1 to 2 mg/kg IV, PO BID
   3. Proton pump inhibitors, such as omeprazole 0.7 to 1 mg/kg PO SID or pantoprazole 0.7 to 1 mg/kg IV SID (dogs)
   4. Dopamine antagonists, such as metoclopramide 0.1 to 0.4 mg/kg SC, followed by 1 to 2 mg/kg/day IV as a constant rate infusion (dogs)
   5. Serotonin 5-HT_3 receptor antagonists, such as dolasetron 0.6 mg/kg IV, SC SID

G. Nursing care and good hygiene are indicated for recumbent animals.
   1. Comfortable bedding
   2. Periodic rotation
   3. Frequent cleaning of animal and cage, especially if diarrhea or vomiting occurs
   4. Skin protectants, such as silver-sulfadiazine, zinc oxide ointments, or talc to avoid urine scald

Monitoring of Animal

I. Maintain body temperature in the normal range.

II. Other parameters to monitor include the following:
   A. Blood pressure
      1. If the animal is hypotensive at presentation, measure blood pressure every 30 minutes or after IV fluid boluses until normotension is achieved.
      2. Measure blood pressure BID to QID thereafter.
      3. Systolic blood pressure is maintained >80 mm Hg.
   B. Measure PCV/TP, blood glucose, and electrolytes every 4 to 12 hours.
   C. Assess mentation hourly.
   D. Assess other neurologic parameters SID to BID.
   E. Closely monitor urine output and renal function.
      1. Urine output is maintained > 1 mL/kg/hour.
      2. Measure BUN, creatinine, and urine specific gravity SID.
   F. Record body weight at least SID; it should remain constant once the animal is rehydrated.
   G. Evaluate CBC and coagulation profiles SID and after plasma transfusions.
   H. Measure central venous pressure every 4 to 6 hours (reference range is 2 to 10 cm H_2O).
   I. Measure colloid osmotic pressure SID (reference range is 18 to 24 mm Hg).
   J. Monitor serum lactate every 24 hours (reference range is 1 ± 0.5 mmol/dL).
   K. Monitor electrocardiography continuously or every 4 to 6 hours.

III. Increase or taper the frequency of monitoring according to the progression of the animal.

IV. The main predictor of outcome is the duration and degree of hyperthermia.
   A. Hypothermia and coma at the time of presentation have been associated with a poor prognosis (Drobatz and Macintire, 1996).
   B. Seizures, hypoglycemia, obesity, and serum creatinine >1.5 mg/dL after 24 hours have been associated with increased mortality (Bruchim et al., 2006).
   C. In one study, 80% of dogs that survived the first 24 hours of hospitalization were later discharged (Drobatz and Macintire, 1996).

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CHAPTER 136

Envenomations

Alisa N. Reniker

VENOMOUS SNAKES

Definition

I. Envenomation occurs when a poisonous secretion is injected into the victim by bite or sting of a reptile, insect, or arachnid.
II. Morbidity or mortality results from localized or systemic reactions.

Causes and Classification

I. There are >3000 snake species worldwide, with approximately 450 species in five families (Colubridae, Crotalidae, Elapidae, Hydrophiidae, Viperidae) being venomous (Gold et al., 2002).
II. Twenty-five of 120 species in the continental United States are venomous (Gold et al., 2004).
  A. All venomous snakes in the United States are pit vipers except the coral snake.
  B. Alaska, Maine, and Hawaii are the only states without venomous snakes.
    1. Pit vipers
      a. Family Viperidae, subfamily Crotalinae, genus *Crotalus* and *Sistrurus* (rattlesnakes) or *Agkistrodon* (cottonmouths and copperheads)
      b. Identifying features: triangle-shaped head, elliptical pupils, heat-sensing foramen between eyes and nostrils, retractable canalized fangs, single row of subcaudal plates
    2. Coral snake
      a. Family Elapidae, genus *Micrurus* and *Micruroides*
      b. Sonoran coral snake bites unlikely to cause significant clinical symptoms
      c. Identifying features: alternating red, yellow, and black stripes with red and yellow adjacent to each other; rounded head; round pupils; short, fixed fangs; no heat-sensing pits

Pathophysiology

I. Snake venom
  A. Composed of enzymes, low-molecular-weight polypeptides, and proteins of 6 to 100 kD (Gold et al., 2002).
  B. Composition varies by species, age of snake, season, time since last envenomation, and geographic location.
  C. Simplification of venom components into neurotoxins, myotoxins, hemotoxins, or cardiotoxins is misleading, as components bind to numerous receptor sites and affect multiple organ systems (Gold et al., 2004).
II. Crotalid venom
  A. They are cytotoxic and necrolytic owing to endopeptidases/proteolytic enzymes.
  B. Immobilization of prey is achieved through induction of hypovolemic shock.
    1. Polypeptides damage vascular endothelial cells, causing loss of intravascular fluid into the interstitium.
    2. Hyaluronidase breaks collagen bonds and facilitates venom dispersion.
    3. Metalloproteinases destroy basement membrane architecture and cause edema, extravasation, and ecchymotic hemorrhages.
    4. Endogenous and exogenous phospholipase A_2 acts upon membrane phospholipids to liberate arachidonic acid and initiate the inflammatory cascade.
    5. Vasodilatory prostaglandins and bradykinins exacerbate hypotension.
III. Elapid venom
  A. It is neurotoxic through the actions of acetylcholinesterase.
    1. Immobilization of prey occurs via nondepolarizing neuromuscular blockade of the postsynaptic junction.
    2. Generalized flaccid paralysis, central nervous system (CNS) depression, and vasomotor tone instability result.
  B. Minimal tissue damage occurs, but hemolysis develops in dogs because of phospholipase A_2 activity.

Clinical Signs

I. Crotalid envenomation
  A. Local wound
    1. Signs usually develop within 30 minutes of the bite and include single or multiple puncture wounds, pain at the bite site, edema or ecchymotic bruising, and serosanguineous to hemorrhagic discharge from puncture wounds.
    2. Up to 25% of pit viper and 50% of coral snake bites may be "dry," with no venom release (Gold et al., 2004).
  B. Systemic effects
    1. Hypovolemic shock leads to tachycardia, weakness, tachypnea, pallor, mental dullness, poor pulse quality,

cold extremities, hypotension, and prolonged capillary refill time.
2. Up to one third of effective circulating volume can be lost to the envenomated area within 1 hour of the bite (Hudelson and Hudelson, 1997).

C. Hematologic effects
1. Disseminated intravascular coagulation (DIC)-like coagulopathy
   a. Thrombin-like components convert fibrinogen to fibrin without activation of factor XIII and stable crosslink formation.
   b. Unstable clot is degraded by plasminogen, and defibrination and elevation in fibrin degradation products (FDP) result because of a net anticoagulative effect.
   c. Effects differ from true DIC in that platelets and Factor VIII are not consumed and D-dimers are not formed.
   d. Normal coagulation and fibrin crosslinking are not inhibited, so life-threatening hemorrhage is rare.
2. Thrombocytopenia
   a. It may occur initially or up to 2 weeks after appropriate therapy.
   b. Possible pathophysiologic mechanisms include platelet aggregating properties of Western diamondback, blacktail, and timber rattlesnake venoms; prostaglandins and endogenous and exogenous phospholipase A_2; and severe polypeptide-mediated endothelial injury, with platelet consumption at the envenomation site.
3. Echinocytes
   a. Erythrocytes with uniformly sized, regularly spaced membrane projections that appear similar to crenation artifact
   b. Possibly from adenosine triphosphate depletion of membrane pumps, alteration of red blood cell (RBC) membrane by phospholipase, or dehydration of RBC via electrolyte depletion
   c. Occur in 89% of envenomated dogs within 24 hours of bite (Walton et al., 1997)
   d. Supportive, but not definitively diagnostic for envenomation

D. Cardiac effects
1. No specific cardiotoxic constituent
2. Hypotension from hypovolemia with subsequent decreased coronary perfusion: multitude of arrhythmias
3. Hyperkalemia from rhabdomyolysis: bradycardia, atrial standstill, potentially cardiac arrest
4. Coagulopathy-induced myocardial hemorrhage: arrhythmias from disrupted conduction

E. Pulmonary effects
1. Acute respiratory distress syndrome (ARDS): tachypnea, progressive hypoxemia, pulmonary crackles, coughing, and cyanosis in the absence of left-sided heart failure or volume overload
2. Severe pulmonary congestion secondary to prostaglandin and phospholipase A_2-mediated endothelial injury, increased vascular permeability, alveolar hemorrhage

F. Neuromuscular effects
1. Hypoventilation or respiratory muscle paralysis
2. Mojave toxin: presynaptic nerve blockade, with greatest effect on the motor axon terminals of the diaphragm (Hudelson and Hudelson, 1997)
3. Crotoxin: neurotransmitter release inhibited through leakage of acetylcholine vesicles at the presynaptic membrane (Hudelson and Hudelson, 1997)

G. Muscular and soft tissue changes
1. Tissue necrosis and wound sloughing occur within 6 to 24 hours of bite.
   a. Rhabdomyolysis may be more common with Mojave and Western diamondback envenomations.
   b. Phospholipase A_2 damages sarcolemma and myocyte mitochondria, with vacuolation and loss of muscle striation.
   c. Collagenase facilitates spread of venom through destruction of connective tissue barriers.
2. Compartment syndrome (constriction of nerves, blood vessels, or tendons from swelling within a closed anatomic space) is more effectively treated by antivenom administration than fasciotomy, and is an uncommon complication in dogs and cats.

H. Nephrotoxicity
1. Azotemia, hyperphosphatemia, hyperkalemia, metabolic acidosis, dehydration, polyuria, or oliguria/anuria may occur secondary to hypotension and hypovolemia.
2. Acute renal failure is more likely with Mojave rattlesnake venom-induced rhabdomyolysis.
   a. Venom toxin causes proximal tubular injury.
   b. Myoglobinuria and hemoglobinuria can result in tubular damage.

II. Elapid envenomation

A. Local wound
1. Elapids envenomate by chewing rather than striking.
2. Fang wounds often are not evident, but small puncture wounds are possible.
3. They differ from crotalid wounds in that substantial tissue necrosis, petechiation, edema, and pain are not characteristic, but local paresthesia is possible.

B. Systemic effects
1. Neurotoxicity occurs secondary to motor axon terminal damage or from a competitive, nondepolarizing, postsynaptic acetylcholine blockade at the neuromuscular junction.
2. Clinical signs include generalized muscle weakness or fasciculations, cranial nerve palsy, vomiting, seizures, tremors, drowsiness or disorientation, dysphagia, salivation, and dyspnea.
3. Aspiration pneumonia, hypotension, and ventricular tachycardia may occur.

4. Death from respiratory failure can occur as quickly as 4 hours after the snakebite.
5. Weakness and progressive paralysis generally begin within 3 hours after the bite, but onset may be delayed up to 48 hours after envenomation.

Diagnosis

I. Crotalid envenomations
   A. Local signs: puncture wounds, edema, pain, serosanguineous discharge
   B. Complete blood count (CBC)
      1. Supportive evidence includes echinocytes and thrombocytopenia.
      2. Hemolysis, anemia, or hemoconcentration are also possible.
   C. Coagulation profiles
      1. Envenomation coagulopathy does not produce D-dimers.
      2. Partial thromboplastin time, prothrombin time, fibrin degradation products, and activated clotting time are potentially elevated.
   D. Urinalysis: renal tubular casts, myoglobinuria, hemoglobinuria
   E. Other diagnostic tests as indicated by clinical signs
      1. Arterial blood pressure: hypotension common with hypovolemia
      2. Serum biochemistry panel: prerenal or renal azotemia, hypoalbuminemia, hyperkalemia, creatine kinase elevations possible
      3. Blood gases
         a. Evaluate ventilatory and oxygenation capabilities of dyspneic animals.
         b. Metabolic acidosis may arise secondary to hypoperfusion, renal disease, or rhabdomyolysis.
         c. Hypoventilation with hypercapnia may occur with Mojave envenomation.
         d. Hypoxemia can occur with ARDS.
      4. Electrocardiography: arrhythmias
      5. Thoracic radiography: diffuse, bilateral pulmonary infiltrates with ARDS

II. Elapid envenomations
   A. Clinical signs: progressive weakness, flaccid paralysis, coma, or dyspnea in conjunction with small puncture wounds and little or no soft tissue swelling
   B. CBC and serial hematocrits: hemolytic anemia (dogs)
   C. Arterial blood gas analysis: elevated carbon dioxide (CO_2), reduced oxygenation
   D. Thoracic radiography to rule out primary pulmonary diseases, respiratory muscle paralysis, or aspiration pneumonia

Differential Diagnosis

I. Crotalid envenomations: animal bites, allergic reactions, insect envenomation, trauma
II. Elapid envenomations: polyradiculoneuritis, tick paralysis, botulism, bromethalin or ionophore poisoning, acute polyneuritis, myasthenia gravis, head or spinal trauma

Treatment and Monitoring

I. Crotalid envenomations
   A. First aid
      1. Incision and suction, tourniquets, constriction bands, and cryotherapy are not recommended owing to high complication rates.
      2. Keep the animal quiet and restrict activity.
   B. Intravenous fluids therapy
      1. Hypovolemic shock occurs with any moderate to severe envenomation, which makes fluid therapy crucial.
      2. Give crystalloid (60 to 90 mL/kg IV) or colloidal solutions (5 to 20 mL/kg IV) as boluses, to effect.
   C. Inotropic and pressor support for persistent hypotension
      1. Inotropic agent: dobutamine 5 to 15 μg/kg/min IV continuous rate infusion (CRI)
      2. Pressor agents: dopamine 5 to 20 μg/kg/min IV as CRI or norepinephrine 0.01 to 0.02 μg/kg/min IV as CRI
      3. Antivenin: helpful for hypotension refractory to above therapies
   D. Analgesia
      1. Nonsteroidal antiinflammatory drugs are contraindicated because they interfere with platelet function and may cause gastrointestinal irritation and nephrotoxicity.
      2. Opioids are safe and efficacious.
         a. Morphine
            (1) Dogs: 0.5 to 2.0 mg/kg IM, SC every 3 to 4 hours or 0.05 to 0.1 mg/kg/hr IV as CRI
            (2) Cats: 0.1 to 0.4 mg/kg IM, SC every 3 to 6 hours with concomitant sedation as needed; may cause histamine release
         b. Hydromorphone
            (1) Dogs: 0.05 to 0.2 mg/kg IV, IM, SC every 2 to 4 hours
            (2) Cats: 0.02 to 0.05 mg/kg IV, IM, SC every 2 to 4 hours with concurrent sedation as needed
         c. Buprenorphine
            (1) Dogs: 0.005 to 0.02 mg/kg IV, IM SC every 6 to 12 hours
            (2) Cats: 0.005 to 0.01 mg/kg IM, IV, SC every 6 to 12 hours; concurrent sedation as needed
   E. Antivenin/antivenom
      1. *Antivenin Crotalidae Polyvalent* (ACP) (Fort Dodge Laboratories, Fort Dodge, Ind.) is an antivenom of equine origin with neutralizing effects against the venom of rattlesnakes; the copperhead and cottonmouth moccasins; Fer-de-lance and other *Bothrops* spp.; tropical rattler, and bushmaster snakes.
         a. There are no controlled trials of antivenom use in companion animals.
         b. Information regarding appropriate case selection and dose is anecdotal.
         c. Reported doses vary from 1 to 10 vials (10 to 100 mL) (Hackett et al., 2002; Willey et al., 2005).

d. As little as 18% of each vial contains protective immunoglobulin (Ig) G, so large doses are often required (Hudelson and Hudelson, 1997).
e. Because of high glycosylation of equine IgG in the antivenin, immune reactions such as anaphylaxis (type I) or serum sickness (type III) are possible.

2. Crotalidae polyvalent immune Fab, ovine (*CroFab;* Savage Laboratories, Melville, N.Y.) is a mixed, monospecific, polyvalent antivenom created via immunization of sheep with Western diamondback, Eastern diamondback, Mojave rattlesnake, and cottonmouth venoms.
a. It is approximately 5.2 times more potent and much less antigenic than ACP.
b. Clinical improvement in coagulation, CNS, gastrointestinal, and cardiovascular abnormalities is common after administration.
c. CroFab has been subject to evidence-based research, and more definitive dosing recommendations are available for humans, who are given an initial IV loading dose (4 to 6 vials) followed by maintenance doses at 6, 12, and 18 hours, as needed.
d. No controlled animal trials or dosing information for CroFab have been published.

3. General recommendations for antivenin administration are as follows:
a. Cottonmouth or copperhead bites are less likely to require antivenin than Eastern diamondback, Western diamondback, or Mojave rattlesnake envenomations.
b. Antivenin is reconstituted with the diluent, warmed to body temperature, and diluted in 50 to 250 mL of crystalloid fluids.
c. Initial vial is infused IV over 30 minutes, watching for allergic reactions (hyperemia, hyperthermia, nausea, vomiting, angioedema).
d. A negative intradermal test does not preclude severe reactions.
e. Administer additional vials as needed based on the clinical response (see Table 136-1).
f. Antivenin is given as soon as possible but may be useful in reversing venom-induced coagulopathies even days after the bite.
g. Consider antivenin in any animal with evidence of progressive injury (e.g., rapidly worsening local injury, clinically significant uncontrolled coagulopathy, and unabated systemic signs, such as hypotension or altered mental status).
h. Smaller pets or animals suffering envenomations of extremities and the tongue or injection of venom intravascularly may require larger doses.

F. Prophylactic antibiotics
1. Antibiotics have been recommended owing to the presence of pathogenic microbes in the oral cavities of venomous and nonvenomous snakes.
2. Although common isolates include *Pseudomonas* spp., *Proteus* spp., *Escherichia coli*, *Enterobacter* spp., *Klebsiella* spp., *Clostridium* spp., *Corynebacterium* spp., and other anaerobes, recent studies indicate very low wound infection rates in people, so prophylactic antibiotic administration is no longer standard (Clark et al., 1993).
3. Wound culture is advocated if evidence of infection is present after local venom effects have subsided.

G. Corticosteroids
1. Administration is controversial.
2. Steroids may block endogenous and exogenous (venom) phospholipase A_2 effects and diminish the inflammatory response.
3. Detrimental effects include immune suppression and gastrointestinal irritation.
4. If corticosteroids are administered, short, rapid-acting preparations (e.g., prednisolone sodium succinate) should be given as soon as possible after envenomation or used only for treatment of anaphylaxis or serum sickness.

H. Antihistamines
1. Although venom components can induce histamine release, neither determination of systemic histamine levels or evaluation of antihistamine efficacy has been undertaken.
2. Hypovolemia and hypotension are relative contraindications for antihistamine use.
3. Antihistamines may be administered in dogs and cats for their sedative effects or for treatment of allergic reactions to antivenin.

I. Blood products
1. Antivenin is the most effective treatment for venom coagulopathy and thrombocytopenia.
2. If venom components are circulating, transfusion efficacy is diminished and antivenom administration to bind the venom is indicated.
3. Because the half-life of venom may exceed that of the antivenin, recurrent coagulopathies may occur.

J. Intubation and mechanical ventilation
1. If $Paco_2$ is >50 to 60 mm Hg, Po_2 <50 mm Hg
2. If substantial breathing effort is noted

K. Monitoring parameters
1. Frequent monitoring is required within the first 24 to 48 hours.
2. Upon admission, measure the wound and submit preliminary laboratory tests.
3. Perform serial evaluations of vital parameters (e.g., heart rate, respiratory rate, blood pressure, capillary refill time, etc.), hematocrit, total solids, coagulation panel, wound progression, and mentation at 1- to 6-hour intervals.

II. Elapid envenomations
A. First aid treatment is no longer advocated.
B. Hospitalize and closely monitor the animal for at least 48 hours, as onset of clinical signs can be delayed for 10 to 18 hours (Peterson and McNally, 2006).

Text continued on p. 1268.

TABLE 136-1

Modified Snakebite Severity Score*

Pulmonary System	Score
No abnormal signs	0
Panting; closed mouth respiration >30 breaths/min; mild increase in inspiratory/expiratory effort	1
Rapid panting; closed mouth respiration >60 breaths/min; moderate increase in effort (abdominal push, use of accessory muscles)	2
Cyanosis; orthopnea; harsh panting; or respiratory arrest	3
Cardiovascular System	
No abnormal signs	0
Tachycardia (giant breeds >140 beats/min, medium to large breeds >160 beats/min, small and toy breeds >180 beats/min, puppies >220 beats/min); benign dysrhythmias (unifocal ventricular premature contractions); hypertension (systolic BP >180 mm Hg, mean BP >120 mm Hg), or injected mucous membranes or hyperdynamic pulses	1
Tachycardia (see above) with mild hypotension (systolic BP <100 mm Hg, mean BP >60 mm Hg) or pallor, or mild decrease in pulse pressure	2
Tachycardia or bradycardia (<60 beats/min) or moderate to severe hypotension (systolic BP <80 mm Hg, mean BP <60 mm Hg), pale mucous membranes, weak pulses, or severe arrhythmias	3
Local Wound Features	
Puncture wounds and mild serosanguineous discharge, with minimal swelling or pain	0
Edema/swelling, pain, petechia, bleeding, erythema within 2 to 4 cm of bite site; wound has not worsened since previous assessment	1
Local wound swelling/pain extending >4 cm past bite site, but involving <50% length of extremity (or not extending past the thoracic inlet for facial bites); minimal worsening of wound since previous assessment	2
Severe ecchymosis, edema, extensive bleeding or necrosis of bite site; swelling involves >50% the length of extremity (or past thoracic inlet); substantial worsening of wound pain, swelling, or bruising since previous assessment	3
Gastrointestinal System	
No abnormal signs	0
Abdominal pain, tenesmus, or nausea	1
Vomiting or diarrhea	2
Repeated vomiting, diarrhea, hematemesis, or hematochezia	3
Hematological System	
Coagulation profile (prothrombin time, partial thromboplastin time, or activated clotting time), platelet count, and PCV all normal	0
Mild elevations of coagulation values (<1.5 × normal value) *or* mild thrombocytopenia (100,000 to 150,000/μL) *or* mild hemoconcentration (PCV >56% but <64%)	1
Moderate elevation of coagulation values (1.5 to 3 × normal value) *or* moderate thrombocytopenia (50,000 to 100,000/μL); *or* PCV >65% but <70%	2
Severe alterations of coagulation values (>3 × normal values) *or* severe thrombocytopenia (<50,000/μL) *or* PCV >70%	3
Central Nervous System	
Normal mentation	0
Lethargic or anxious, but responsive to external stimuli	1
Moderate to severe depression, ataxia, or responsive only to noxious stimuli	2
Loss of consciousness or seizures	3

BP, Blood pressure; *PCV,* packed cell volume.

*Although not validated for animals, a scoring system, such as the modified Snakebite Severity Score, may provide more objective serial assessment of envenomations. Total score is derived by adding scores for each category. Animals with low or static scores are likely to have mild to moderate envenomations, whereas those with high or rapidly increasing scores are likely to have suffered a more severe envenomation and require aggressive intervention. Evaluate upon admission, then at 1, 2, 6, 12, and 18 hours after initial hospitalization. This tool is also useful when comparing severity of envenomation and outcomes.

TABLE 136-2

Insect, Scorpion, and Spider Envenomations

ORDER	INSECT CLASSIFICATION	PATHOPHYSIOLOGY	CLINICAL SIGNS	DIFFERENTIAL DIAGNOSIS	TREATMENT AND MONITORING
Hymenoptera	Families: 1. Apidea: bees 2. Vespidae: hornets, yellow jackets, wasps 3. Formicidae: fire ants	Localized or generalized hypersensitivity or toxic reactions arise from vasoactive substances (e.g., histamine, serotonin, acetylcholine, apamin, phospholipase, hyaluronidase, melittin, kinins), immunoglobulin E antibodies, mast cells, and basophils	Localized reaction: pain/swelling Localized hypersensitivity reaction: angioedema of face, pinnae, oropharynx, extremities Generalized signs: urticaria to anaphylaxis Possible neurologic signs: ataxia, cranial nerve abnormalities, seizures GI signs: melena, hematemesis, hematochezia Coagulation abnormalities Shock, hypotension Serum sickness: type III immune reaction develops 3 days to 2 weeks after sting and causes vasculitis, glomerulonephritis, or neuropathy Massive envenomation: lethal dose = 20 stings/kg Rhabdomyolysis, acute renal failure, immune-mediated hemolytic anemia, neurologic deficits, and GI bleeding may occur	Other causes of anaphylactic shock Contact dermatitis Drug reaction Crotalid envenomation	Localized reaction: Remove stinger, apply cool compress Localized hypersensitivity: Diphenhydramine 1 mg/kg SC, IM BID Dexamethasone sodium phosphate 0.1 to 0.2 mg/kg IV or prednisolone sodium succinate 0.5 to 1 mg/kg IV once, followed by prednisone 0.5 to 1 mg/kg PO SID and tapered over 5 to 7 days for severe swelling Hospitalization and observation for rapid progression of swelling Generalized signs: Provide supplemental oxygen and ensure patent airway (oral intubation or tracheostomy) as needed for respiratory distress Fluid administration as needed for hypovolemic shock Anaphylactic shock: IV fluid resuscitation Epinephrine (1:10,000) 0.01 to 0.1 mL/kg IV once Diphenhydramine 1 mg/kg IM Prednisolone sodium succinate 5 to 10 mg/kg IV Possible supportive measures include blood transfusions, inotropic or pressor support, treatment for cardiac arrhythmias, and analgesics Hospitalization is recommended for at least 24 hours after resolution of clinical symptoms

GI, Gastrointestinal.

TABLE 136-2

Insect, Scorpion, and Spider Envenomations—*cont'd*

ORDER	INSECT CLASSIFICATION	PATHOPHYSIOLOGY	CLINICAL SIGNS	DIFFERENTIAL DIAGNOSIS	TREATMENT AND MONITORING
Scorpion	Most native scorpions are harmless In certain states (Arizona, Texas New Mexico, Nevada, California), and Mexico, *Centruroides exilicauda (sculpturatus)* is venomous	Venom contains phosphodiesterase, hyaluronidase, histamine, glycosaminoglycan, serotonin, and tryptophan	Most stings result in localized pain and swelling *Centruroides* stings cause immediate pain followed by tachycardia, hypotension, tachypnea, hypersalivation, and weakness Adverse effects on neurological, renal, cardiac, and hemolymphatic systems are caused by altered ion channel permeability	Organophosphate, carbamate, or pyrethrin toxicity Idiopathic epilepsy	Specific antivenom is not available. Provide supportive care with IV fluids, seizure control (benzodiazepines or barbiturates), and analgesia
Arachnid	Black widow: *Latrodectus* spp. Brown recluse: *Loxosceles* spp. cause significant envenomation of small animals	Female black widow: Alpha-latrotoxin causes excessive neurotransmitter release Brown recluse: Cytotoxic and necrolytic reactions arise from hyaluronidase, sphingomyelinase D, and other proteolytic enzymes. Chemotaxis of neutrophils by sphingomyelinase D mediates tissue injury	Black widow: Some bites (15%) are dry Severity depends on spider size, season, victim size and age, and bite location Cats are more severely affected than dogs, with death from respiratory muscle paralysis Vocalization, salivation, restlessness, muscle spasms, cramping, abdominal and pelvic rigidity may occur and be followed by flaccid paralysis, vomiting, seizures, or ataxia Brown recluse: "Bull's eye" lesion (necrotic center surrounded by concentric ischemic/erythematous rings) may be confined or be accompanied by extensive tissue necrosis Fever, arthralgia, hemolytic anemia, renal dysfunction, DIC, or seizures are possible	Black widow: Acute abdominal conditions Arterial thromboembolism Intervertebral disk disease Rabies Brown recluse: Toxic epidermal necrolysis Decubital ulcer Third-degree burn Bacterial skin infection Idiopathic immune-mediated hemolytic anemia	Black widow: Lyovac antivenin is available Dose is reconstituted in 50 to 100 mL of 0.9% NaCl and administered IV over 15 to 30 minutes Fluid resuscitation with IV crystalloids and colloids is given as needed Narcotic analgesics Calcium gluconate (10%) for hypocalcemic muscle spasms (0.5 to 1.5 mL/kg IV) Benzodiazepines for muscle tremors if normocalcemic Glucocorticoids and antihistamines are indicated if allergic reaction to antivenin occurs Brown recluse: No specific antivenin is available Surgical wound excision is not recommended Serial wound lavage and debridement may be necessary Broad-spectrum antibiotics are given for secondary pyoderma Dapsone 1 mg/kg PO SID × 14 days may help to ameliorate wound injury by inhibiting neutrophils

DIC, disseminated intravascular coagulopathy.

C. Care is largely supportive and may include IV fluid therapy, nutritional support, and mechanical ventilation.
D. Antibiotic usage is controversial.
E. An equine origin *Micrurus* spp. antivenin is no longer in production, and no other approved North American coral snake antivenin is available.
F. Murine studies suggest Australian tiger snake and Mexican coral snake antivenin may be protective.
   1. Antivenin administration is considered in any animal with suspected coral snake envenomation.
   2. Once signs of neurotoxicity have appeared, reversal of clinical abnormalities may not be possible.
   3. Dosage of antivenin depends upon the amount of venom injected relative to the body mass.
      a. As little as 4 to 5 mg of venom is lethal to a person, and a large coral snake may inject up to 20 mg (Peterson and McNally, 2006).
      b. Each vial of antivenin neutralizes approximately 2 mg of venom.

INSECTS, SCORPIONS, SPIDERS

See Table 136-2.

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Appendix I
Normal Physiologic Values

Normal Parameters for Patient Monitoring*

PARAMETER	NORMAL VALUE
Body temperature	101.5° F (38.6° C)
Heart rate (beats/min)	
Dog	70-160
Cat	140-210
Respiratory rate (breaths/min)	
Dog	16-20
Cat	20-24
Capillary refill time (CRT) (sec)	<2
Blood pressure (mm Hg)†	
Systolic	130-170
Diastolic	60-100
Urine output (mL/kg/hr)	1-2
Central venous pressure (CVP) (cm H_2O)	
Normal	0-10
Shock	0
Overhydration	8-12
Heart failure	20
Cardiac tamponade	22-25
Arterial blood gases (room air)	
pH	7.35-7.45
$Paco_2$ (mm Hg)	29-36
Pao_2 (mm Hg)	85-95
HCO_3 (mEq/L)	17-25
Venous blood gases	
pH	7.35-7.45
Pco_2 (mmHg)	29-42
Po_2 (mmHg)	40-60
Lactic acid (mmol/L)	<1.0

*Modified from Morgan (1985).

†Data from Weiser et al. (1977) and Morgan (1986).

Normal Cerebrospinal Fluid Values

PARAMETER	DOG	CAT
Color	Clear, colorless	Clear, colorless
Pressure (mm H_2O)	<170	<100
Cell count/μL		
Mononuclear WBCs	<5-8	<5-8
RBCs	None	None
Cell types	Small lymphocytes, few monocytes	
Protein (mg/dL)	<25	<20
Glucose (mg/dL)	61-116	85

Modified from Bentinck-Smith (1983).

WBCs, White blood cells; *RBCs*, red blood cells.

Normal Hematologic Values

PARAMETER	DOG	CAT
PCV (%)	37-55	27-45
Hemoglobin (g/dL)	12-18	9-15
Erythrocytes (10^6/μL)	5.5-8.5	6-10
MCV (fL)	60-77	37-50
MCHC (g/dL)	32-36	30-36
RBC life span (days)	120	70
Reticulocyte count (%)	0-1.5	0-0.4
Platelets (10^3/μL)	175-500	190-400
Leukocytes (/μL)	6000-17,000	5000-19,500
Segmented neutrophils (/μL)	3000-11,500	2500-12,500
Band neutrophils (/μL)	0-300	0-300
Lymphocytes (/μL)	1000-4800	1500-7000
Monocytes (/μL)	150-1350	0-850
Eosinophils (/μL)	100-750	0-750
Basophils (/μL)	Rare	Rare
Total solids (g/dL)	6-8	6-8

PCV, Packed cell volume; *MCV*, mean cell volume; *MCHC*, mean corpuscular hemoglobin concentration; *RBC*, red blood cell.

Corrections for Reticulocyte Counts

(1) Corrected reticulocyte count (%) = observed reticulocyte count (%) × actual PCV ÷ normal PCV

(2) $$\text{Reticulocyte index} = \text{reticulocyte count (\%)} \times \frac{\text{actual PCV}}{\text{normal PCV}} \times \frac{1}{\text{Reticulocyte maturation time (days)}}$$

Reticulocyte Maturation Time for Various Packed Cell Volumes

PACKED CELL VOLUME (%)	MATURATION TIME (days)
45	1.0
35	1.5
25	2.0
15	2.5

Insert corresponding maturation time into Equation 2.

Normal Urinalysis Values

PARAMETER	DOG	CAT
Color	Light yellow	Yellow
Turbidity	Clear	Clear
Specific gravity	1.015-1.045	1.015-1.060
Osmolality (mOsm/kg)	500-2400	1200-3200
Volume (mL/kg/day)	24-40	22-30
Semiquantitative Tests		
Protein	0-1	0-1
Ketones, glucose	0	0
Urobilinogen	0-1	0-1
Bilirubin	1+	0-1
pH	5.0-7.0	5.0-7.0
Quantitative Tests		
Creatinine (mg/dL)	100-300	110-280
Urea (g/dL)	1.0-2.5	1.0-3.0
Protein (mg/dL)	0-30	0-20
Sodium (mEq/L)	20-165	
Potassium (mEq/L)	20-120	
Calcium (mEq/L)	2-10	
Phosphorus (mEq/L)	50-180	
Amylase (SU)	50-150	3-120

Modified from Bentinck-Smith (1983).

Normal Coagulation Values

TEST	DOG	CAT
Platelet count (/μL)	175,000-500,000	190,000-400,000
Clot retraction at 37° C (hr)	1-2	1-2
Bleeding time, buccal mucosal (min)	2-4	1-5
Cuticle bleeding time (min)	3-6	3-6
Partial thromboplastin time (aPTT) (sec)	14-25	14-28
Activated clotting time (ACT), room temperature (sec)	60-120	70-120
Activated clotting time, 37° C (sec)	64-95	<65
Prothrombin time (PT) (sec)	7-10	5-9
Russell's viper venum time (RVVT) (sec)	8-14	8-14
Thrombin time (TT) (sec)	8-13	8-14
Fibrinogen (mg/dL)	150-400	150-290
Fibrin split products (FSP) (μg/mL)	<20	<10

Normal Chemistry Values*

CHEMISTRY	COMMON UNITS			SYSTÈME INTERNATIONAL D'UNITÉS		
	DOG	CAT	UNIT	DOG	CAT	SI UNIT
Glucose	60-110	70-150	mg/dL	3.9-6.1	3.9-8.0	mmol/L
BUN	10-25	17-30	mg/dL	3.5-7.1	5.9-10.5	mmol/L
Creatinine	0.6-2.0	0.6-2.0	mg/dL	50-180	50-180	µmol/L
Calcium	8.8-11.2	8.8-10.4	mg/dL	2.2-2.7	2.2-2.5	mmol/L
Phosphorus	2.5-5.9	1.8-7.0	mg/dL	0.8-1.6	0.58-2.2	mmol/L
Sodium	140-155	146-158	mEq/L	140-155	146-158	mmol/L
Potassium	3.5-5.0	3.5-5.2	mEq/L	3.5-5.0	3.5-5.2	mmol/L
Chloride	105-131	114-126	mEq/L	105-131	114-126	mmol/L
Magnesium	1.8-3.0	1.90-2.28	mg/dL	0.8-1.2	0.8-0.9	mmol/L
Iron	80-190	70-215	µg/dL	14-34	12-38.5	µmol/L
Total iron binding	280-340	295-400	µg/dL	63-81	53-57	µmol/L
Triglyceride	10-42	6-58	mg/dL	0.56	0.56	mmol/L
Cholesterol	100-265	87-197	mg/dL	2.5-5.9	2.1-5.1	mmol/L
Bilirubin						
Total	0.1-0.6	0.1-0.6	mg/dL	2-17	2-17	µmol/L
Direct (conjugated)	0-0.14	0-0.15	mg/dL	0-2	0-2	µmol/L
Indirect (unconjugated)	0.07-0.60	0.09-0.20	mg/dL	0-15	0-15	µmol/L
Total protein	5.0-7.1	5-8	g/dL	50-71	50-80	g/L
Albumin	2.8-4.0	2.3-3.5	g/dL	28-40	23-35	g/L
Globulin	3.0-4.7	2.6-5.0	g/dL	30-47	26-50	g/L
SAP	20-150	10-100	IU/L	20-150	10-100	U/L
SALT	15-70	10-50	IU/L	15-70	10-50	U/L
SAST	10-50	10-40	IU/L	10-50	10-40	U/L
LDH	50-495	75-495	IU/L	50-495	75-495	U/L
GGT	1-11.5	1-10	IU/L	1-11.5	1-10	U/L
Bile acids, fasting	<10	<5	µmol/L	<10	<5	µmol/L
Bile acids, postprandial	<25	<15	µmol/L	<25	<15	µmol/L
Amylase	300-2000	500-1800	IU/L	300-2000	500-1800	U/L
Lipase	25-750	25-700	IU/dL	25-750	25-700	U/L
CK	30-200	26-450	IU/L	30-200	26-450	U/L
CO_2	22-27	20-23	mEq/L	22-28	20-25	mmol/L
HCO_3	22-25	22-25	mEq/L	22-25	22-25	mmol/L
NH_3	<120-150		µg/dL	69-87		µmol/L
Lactate	5-20		mg/dL	0.5-2.0		mmol/L
Pyruvate	0.1-0.2		mEq/L			
pH	7.31-7.42	7.24-7.40				
Osmolality	280-305	280-305	mOsm/kg	280-305	280-305	mmol/kg
Blood lead	<25	<25	µg/dL	<1.21	<1.21	µmol/L

Modified from Lumsden (1982).

BUN, Blood urea nitrogen; *SAP,* serum alkaline phosphatase; *SALT,* serum alanine transaminase; *SAST,* serum aspartate transaminase; *LDH,* lactate dehydrogenase; *GGT,* gammaglutamyl transferase; *CK,* creatine kinase; *CO_2,* carbon dioxide; *HCO_3,* bicarbonate; *NH_3,* ammonia.

*It is important to realize that normal values (reference ranges) vary among individual laboratories.

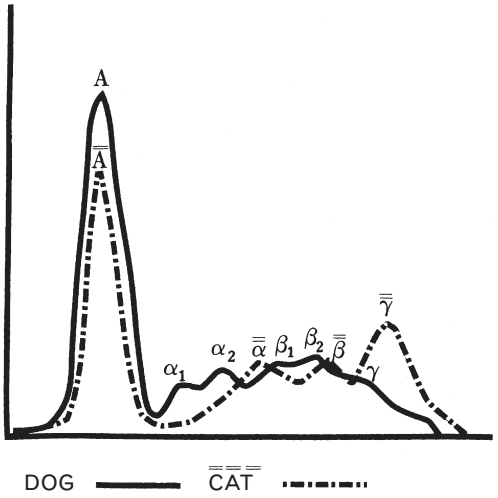

FIGURE A-1 Normal serum protein electrophoretic patterns in the dog and cat.

Normal Serum Protein Electrophoresis

PROTEIN COMPONENT	COMMON UNITS (g/dL)		SI UNITS (g/L)	
	DOG	CAT	DOG	CAT
Albumin	2.3-3.4	2.3-3.5	23-34	23-35
Globulins	3.0-4.7	2.6-5.0	30-47	26-50
$Alpha_1$	0.3-0.8	0.3-0.5	3-8	3-5
$Alpha_2$	0.5-1.3	0.4-1.0	5-13	4-10
Beta	0.7-1.8	0.6-1.9	7-18	6-19
Gamma	0.4-1.0	0.5-1.5	4-10	5-15
Total protein	5.5-8.0	6-8	55-80	60-80

Modified from Tvedten (1981) and Bentinck-Smith (1983).

Bone Marrow Evaluation

CELL TYPES	DOG	CAT
Myeloid:Erythroid (ME) Ratio		
Range	0.75-2.50:1.00	0.6-3.9:1.0
Average	1.15:1.00	2.47:1.00
Erythrocytic Series (%)		
Rubriblasts	0.2	1.71
Prorubricytes	3.9	12.50
Rubricytes	27.0	—
Metarubricytes	15.3	11.68
Total	46.4	25.89
Granulocytic Series (%)		
Myeloblasts	0	1.74
Progranulocytes	1.3	0.88
Neutrophilic myelocytes	9.0	9.76
Eosinophilic myelocytes	0	1.47
Neutrophilic metamyelocytes	7.5	7.32
Eosinophilic metamyelocytes	2.4	1.52
Band neutrophils	13.6	25.80
Band eosinophils	0.9	—
Neutrophils	18.4	9.24
Eosinophils	0.3	0.81
Basophils	0	0.002
Total	53.4	58.542
Others (%)		
Lymphocytes	0.2	7.63
Plasma cells	0	1.61
Reticulum cells	0	0.13
Mitotic cells	0	0.61

From Bentinck-Smith J: A roster of normal values for dogs and cats. p. 1206. In Kirk RW (ed): Current Veterinary Therapy VIII: Small Animal Practice. WB Saunders. Philadelphia, 1983; with permission.

Commonly Used Equations

Serum Osmolality

$$2\,(\text{Na} + \text{K}\ [\text{mEq/L}]) + \frac{\text{glucose (mg/dL)}}{20} + \frac{\text{BUN (mg/dL)}}{3}$$

Normal = 305 mOsm/kg

Adjusted Calcium Values (Dogs)

Adjusted calcium = calcium (mg/dL) – albumin (g/dL) + 3.5
= calcium (mg/dL) – 0.4 × total protein + 3.3

Hypocalcemia: <6.5 mg/dL
Hypercalcemia: >12.0 mg/dL

Base Deficit

Bicarbonate need (mEq/L) = base deficit × 0.3 × body weight (kg)

Fluid Therapy

I. Replacement needs:

Need (L) = % dehydration × body weight (kg) × 1 L + losses from vomiting, diarrhea

II. Maintenance requirements:

Maintenance = 10 – 15 mL × body weight (kg) QID

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Appendix II
Units, Abbreviations, and Equivalents

Units

Weights

oz	ounce
lb	pound
kg	kilogram (10^3 g)
g	gram (1 g)
mg	milligram (10^{-3})
µg	microgram (10^{-6} g)
ng	nanogram (10^{-9} g)
pg	picogram (10^{-12} g)
gr	grain (1 gr = 65 mg)

Fluids

L	liter (10^3 mL)
dL	deciliter (10^2 mL)
mL	milliliter (1 mL or 10^{-3} L)
µL	microliter (10^{-6} L)
tsp	teaspoon
tbsp	tablespoon

Pressure

mm Hg	millimeters of mercury
cm H_2O	centimeters of water

Distance, Surface Area

mm	millimeters
cm	centimeters
in	inches
m^2	meters squared

Time

sec	second
min	minute
hr, h	hour
q	every
day	day
wk	week
mo	month
yr	year

Concentration of Solutions

mEq/L	milliequivalents per liter
g/dL	grams per deciliter
mg/dL	milligrams per deciliter
pg/dL	picograms per deciliter
mOsm/kg	milliosmoles per kilogram
µU/mL	microunits per milliliter
µg/dL	micrograms per deciliter
µmol/L	micromoles per liter
mmol/L	millimoles per liter
pmol/L	picomoles per liter
mmol/kg	millimoles per kilogram
g/L	grams per liter
U/L	units per liter
IU/L	international units per liter
ppm	parts per million

Modified from Morgan RV: Manual of Small Animal Emergencies. Churchill Livingstone, New York, 1985.

Abbreviations

Routes of Administration

PO	per os, oral
IC	intracardiac
IM	intramuscular
IV	intravenous
SC	subcutaneous
IT	intratracheal
IO	intraosseous
IP	intraperitoneal

Dosage Schedules

QID	four times daily; every 6 hours
TID	three times daily; every 8 hours
BID	twice daily; every 12 hours
SID	once daily; every 24 hours
QOD	once every other day; every 48 hours
q	every

Equivalents of Centigrade (Celsius) and Fahrenheit Temperatures

° C	° F
23	73.4
24	75.2
25	77.0
26	78.8
27	80.6
28	82.4
29	84.2
30	86.0
31	87.8
32	89.6
33	91.4
34	93.2
35	95.0
36	96.8
37	98.6
38	100.4
39	102.2
40	104.0
41	105.8
42	107.6
43	109.4
44	111.2
45	113.0
46	114.8

Appendix III
Calibration Tables for Schiøtz Tonometry

Calibration Table for Schiøtz Tonometry in Dogs

SCHIØTZ SCALE READING	IOP (mm Hg) 5.5 g wt	IOP (mm Hg) 7.5 g wt	IOP (mm Hg) 10.0 g wt
0.5	46	61	75
1.0	44	59	73
1.5	43	56	70
2.0	40	53	66
2.5	33	47	61
3.0	26	40	55
3.5	23	35	49
4.0	21	32	44
4.5	20	29	41
5.0	19	27	38
5.5	18	26	36
6.0	17	24	33
6.5	16	23	31
7.0	15	22	30
7.5	—	20	28
8.0	14	19	27
8.5	13	—	25
9.0	—	18	24
9.5	12	17	23
10.0	—	16	22
10.5	11	15	21
11.0	—	—	20
11.5	10	14	19
12.0	—	13	18
12.5	—	—	17
13.0	—	12	16
13.5	8	11	15
14.0	—	—	—
14.5	—	10	14
15.0	7	—	13
15.5	—	9	12
16.0	—	—	—
16.5	6	8	11
17.0	—	—	10
17.5	—	7	—
18.0	5	—	9
18.5	—	6	—
19.0	—	—	8
19.5	—	—	7
20.0	—	5	—

From Pickett JP, Miller PE, Majors LJ: Calibration of the Schiøtz tonometer for the canine and feline eyes. Proc Am Coll Vet Ophthalmol 19:47, 1988; with permission.

IOP, Intraocular pressure.

Calibration Table for Schiøtz Tonometry in Cats

SCHIØTZ SCALE READING	IOP (mm Hg) 5.5 g wt	IOP (mm Hg) 7.5 g wt	IOP (mm Hg) 10.0 g wt
0.5	44	73	—
1.0	42	71	—
1.5	40	68	—
2.0	37	65	80
2.5	33	61	76
3.0	30	56	71
3.5	27	48	66
4.0	25	42	61
4.5	24	37	56
5.0	22	34	51
5.5	21	31	47
6.0	20	29	44
6.5	18	27	40
7.0	—	25	37
7.5	17	24	35
8.0	16	22	33
8.5	15	21	31
9.0	14	20	29
9.5	13	19	27
10.0	—	18	25
10.5	—	17	23
11.0	12	16	22
11.5	11	15	20
12.0	—	14	19
12.5	10	13	18
13.0	—	12	17
13.5	9	—	15
14.0	—	11	14
14.5	8	10	13
15.0	—	—	12
15.5	—	9	11
16.0	7	8	10
16.5	—	—	9
17.0	6	7	8
17.5	—	6	7
18.0	—	—	6
18.5	5	5	5
19.0	—	—	—
20.0	—	—	—

From Pickett JP, Miller PE, Majors LJ: Calibration of the Schiøtz tonometer for the canine and feline eyes. Proc Am Coll Vet Ophthalmol 19:47 1988; with permission.

IOP, Intraocular pressure.

Appendix IV
Recommended Drug Dosages

Every effort has been made to provide precise dosages for specific clinical situations; however, individual needs or circumstances may necessitate alterations in both the dosage and the frequency of administration of any of the medications listed on the following pages.

Multiple uses for a drug are listed in order under the original drug entry. Dosages are designated for either the dog or cat. If no species is listed before the dose, that dose is applicable to both dogs and cats.

DRUG (BRAND NAME OR ABBREVIATION)	PURPOSE OR USE	CHAPTERS WHERE CITED	DOSAGE
Acarbose *(Precose)*	Diabetes mellitus	44	Dog: <10 kg: 25-50 mg PO BID ≥10 kg: 50-100 mg PO BID Use with insulin Cat: 12.5 mg PO BID Use with insulin
Acetazolamide *(Diamox)*	Hydrocephalus, (decrease volume of CSF) hydranencephaly, porencephaly	23	Dog: 0.1 mg/kg PO TID
	Diuretic	24	Dog: 10 mg/kg PO TID-QID Use with caution; side effects common
Acetylcysteine 5%-10% *(Mucomyst PO, Acetadote IV)*	Degenerative myelopathy	24	Dog: 70 mg/kg PO TID × 2 wk, then TID q 48 hr
	Liver protectant, acetaminophen and zinc phosphide toxicoses	64, 124, 127	140-280 mg/kg PO, IV as loading dose; then 70 mg/kg PO, IV TID-QID × 7-17 Rx
Acetylpromazine *(Acepromazine)*	Preanesthetic, restraint, sedation	1, 4, 15	Dog: 0.01-0.05 mg/kg IV, SC, IM; max = 2.5 mg Cat: a) 0.05 mg/kg IV, with ketamine b) 0.01-0.03 mg/kg SC, IM, IV; max = 1 mg
	Arterial thromboembolism, vasodilator, acute feline idiopathic cystitis	10, 50	Cat: a) 0.05-0.1 mg/kg SC, IV, IM q 4-6 hr b) 0.25-1 mg/kg PO BID
	Urine retention disorders, decrease urethral sphincter tone	51	Cat: a) 0.1 mg/kg SC, IV SID-BID b) 1-2 mg/kg PO SID-BID
	Increase milk production	60	Dog: 0.125-0.5 mg/kg PO BID-TID
	Nausea from vertigo	108	Dog: 1 mg/kg PO SID
	Agitation, restlessness from ephedrine/ pseudoephedrine toxicosis	129, 130	Dog: 0.05-1 mg/kg IV, IM, SC PRN Use with caution

CNS, Central nervous system; *CRI,* constant rate infusion; *CSF,* cerebrospinal fluid; *dd,* divided; *DIC,* disseminated intravascular coagulopathy; *DJD,* degenerative joint disease; *DOCP,* desoxycorticosterone pivalate; *D/W,* dextrose in water; *EDTA,* ethylenediamine tetraacetic acid; *FeLV,* feline leukemia virus; *FIP,* feline infectious peritonitis; *GI,* gastrointestinal; *ID,* intradermally; *IP,* intraperitoneally; *IT,* intratracheally; *KCS,* keratoconjunctivitis sicca; *max,* maximum; *o.o.,* ophthalmic ointment; *PCV,* packed cell volume; *PRN,* as needed; *Rx,* treatment(s); *SLE,* systemic lupus erythematosus; *soln,* solution; *tab,* tablet; T_4, thyroxine; *UTI,* urinary tract infection.

Continued

DRUG (BRAND NAME OR ABBREVIATION)	PURPOSE OR USE	CHAPTERS WHERE CITED	DOSAGE
Acetylsalicylic acid (Aspirin)	Arterial thromboembolism, anticoagulation therapy, acquired platelet dysfunction	10, 67, 68	Dog: 0.5 mg/kg PO BID Cat: 6-10 mg/kg PO q 2-3 days
	Glomerulonephritis	48	Dog: 0.5-2 mg/kg PO SID Cat: 0.5-2 mg/kg PO QOD
	Immune-mediated hemolytic anemia (unresponsive)	64	Dog: 0.5 mg/kg PO SID, with azathioprine
	Antipyretic, analgesic, anti-inflammatory ocular effects	73, 98, 99, 103	Dog: 5-20 mg/kg PO SID-BID Cat: 3-6 mg/kg PO q 2-3 days
	Musculoskeletal pain, inflammation	127	Dog: 10-20 mg/kg PO BID Cat: 6-10 mg/kg PO q 2-3 days
Acitretin *(Soriatane)*	Primary seborrhea, sebaceous adenitis	93	Dog: 0.5-1 mg/kg PO SID indefinitely
	Ichthyosis	93	Dog: 1-2 mg/kg PO SID × 3 mo or until remission; then decrease to QOD
Aclarubicin	Myelodysplastic syndrome	66	Dog: 5 mg/m^2 IV SID × 5 days
Actinomycin D *(Cosmegen)*	Chemotherapy	72	Dog: 0.5-0.9 mg/m^2 IV slowly q 3 wk
Activated charcoal *(Toxiban, Actidose-Aqua, CharcoAid)*	Ingestion of vitamin K antagonists	68	2-5 g/kg PO, with sorbitol
	GI adsorbent and decontamination	123, 124, 126, 127, 129-131	Powdered form: a) 1-2 g/kg PO BID-TID, mixed with 50-200 mL of water (given as slurry); repeat q 6-12 hr at half the original dose b) 1-2 g/kg PO TID-QID for 24 hr Oral suspension: 10-20 mL/kg PO; repeat q 6-12 hr at half the original dose
	Rodenticide toxicoses	124	6.6-11 mL/kg PO, with sorbitol
	Avermectin toxicosis	125	6.6-11 mL/kg PO initially; then 3.3-5.5 mL/kg PO TID × 1-2 days
Acyclovir *(Zovirax)*	Feline herpesvirus keratitis	98	Cat: 200 mg PO BID-QID × 2 wk Caution: Not labeled for use in cats; potentially toxic
Aglépristone *(Alizine)**	Mammary fibroadenomatous hyperplasia	60	10 mg/kg SC SID × 4-5 days
Albendazole *(Albenza)*	Giardiasis	116	Dog: 25 mg/kg PO BID × 2 days Use with caution; do not use in cats
Albuterol *(Albuterol, Ventolin, Proventil)*	Sinus bradycardia	6	Dog: 0.02-0.05 mg/kg PO BID-TID
	Bronchodilator	16-18, 114	20-50 μg/kg PO BID-TID or aerosolized and inhaled Cat: a) 90 μg per inhalation q 30 min for up to 4-6 hr via metered dose inhaler, then SID-QID b) 0.5 mL of 2.5 mg/3 mL soln in 3.5 mL saline by delivered nebulization via face mask SID-QID

CNS, Central nervous system; *CRI,* constant rate infusion; *CSF,* cerebrospinal fluid; *dd,* divided; *DIC,* disseminated intravascular coagulopathy; *DJD,* degenerative joint disease; *DOCP,* desoxycorticosterone pivalate; *D/W,* dextrose in water; *EDTA,* ethylenediamine tetraacetic acid; *FeLV,* feline leukemia virus; *FIP,* feline infectious peritonitis; *GI,* gastrointestinal; *ID,* intradermally; *IP,* intraperitoneally; *IT,* intratracheally; *KCS,* keratoconjunctivitis sicca; *max,* maximum; *o.o.,* ophthalmic ointment; *PCV,* packed cell volume; *PRN,* as needed; *Rx,* treatment(s); *SLE,* systemic lupus erythematosus; *soln,* solution; *tab,* tablet; T_4, thyroxine; *UTI,* urinary tract infection.

*Not available in the United States.

DRUG (BRAND NAME OR ABBREVIATION)	PURPOSE OR USE	CHAPTERS WHERE CITED	DOSAGE
Allopurinol *(Allopurinol, Aloprim)*	Ammonium urate urolithiasis	48-50	Dog: 10-15 mg/kg PO BID × 4 wk, then SID Cat: 9 mg/kg PO SID × 4 wk; use with caution
	Leishmaniasis	89, 90, 116	Dog: 10-20 mg/kg PO SID-BID × ≥6 mo, with antimonials
D-Alpha-tocopheryl-1000-polyethylene glycol succinate *(Liqui-E)*	Antioxidant for canine chronic hepatitis/cirrhosis, feline chronic cholangiohepatitis, hepatic necrosis/failure, pansteatitis	37	25 IU/kg PO BID
Alprazolam *(Alprazolam, Xanax)*	Certain behavioral disorders	117	Dog: 0.02 mg/kg PO q 4 hr; max = 4 mg/day Cat: 0.2-1 mg/kg PO BID
	Appetite stimulant	122	Dog: 0.01-0.1 mg/kg PO PRN; max = 4 mg/day Cat: 0.05-0.2 mg/kg PO SID-BID
Altrenogest *(Regumate)*	Hypoluteoidism	61	Dog: 0.088 mg/kg PO SID
Aluminum carbonate *(Basalgel)*	Hyperphosphatemia	48	30-90 mg/kg/day PO dd BID-QID; give with food
Aluminum hydroxide *(AlternaGEL, Amphojel)*	Hyperphosphatemia, dietary phosphorus binder	48, 127	30-90 mg/kg/day PO dd BID-QID, give with food
	Cholecalciferol toxicosis	124	10-30 mg/kg PO TID
Aluminum/magnesium hydroxide *(Maalox)*	Zinc phosphide toxicosis, to increase gastric pH	124	90-180 mg/kg PO TID
Amantadine *(Symmetrel)*	Analgesic	72	Dog: 3-4 mg/kg PO BID Cat: 3 mg/kg PO SID
Amikacin *(Amikin)*	Acute endocarditis, bartonellosis	9	Dog: 20 mg/kg IV SID × 1-2 wk, with Timentin or imipenem
	Bacterial gastroenteritis, salmonellosis	33	6-8 mg/kg IM, IV SID alone or with a cephalosporin
	Serious infections, septic peritonitis, acute abdominal syndrome, resistant bacterial cystitis	38, 112	Dog: 15-30 mg/kg IV, IM, SC SID Cat: 10 mg/kg IV SID
	Bacterial keratitis	98	25-125 mg subconjunctivally
Amino acid supplements	Hepatocutaneous syndrome	37	Dog: 1-2 g/5-10 kg PO TID
Aminocaproic acid *(Amicar)*	Degenerative myelopathy	24	Dog: 500 mg PO TID
Aminophylline *(Aminophylline, Phyllocontin)*	Bronchodilator	17, 18, 133	Dog: 6-11 mg/kg IV, IM, PO TID Cat: 4-8 mg/kg IV, IM, PO BID-TID Use caution with IV administration
Aminopromazine fumarate (not currently available)	Urge incontinence	51	2 mg/kg PO BID
Amiodarone *(Cordarone)*	Refractory ventricular tachycardia	6	Dog: a) 10 mg/kg PO BID × 1 wk, then 5 mg/kg PO SID b) 5-10 mg/kg IV bolus
	Cardiopulmonary arrest electroconversion	7	Dog: 5 mg/kg IV; may repeat once at half of initial dose
Amitraz *(Mitaban)*	Canine demodicosis	86	Dog: Mix 1 bottle with 2 gal water; dip wet dog and air dry; repeat q 2 wk × 3-6 Rx
Amitriptyline *(Elavil, Amitriptyline)*	Cataplexy	22	1-2 mg/kg PO BID
	Chronic feline idiopathic cystitis	50	Cat: 2.5-12.5 mg PO SID
	Feline psychogenic alopecia	87	Cat: 5 mg PO BID
	Certain behavioral disorders, tricyclic antidepressant	117	Dog: 1-6 mg/kg PO BID Cat: 0.5-2 mg/kg PO SID-BID

Continued

DRUG (BRAND NAME OR ABBREVIATION)	PURPOSE OR USE	CHAPTERS WHERE CITED	DOSAGE
Amlodipine *(Norvasc)*	Congestive heart failure, hypertension, reduce left-to-right shunting	8, 9, 48	Dog: 0.05-0.4 mg/kg PO SID-BID Cat: 0.625-1.25 mg PO SID
Ammonium chloride (NH_4Cl)	Strychnine, ephedrine/pseudoephedrine toxicoses; urine acidification	124, 130	Dog: 50 mg/kg PO QID Cat: 20 mg/kg PO BID
Amoxicillin *(Amoxidrops, Amoxitabs)*	Serious infections	24, 27, 34, 37, 48, 98, 103, 113, 114	20-22 mg/kg PO, SC, IM BID-TID
	Routine infections	50, 114, 126	10-20 mg/kg PO, IM, SC, BID-TID
	Actinomycosis	89	20-40 mg/kg IM, SC, PO QID
Amoxicillin/clavulanate *(Clavamox)*	Chronic endocarditis, bacterial pneumonia, osteomyelitis	9, 18, 81	Dog: 20 mg/kg PO TID
	Stomatitis, gingivitis, glossitis	27	Dog: 12.5-25 mg/kg PO BID Cat: 62.5 mg PO BID
	Sialadenitis, salivary gland fistula, feline acute cholangiohepatitis, canine chronic hepatitis/cirrhosis, canine bacterial pyoderma, mucocutaneous pyoderma, upper respiratory infections	16, 29, 37, 88, 90, 91, 114	13.75 mg/kg PO BID
	Subcutaneous abscesses and cellulitis, chorioretinitis	88, 102, 103	15-22 mg/kg PO BID
Amphotericin B deoxycholate *(Fungizone, Amphocin)*	Systemic mycotic and algal infections	14, 23, 24, 89, 102, 111	Dog: 0.5-0.8 mg/kg IV 2-3 times/wk to total dose of 5-10 mg/kg Cat: 0.1-0.5 mg/kg IV q 48-72 hr, to total dose of 4-8 mg/kg Discontinue if azotemia occurs
Amphotericin B lipid complex *(Abelcet)*	Gastric pythiosis	31	Dog: 2-3 mg/kg IV QOD to total dose of 24-27 mg/kg
	Systemic mycoses	89, 111	Dog: 1-2 mg/kg IV q 48-72 hr to total dose of 12-24 mg/kg Discontinue if azotemia occurs
Ampicillin *(Amp-Equine, Polyflex)*	Various infections, borreliosis, leptospirosis	33, 48, 50, 103, 112-114	10-22 mg/kg IV, IM, SC TID-QID
	Acute colitis, hepatic abscess, feline acute cholangiohepatitis, canine chronic hepatitis/cirrhosis, hepatic encephalopathy	34, 37	22 mg/kg PO TID
	Septic peritonitis, nocardiosis, acute abdominal syndrome	38, 39, 89	20-40 mg/kg IV, IM, SC, PO TID-QID, possibly combined with amikacin or gentamicin
	Metritis	61	Dog: 20 mg/kg PO TID × 14 days
	Bacterial keratitis	98	50-100 mg subconjunctivally
Amprolium *(Corid)*	Enteric coccidiosis	116	60-100 mg (total per day) PO SID × 5 days
Antivenin Crotalidae Polyvalent *(CroFab)*	Antivenom	136	10-100 mL (1-10 vials); dilute in 50-250 mL of crystalloid fluids; initial vial infused IV over 30 min, then additional vials PRN
Antidiuretic hormone *See* Desmopressin acetate			
Apomorphine hydrochloride (compounding pharmacies)	Emesis, decontamination	123, 130	Dog: a) ≤1 tab in conjunctival sac or dissolve tab in water and instill in eye b) 0.03-0.04 mg/kg IV c) 0.04-0.08 mg/kg IM, SC

DRUG (BRAND NAME OR ABBREVIATION)	PURPOSE OR USE	CHAPTERS WHERE CITED	DOSAGE
Ascorbic acid (Vitamin C)	Reduction of methemoglobin, acetaminophen toxicosis	127	30 mg/kg PO BID-QID
	Urine acidification, ephedrine/ pseudoephedrine toxicosis	130	20-30 mg/kg PO, IM, IV TID
L-Asparaginase *(Elspar)*	Lymphoma	69, 72	Dog: a) 10,000-20,000 IU/m^2 IM, SC in a protocol b) 400 IU/kg IM, SC in a protocol Cat: 400 IU/kg SC, IP in a protocol
Atenolol *(Tenormin)*	Atrial flutter, ventricular tachycardia, orthodromic atrial reciprocating tachycardia	6, 48	Dog: 0.25-2 mg/kg PO SID-BID Cat: 6.25-12.5 mg PO SID-BID
	Pulmonic/subaortic stenosis, right ventricular hypertrophy	8	1-2 mg/kg PO BID
	Feline hypertrophic cardiomyopathy, feline hyperthyroidism	10, 42	Cat: 6.25-12.5 mg PO SID-BID
Atipamezole *(Antisedan)*	Amitraz toxicosis	125	0.05 mg/kg IM PRN
Atovaquone *(Malarone)*	*Babesia gibsoni* infection	64, 116	Dog: 13.3 mg/kg PO TID × 10 days, with azithromycin
Atropine (Atropine sulfate)	Atropine response test, empirical vagolytic therapy	6, 7	0.01-0.04 mg/kg IM, IV
	Sinus bradycardia	7, 76, 129, 130	0.02-0.04 mg/kg IV, IM, SC PRN
	Cardiopulmonary arrest	7	0.08 mg/kg IT
	Cholinergic crisis	25	0.05 mg/kg IV
	Ptyalism	29	a) 0.02-0.04 mg/kg SC PRN b) 0.04 mg/kg PO TID-QID *(Sal-Tropine)*
	Preanesthetic	61, 71	Dog: 0.04 mg/kg IM Cat: 0.01 mg/kg IV, with ketamine and diazepam
	Relaxation of gastric smooth muscle for enterogastric lavage	123	0.02 mg/kg IV
	Muscarinic signs from insecticide toxicosis	125	a) 0.05-0.5 mg/kg IV to effect b) 0.15-1.5 mg/kg SC, IM to effect
Atropine 1% (ophthalmic)	Bacterial/fungal keratitis, corneal ulceration, anterior uveitis, hyphema	98, 99	Apply to affected eye SID-QID
	Feline corneal sequestration	98	Apply to affected eye SID-BID
Aurothioglucose (Gold salts, *Solganal*)	Lymphoplasmacytic stomatitis	27	1 mg/kg IM weekly × 10-20 wk, then taper to once monthly
	Rheumatoid arthritis	80	Dog: 1 mg/kg IM weekly
	Feline plasma cell pododermatitis	90	Cat: 1 mg/kg IM q 7 days × 2-3 mo, then q 14 days for 2-3 Rx, then q 30 days for maintenance
	Pemphigus complex	91	Test dosage of 1 mg (dog ≤10 kg) or 5 mg (dog >10 kg) IM; then 1-2 mg/kg IM weekly, then taper to q 2-4 wk PRN
Azathioprine (*Imuran*)			*Not* recommended in cats
	Pulmonary eosinophilic diseases	18	Dog: 2 mg/kg PO SID × 7-10 days, then QOD
	Refractory canine meningeal polyarteritis	23	Dog: 1.5 mg/kg PO SID-QOD, then alternate with prednisone QOD
	Refractory acquired myasthenia gravis, chronic inflammatory demyelinating neuropathy	25	Dog: 1-2 mg/kg PO SID

Continued

DRUG (BRAND NAME OR ABBREVIATION)	PURPOSE OR USE	CHAPTERS WHERE CITED	DOSAGE
Azathioprine *(Imuran)—cont'd*	Lymphoplasmacytic stomatitis, inflammatory bowel disease, chronic hepatitis/cirrhosis, membranous glomerulonephritis, proliferative urethritis	27, 33, 37, 48, 52	Dog: 1-2 mg/kg PO SID, taper to QOD
	Chronic histiocytic ulcerative colitis	34	Dog: 2 mg/kg PO SID × 2 wk, then QOD
	Perianal fistula	35	Dog: a) 50 mg PO SID × 4-6 wk b) 1.5-2.2 mg/kg PO SID × 2-4 wk then QOD, with prednisone
	Immune-mediated hemolytic anemia, immune-mediated thrombocytopenia	64, 76	Dog: 1-2 mg/kg PO SID, then taper to 0.5-1 mg/kg PO QOD, with prednisone
	Chronic idiopathic myelofibrosis	66	Dog: 2 mg/kg PO QOD
	SLE, refractory erosive/nonerosive arthritis	76, 80	Dog: 2 mg/kg PO SID × 7-21 days, then QOD × 1 mo beyond remission
	Cutaneous histiocytosis, masticatory myositis, polymyositis, extraocular myositis, sterile granuloma and pyogranuloma	77, 82, 89, 103	Dog: 2 mg/kg PO SID until remission, then taper
	Cutaneous immune-mediated diseases, uveodermatologic syndrome	90-92	Dog: a) 1.0-2.5 mg/kg PO SID, then taper b) 50 mg/m^2 PO SID, then taper to QOD
	Blepharitis, episcleritis, immune-mediated uveitis, ligneous conjunctivitis, chorioretinitis	95, 96, 98, 99, 102	Dog: 2-2.2 mg/kg PO SID, then taper to QOD
Azithromycin *(Zithromax)*	Chronic endocarditis	9	Dog: 5 mg/kg PO SID × 7 days, then QOD × 6-8 wk
	Bacterial meningoencephalitis	23	5-10 mg/kg PO, IV SID
	Campylobacter spp., *Helicobacter* spp. infections	33	5 mg/kg PO SID
	Leptospirosis carrier state	48	Dog: 20 mg/kg PO SID × 1 wk
	Babesia gibsoni infection	64, 116	Dog: 10 mg/kg PO SID, with atovaquone
	Cryptosporidiosis	116	Dog: 5-10 mg/kg PO BID × 5-7 days Cat: 7-15 mg/kg PO BID × 5-7 days
Bacitracin-neomycin-gramicidin (ophthalmic)	Conjunctivitis	96	Apply to affected eye TID-QID
Bacitracin-neomycin-polymyxin (ophthalmic)	Neonatal ophthalmia, conjunctivitis	95, 96	Apply to affected eye TID-QID
Bacitracin-neomycin-polymyxin-hydrocortisone (ophthalmic ointment)	Conjunctivitis	96	Apply to affected eye SID-QID
Benazepril *(Lotensin)*	Chronic congestive heart failure	9, 10	Dog: 0.25-0.5 mg/kg PO SID Cat: 0.5 mg/kg PO SID
	Glomerulonephritis, chronic renal failure	48	Dog: 0.25-1 mg/kg PO SID-BID

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DRUG (BRAND NAME OR ABBREVIATION)	PURPOSE OR USE	CHAPTERS WHERE CITED	DOSAGE
Benzoyl peroxide gel *(Pyoben gel, Oxydex gel)*	Acute moist dermatitis, deep bacterial pyoderma and furunculosis	85, 88	Shampoo and leave on for 10-15 min, then rinse; repeat 1-3 times/wk until resolution
	Canine demodicosis, canine/feline acne, staphylococcal pyoderma and folliculitis, impetigo, intertrigo	86, 88	Dog: Apply topically SID to affected areas × 7-14 days or until lesions resolve Cat: Apply topically SID-QOD until acne lesions resolve, then PRN
Betamethasone *(Celestone Soluspan)*	Episcleritis, severe pannus	96, 98	Apply 1-2 mg subconjunctivally BID-QID
Betamethasone valerate 0.14% cream *(DVM Max)*	Cutaneous or discoid lupus erythematosus, Pemphigus erythematosus	90, 91	Apply topically initially BID × 5-7 days, then taper
Betaxolol 0.5% *(Betoptic)*	Glaucoma	100	Apply 1 drop to affected eye BID, with other therapy
Bethanechol chloride *(Urecholine)*	Urine retention disorders, enhance detrusor muscle contraction	51	Dog: 5-25 mg PO TID Cat: 1.25-5 mg PO TID
	Dysautonomia (Key-Gaskell Syndrome)	105	a) 2.5-5 mg PO BID-TID b) 0.0375 mg/kg SC
Bimatoprost 0.03% *(Lumigan)*	Glaucoma	100	Dog: Apply 1 drop to affected eye SID-BID
Biotin	Idiopathic claw disorders	90	5 µg/kg/day PO indefinitely
Bisacodyl *(Dulcolax)*	Stool softener		Dog: 10 mg PO PRN Cat: 5 mg PO PRN
Bismuth subsalicylate *(Pepto-Bismol)*	GI tract protectant, acute colitis, helicobacteriosis	31, 33, 34, 113	Dog: 0.5-2 mL/kg PO q 4-8 hr Cat: 0.25 mL/kg PO BID; use with caution
Brinzolamide 1% *(Azopt)*	Glaucoma	100	Apply 1 drop to affected eye BID-TID
Bromocriptine (Bromocriptine mesylate)	Galactorrhea, decrease milk production in pseudocyesis	60, 61	Dog: 20-30 µg/kg PO SID for up to 10-16 days
Bupivacaine 0.5% *(Marcaine, Sensor)*	Local, regional blockade anesthesia	1, 19, 81	Dog: a) 0.5-2 mg/kg SC, perilesional or perineural infiltration b) 0.3 mg/kg or 1 mL/15 kg with morphine, given as epidural c) 1 mL/15 kg with morphine, given as epidural for pelvic limb fracture d) 1 mL/20 kg with morphine and saline, given as epidural for thoracic limb fracture e) Max = 2 mg/kg Cat: a) 0.2-0.5 mg/kg SC, perilesional or perineural infiltration b) 0.1 mg/kg with morphine, given as epidural
Buprenorphine *(Buprenex)*	Sedation, analgesia, pain control	1, 10, 32, 39, 50, 72, 81, 126, 128, 133, 136	Dog: 0.005-0.02 mg/kg IV, IM, SC, PO BID-QID Cat: 0.005-0.01 mg/kg IV, IM, SC, PO BID-QID
Buspirone *(BuSpar)*	Chronic feline idiopathic cystitis	50	Cat: 5-10 mg PO BID-TID
	Anxiolytic drug	117	Dog: 0.5-2 mg/kg PO BID-TID Cat: 0.5-1 mg/kg PO BID
Busulfan *(Myleran)*	Chronic granulocytic leukemia	66	Dog: 0.1 mg/kg/day PO

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DRUG (BRAND NAME OR ABBREVIATION)	PURPOSE OR USE	CHAPTERS WHERE CITED	DOSAGE
Butorphanol *(Torbutrol, Torbugesic)*	Analgesia, sedation, pain control	1, 3, 8, 10, 15, 36, 39, 50, 71, 72, 81,103, 126, 127, 133	Dog: a) 0.2-0.6 mg/kg IV, IM, SC, PO q 1-6 hr b) 0.1-0.4 mg/kg/hr IV as CRI Cat: a) 0.005-0.01 mg/kg IV, IM, SC, PO q 4-12 hr b) 1-2.5 mg PO SID-BID
	Cough suppressant	9, 15-17, 114	Dog: 0.5-1.1 mg/kg PO BID-QID
	Emesis	46	0.4 mg/kg IM PRN
Cabergoline *(Galastop, Dostinex)*	Galactorrhea, decrease milk production in pseudocyesis	60, 61	Dog: 1.5-5.0 µg/kg PO SID × 2-10 days
	Induce estrus	61	Dog: 5 µg/kg PO SID × 7-10 days
Calcitonin *(Calcimar)*	Hypercalcemia, cholecalciferol toxicosis, calcipotriene toxicosis	124, 127	4-7 IU/kg SC, IM BID-TID
Calcitriol *(Rocaltrol)*	Hypoparathyroidism, hypocalcemia	43	20-30 ng/kg PO SID × 3-4 days; then 5-15 ng/kg PO SID
	Chronic renal disease, secondary hyperparathyroidism	48, 127	Dog: 2.5-3.5 ng/kg PO SID
	Primary seborrhea to inhibit keratinocyte proliferation	93	Dog: 10 ng/kg PO SID Use with caution
Calcium acetate *(PhosLo GelCaps)*	Hyperphosphatemia	48	60-90 mg/kg/day PO
Calcium carbonate, elemental *(Monocal, Tums, Calcifol)*	Hypoparathyroidism, hypocalcemia	43	25-50 mg/kg/day PO dd BID-QID
	Eclampsia	61	Dog: 1-3 g/day PO, with vitamin D
Calcium EDTA *(Versenate)*	Lead poisoning	126	100 mg/kg/day × 5 days SC = total dose; make soln of 10 mg/mL in 5% D/W, divide into 20 aliquots and give 1 dose SC QID × 5 days Dog: Do not exceed 2 g/day
Calcium gluconate (*Calcet,* Ca gluconate injection)	Atrial standstill, asystole	6	10% soln: 0.5 mL/kg IV slowly
	Hypoparathyroidism, hypocalcemia, severe hyperkalemia, calcium channel-blocker intoxication	7, 43, 45, 48, 49	10% soln: a) 0.4-1.5 mL/kg slowly IVto effect over 10-20 min b) 5-15 mg/kg slowly IV to effect over 10-15 min
	Hypocalcemia, dystocia, eclampsia	61	Dog: a) 10% soln: 0.2-0.4 mL/kg IM, SC; severe case: 1-10 mL IV to effect b) Oral: 1-3 g/day, with vitamin D
Carboplatin *(Paraplatin)*	Chemotherapy, in a protocol	27, 72	Dog: a) Large dog: 300 mg/m^2 IV q 3 wk b) Small dog: 250 mg/m^2 or 10 mg/kg IV q 3 wk Cat: 180 mg/m^2 IV q 4 wk
Carprofen *(Rimadyl)*	Anterior uveitis, antiinflammatory, analgesia	1, 24, 80-82, 98, 99, 103, 127	Dog: a) 2.2-4 mg/kg SC, slowly IV once b) 2-2.2 mg/kg PO BID Cat: 2.2 mg/kg SC once
L-Carnitine	Nutritional supplement, cardiomyopathy	10	Dog: 50 mg/kg PO BID-TID
	Carnitine deficiency	122	Dog: 50-100 mg/kg PO TID
Cefadroxil *(CefaTabs, Duricef)*	Canine chronic hepatitis/cirrhosis, bacterial pyoderma	37, 88	Dog: 22 mg/kg PO BID
	Oral infections	126	20 mg/kg PO BID

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DRUG (BRAND NAME OR ABBREVIATION)	PURPOSE OR USE	CHAPTERS WHERE CITED	DOSAGE
Cefazolin *(Ancef, Kefzol)*	Discospondylitis, osteomyelitis, *Staphylococcus* spp. infection, bacterial arthritis, serious infections	24, 80, 81, 112	Dog: 20 mg/kg IV, IM, SC TID-QID
	Perioperative antibiotic	32	Dog: 22 mg/kg IV
	Hepatic abscess, feline acute cholangiohepatitis, septic peritonitis	37, 38	22 mg/kg IV TID
	Bacterial keratitis	98	100 mg subconjunctivally
Cefotaxime *(Claforan)*	Infectious meningomyelitis, bacterial infections, septic peritonitis	24, 38	Dog: 30-40 mg/kg IV, IM, SC TID-QID
Cefoxitin *(Mefoxin)*	Septicemia, endotoxemia, hepatic abscess, feline acute cholangiohepatitis, septic peritonitis, acute abdomen syndrome	33, 37-39, 112	15-30 mg/kg IV, IM TID-QID
	Perioperative antibiotic	35	30 mg/kg IV 30 min before surgery, then 30 mg/kg IM q 1.5 hr for 2 more doses
	Canine infectious tracheobronchitis, feline upper respiratory infection complex	114	22 mg/kg IV TID
Cefpodoxime proxetil *(Simplicef)*	Bacterial pyoderma, blepharitis	88, 95	Dog: 5-10 mg/kg SID
Ceftazidime *(Cefazima)*	Infectious meningomyelitis, bacterial infections, septic peritonitis	24, 38	20-50 mg/kg IV BID-TID
Cephalexin *(Keflex, Biocef)*	Serious infections	18, 37, 90, 95, 102, 103	20-40 mg/kg PO, SC, IM, IV BID-TID
	Discospondylitis, osteomyelitis, *Staphylococcus* spp. infection	24, 80, 88, 91	Dog: 20-30 mg/kg PO TID
	Stomatitis, gingivitis, glossitis, hepatic abscess, canine chronic hepatitis/ cirrhosis, bacterial cystitis	27, 37, 50	22 mg/kg PO, IM, SC TID
	Sialadenitis, salivary gland fistula	29	30 mg/kg PO BID
	Perianal fistula	35	20 mg/kg PO BID
	Bacterial arthritis	80	11-33 mg/kg PO TID
Charcoal, activated *See* Activated charcoal			
Chlorambucil *(Leukeran)*	Lymphoplasmacytic stomatitis	27	Dog: 0.1-0.2 mg/kg PO SID-QOD, with corticosteroids Cat: 0.25-0.33 mg/kg PO q 72 hr, with corticosteroids
	Feline small cell GI lymphoma	31, 34, 72	Cat: a) 4-6 mg/m^2 PO SID-QOD b) 6-15 mg/m^2 PO SID × 4 days; repeat q 3 wk Dosage varies greatly among protocols
	Inflammatory bowel disease	33	Cat: 1.5 mg/m^2 PO SID-QOD
	Chronic lymphocytic leukemia	65, 72	Dog: 0.2 mg/kg or 6 mg/m^2 PO SID × 7-14 days, then 0.1 mg/kg or 3 mg/m^2 PO SID, then long-term maintenance at 2.0 mg/m^2 QOD, with prednisone Cat: 0.2 mg/kg or 2 mg/cat PO QOD, with prednisone
	Lymphoma	69	Cat: 1.4 mg/kg PO in a protocol
	Primary macroglobulinemia	77	Dog: 0.2 mg/kg PO SID
	SLE, Pemphigus vulgaris or foliaceus, other cutaneous immune-mediated diseases	90, 91	Dog: a) 0.1-0.2 mg/kg PO SID b) 2-6 mg/m^2 PO SID, then taper to QOD Cat: 0.1-0.2 mg/kg PO SID-QOD
	FIP	112	Cat: 20 mg/m^2 PO q 2-3 wk

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DRUG (BRAND NAME OR ABBREVIATION)	PURPOSE OR USE	CHAPTERS WHERE CITED	DOSAGE
Chloramphenicol 1% (ophthalmic)	Conjunctivitis from *Chlamydophila* spp. or *Mycoplasma* spp.	96	Apply to affected eye TID-QID
Chloramphenicol *(Chloromycetin)*	Bronchiectasis, bacterial and rickettsial infections, chronic prostatitis, infectious tracheobronchitis, chorioretinitis	17, 24, 53, 102, 114, 115	Dog: 15-50 mg/kg IV, PO, SC, IM TID
	Bacterial meningoencephalitis	23	Dog: 50 mg/kg IV, IM, SC, PO BID
	Resistant bacterial cystitis	50	Dog: 33 mg/kg PO TID Cat: 25 mg/kg PO BID
Chlordiazepoxide-clindinium *(Librium, Mitran)*	Anxiety with irritable bowel syndrome	34	Dog: 0.10-0.25 mg/kg of clidinium PO BID-TID
	Certain behavioral disorders	117	Dog: 2-6.5 mg/kg PO TID Cat: 0.2-1 mg/kg PO BID
Chlorhexidine (shampoo, ointment, cream, or spray)	Staphylococcal pyoderma and folliculitis, impetigo, intertrigo	88	Dog: Apply topically SID-QOD × 7-14 days
Chlorhexidine 2%/ Miconazole 1% shampoo *(Malaseb)*	*Malassezia* dermatitis	85	Use 1-2 times/wk until resolution
Chlorothiazide *(Diuril)*	Nephrogenic diabetes insipidus	41	10-40 mg/kg PO BID
Chlorpheniramine *(Chlor-Trimeton, Chlo-Amine)*	Antihistamine, atopic dermatitis	85	Dog: 0.4 mg/kg PO TID Cat: 2 mg PO BID
Chlorpromazine *(Thorazine)*	Antiemetic	31, 33, 39, 48, 126-128	Dog: a) 0.1-0.5 mg/kg IM, SC BID-QID b) 0.05 mg/kg IV TID-QID
	Agitation, restlessness from ephedrine/ pseudoephedrine toxicosis	129, 130	Dog: 0.1-1 mg/kg IV, IM PRN
Chlorpropamide *(Diabinese)*	Central diabetes insipidus	41, 127	a) 125-250 mg/day PO b) 10-40 mg/kg/day PO
Cholestyramine *(Questran)*	Binding of bile acids	33	Dog: 200-300 mg/kg PO BID
Chondroitin sulfate	Canine hip dysplasia, osteoarthritis	80	Dog: 8.8 mg/kg PO SID, with glucosamine hydrochloride
	Corneal erosions	98	Dog: 100 mg/mL, with tobramycin or ciprofloxacin, applied to affected eye BID-QID
Chorionic gonadotropin, human *(APL, Profasi)*	Luteinize an ovarian follicular cyst, induce ovulation	55, 62	Dog: 22 IU/kg IM; may repeat once 48 hr later Cat: 250-500 IU IM; give 15-30 hr before artificial insemination
Cimetidine *(Tagamet)*	Esophagitis, acid reflux	30	Dog: 10 mg/kg PO TID-QID Cat: 5 mg/kg PO TID
	Chronic gastritis, GI tract ulceration and erosion, enteritis, acetaminophen toxicosis	31, 32, 39, 48, 73, 112, 127	4-10 mg/kg PO, IV, SC, IM BID-QID
Ciprofloxacin with chondroitin sulfate	Corneal erosions	98	Dog: 3 mg/mL applied to affected eye TID-QID
Cisapride (compounding pharmacies)	Gastric acid reflux, megacolon, gastric motility disorders	30, 31, 34, 37, 48	Dog: 0.1-0.5 mg/kg PO BID-TID Cat: 2.5-5 mg PO BID-TID
	Urine retention disorders, enhance detrusor muscle contraction	51	Dog: a) 0.5 mg/kg PO TID b) 2.5-10 mg PO TID Cat: 1.25-5 mg PO TID
Cisplatin *(Platinol)*	Chemotherapy, in a protocol	19, 27, 72	Dog: 50-70 mg/m^2 IV q 3 wk, with saline infusion

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DRUG (BRAND NAME OR ABBREVIATION)	PURPOSE OR USE	CHAPTERS WHERE CITED	DOSAGE
Clarithromycin *(Biaxin)*	Atypical mycobacteriosis	89	5-15 mg/kg PO BID
	Feline leprosy, *Nocardia farci* infection	113	Cat: 62.5 mg PO BID, with clofazimine or rifampin
Clemastine *(Tavist)*	Antihistamine, atopic dermatitis	85	Dog: 0.05-0.1 mg/kg PO BID Cat: 0.67 mg PO BID
Clindamycin *(Antirobe)*	Bronchiectasis	17	10 mg/kg PO BID
	Toxoplasma gondii, *Hepatozoon americanum* or *Neospora caninum* infections; protozoal polyradiculoneuritis or myositis	23-25, 33, 82, 102, 116	10-25 mg/kg PO, IM BID-TID
	Stomatitis, gingivitis, glossitis, sialadenitis, salivary gland fistula, *Clostridium* spp. infection, acute abdominal syndrome, chronic prostatitis	27, 29, 33, 39, 53	5-11 mg/kg PO BID
	Osteomyelitis	81	11 mg/kg IV, IM, PO BID-TID
	Mucocutaneous pyoderma	88, 91	Dog: a) 5-33 mg/kg PO BID b) 11 mg/kg PO SID
	Actinomycosis	89	5 mg/kg SC BID
Clofazimine *(Lamprene)*	Feline leprosy	113	Cat: 25 mg PO SID or 50 mg PO QOD, with clarithromycin or rifampin
Clomipramine *(Clomicalm, Anafranil)*	Chronic feline idiopathic cystitis	50	Cat: 0.5 mg/kg PO SID
	Feline psychogenic alopecia	87	Cat: 1.25-2.5 mg PO SID
	Certain behavioral disorders, tricyclic antidepressant	117	Dog: 1-3 mg/kg PO BID Cat: 0.25-1.3 mg/kg PO SID
Clonazepam *(Klonopin)*	Certain behavioral disorders	117	Dog: 0.1-0.5 mg/kg PO TID Cat: 0.015-0.2 mg/kg PO TID
Clopidogrel *(Plavix)*	Thrombosis, inhibit platelet aggregation	10, 68	Cat: 18.75 mg PO SID
Clorazepate *(Tranxene-SD)*	Certain behavioral disorders	117	Dog: 0.5-2 mg/kg PO QID Cat: 0.5-2 mg/kg PO BID
Clotrimazole 1% *(Lotrimin)*	Nasal aspergillosis	14	Dog: Apply 50 mL per nasal cavity and allow contact time of 60 min; repeat Rx PRN
Codeine (guaifenesin with codeine)	Cough suppressant	17	Dog: 1-2 mg/kg PO BID-QID
Coenzyme Q (CO-Q 10)	Canine cardiomyopathy	10	Dog: 30-90 mg PO BID
Colchicine *(Colchicine)*	Chronic hepatic fibrosis	37	Dog: 0.03 mg/kg PO SID
	Amyloidosis	48	Dog: 0.01-0.03 mg/kg PO SID
Coumarin (nonanticoagulant form)	Lymphedema		Dog: 400 mg/kg/day PO
Crotalidae Polyvalent immune Fab, ovine *(CroFab)* *See* Antivenom			
Cryoprecipitate	Platelet disorders, von Willebrand disease	67	1 U/10 kg IV; repeat q 6-12 hr PRN
	Coagulopathy, Factor VIII deficiency, fibrinogen deficiency	68	1-5 mL/kg IV over 1 hr
Cyanocobalamin (Vitamin B_{12}, *Neogen*)	Cobalamin malabsorption	33, 65	Dog: 0.25-1 mg SC, IM weekly × 1 mo, then q 3-6 mo
	Dietary supplement, B_{12} deficiency	33, 36	250 µg SC, IM weekly or 1 mg SC q 2 wk × 1-3 mo
			Cat: 250 µg SC q 7 days × 6 wk, then q 14 days × 6 wk, then q 28 days

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DRUG (BRAND NAME OR ABBREVIATION)	PURPOSE OR USE	CHAPTERS WHERE CITED	DOSAGE
Cyclophosphamide *(Cytoxan)*	Pulmonary eosinophilic diseases	18	Dog: 50 mg/m^2 PO QOD, with prednisone
	Infectious meningomyelitis, granulomatous urethritis	24, 52	2 mg/kg PO SID × 4 days/wk
	Membranous glomerulonephritis	48	50 mg/m^2 PO SID × 3-4 days, then off for 3-4 days
	Feline mammary cancer	60	Cat: 50-100 mg/m^2 PO, in a protocol with doxorubicin
	Immune-mediated hemolytic anemia	64	Dog: a) Initial single dose: 200 mg/m^2 IV, PO b) Maintenance dose: 50 mg/m^2 PO, IV SID × 4 days/wk or 75-90 mg/m^2 PO SID
	Immune-mediated thrombocytopenia	67	Dog: 50 mg/m^2 PO SID × 4 days/wk, with prednisone Use with caution
	Lymphoma	69, 72	Dog: a) 50 mg/m^2 PO SID-QOD or once weekly, in a protocol b) 250 mg/m^2 IV once weekly, in a protocol Cat: a) 10 mg/kg IV once weekly, in a protocol b) 300 mg/m^2 PO once weekly, then q 3 wk × 1 yr, in a protocol c) 200 mg/m^2 IV once weekly, in a protocol
	Refractory erosive/nonerosive arthritis, masticatory myositis, polymyositis	80, 82	Dog: 1.5-2.5 mg/kg PO SID × 4 days/wk, with prednisone
	FIP	112	Cat: 2.2 mg/kg PO 4 days/wk
Cyclosporine *(Sandimmune, Neoral)*	Feline allergic bronchitis	17	Cat: 10 mg/kg PO BID
	Granulomatous meningoencephalomyelitis	23	Dog: 5-10 mg/kg PO BID
	Gingivitis, glossitis, lymphoplasmacytic stomatitis	27	Dog: 2-5 mg/kg BID initially, then SID-QOD Cat: 1-4 mg/kg PO SID or dd BID × 4-6 wk
	Inflammatory bowel disease, feline chronic cholangiohepatitis	33, 37	5 mg/kg PO SID-BID
	Perianal fistula	35	Dog: 4-8 mg/kg PO BID × 6-12 wk, then taper, for a total of 18-20 wk
	Immune-mediated hemolytic anemia	64	Dog: a) 10 mg/kg PO SID b) 6 mg/kg PO BID
	Myelodysplastic syndrome	66	Cat: 2.5-5 mg/kg PO SID, with prednisolone
	Cutaneous histiocytosis, exfoliative cutaneous lupus erythematosus, vasculitis, other cutaneous immune-mediated diseases, nodular panniculitis, atopic dermatitis	77, 85, 89, 91	Dog: 5 mg/kg PO SID-QOD × 4-6 wk until remission, then taper

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DRUG (BRAND NAME OR ABBREVIATION)	PURPOSE OR USE	CHAPTERS WHERE CITED	DOSAGE
Cyclosporine *(Sandimmune, Neoral)—cont'd*	Feline eosinophilic granuloma complex	91	Cat: 25 mg PO SID
	Sebaceous adenitis	93	Dog: 5 mg/kg PO BID Cat: 5 mg/kg PO SID, then taper to QOD
	Idiopathic facial dermatitis	93	Cat: 6-7 mg/kg PO SID
	Allergic blepharitis	95	Dog: 5 mg/kg PO SID × 2-4 wk, then taper
Cyclosporine 0.2% *(Optimmune)* or 1%-2% soln (compounding pharmacies)	KCS, pannus, ligneous conjunctivitis	96-98	Apply to affected eye BID-TID
Cyproheptadine *(Ciplactin, Periactin)*	Allergic bronchitis	17	Cat: 2 mg PO BID
	Appetite stimulant	48, 73, 111, 122	Cat: 1-4 mg PO SID-BID
	Vocalization, serotonin syndrome, psilocybin/amphetamine toxicoses, hyperthermia	127, 129, 130	Dog: 1.1 mg/kg PO QID or dissolve tablet in saline and give rectally TID Cat: 2-4 mg PO QID or dissolve tablet in saline and give rectally TID
Cytarabine or Cytosine arabinoside *(Cytosar, DepoCyt)*	Granulomatous meningoencephalomyelitis	23	Dog: 50 mg/m^2 SC BID × 2 days, then q 3 wk
	Myelodysplastic syndrome	66	Cat: a) 0.7-1.4 mg/kg SC SID × 2-4 wk, with prednisolone b) 100 mg/m^2 SC SID × 4 days over 3 wk, with other drugs
	Renal, CNS lymphoma	72	a) 200-300 mg/m^2 SC BID × 2 days b) 100 mg/m^2/day CRI IV × 3-4 days
Dacarbazine *(DTIC-Dome)*	Chemotherapy, in a protocol	72	Dog: 200 mg/m^2 IV slowly SID × 5 days q 3 wk
Dalteparin *(Fragmin)*	Arterial thromboembolism	10, 68	Dog: 150 U/kg SC BID Cat: a) 100-150 U/kg SC BID b) 1 mg/kg SC BID-TID
Danazol *(Danocrine)*	Immune-mediated hemolytic anemia	64	Dog: 3-12 mg/kg PO BID then slowly taper, with prednisone
	Immune-mediated thrombocytopenia	67	Dog: 5 mg/kg PO BID, with prednisone
Dantrolene *(Dantrium)*	Urine retention disorders, decrease urethral sphincter tone	51	Dog: 3-15 mg/kg PO TID Cat: 0.15-0.6 mg/kg PO TID
	Urethral spasms	52	Dog: 0.5-2 mg/kg PO TID, with diazepam
	Skeletal muscle relaxant, malignant hyperthermia	82, 126, 131	Dog: a) 2-5 mg/kg IV once b) 3.5 mg/kg PO BID × 3 days
Dapsone *(Dapsone)*	Jack Russell terrier vasculopathy, vasculitis, sterile eosinophilic pustulosis, subcorneal pustular dermatosis	88, 91, 93	Dog: 1 mg/kg PO TID × 2-4 wk until resolution, then taper; use alone or with prednisone and vitamin E
Darbepoetin *(Aranesp)*	Anemia	48	0.45 µg/kg SC once weekly, then taper to q 2-3 wk
Daunorubicin *(Cerubidine)*	Myelodysplastic syndrome	66	Cat: 20 mg/m^2 IV SID × 3 days over 3 wk, with other drugs
Decoquinate *(Deccox)*	*Hepatozoon americanum*	116	10-20 mg/kg PO BID in food × 2 yr or indefinitely
Deferoxamine *(Desferal)*	Iron toxicosis, chelation therapy	127	40 mg/kg IM TID-QID
Delmadinone acetate *(Tardak)**	Galactorrhea	60	Dog: 1-1.5 mg/kg SC

*Not available in the United States.

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DRUG (BRAND NAME OR ABBREVIATION)	PURPOSE OR USE	CHAPTERS WHERE CITED	DOSAGE
Demecarium bromide 0.125% (compounding pharmacies)	Glaucoma	100	Dog: Apply 1 drop to affected eye BID
l-Deprenyl *See* Selegiline			
Deracoxib *(Deramaxx)*	Analgesia	80-82, 127	Dog: 1-2 mg/kg PO SID
Desipramine *(Norpramin)*	Cataplexy	22	3 mg/kg PO BID
Desmopressin acetate (DDAVP)	Cardiopulmonary arrest	7	a) 1.6 U/kg IT b) 0.8 U/kg IV once
	Central diabetes insipidus	41	Intranasal form: a) 0.1 mL (2-4 drops) in each nostril or conjunctival sac SID-BID, with frequency titrated b) 2-5 μg SC administered through bacteriostatic filter Oral tab: 0.1 mg PO TID, then decrease to effect Parenteral form: 0.5-2 μg SC SID-BID
	von Willebrand disease	67	Dog: 1 μg/kg SC
Desoxycorticosterone pivalate (DOCP; *Percorten V*)	Hypoadrenocorticism, post-adrenalectomy therapy	45	Dog: 1.5-2.2 mg/kg IM, SC q 25 days Cat: 12.5 mg IM q 3-4 wk
Dexamethasone 0.1% (ophthalmic)	Conjunctivitis	96	Apply to affected eye BID-QID
	Feline eosinophilic keratitis	98	Cat: Apply to affected eye 2-6 times/day, then PRN
	Pannus, episcleritis, anterior uveitis, hyphema	98, 99	Apply to affected eye 1-8 times/day, taper slowly
Dexamethasone ($NaPO_4$ = *Dexajet SP, Azium SP;* polyethylene glycol = *Azium*)	Inflammation	15, 103	a) 0.5-2.2 mg/kg IV, SC, IM; repeat in 4-6 hr b) 0.5-1 mg/kg IV, SC once
	Acute bronchitis, airway inflammation	17, 111	0.1-0.2 mg/kg IV, IM, SC, PO BID × 3 days
	Feline allergic bronchitis	17	Cat: 0.2-2.2 mg/kg IV, IM
	Hydrocephalus, hydranencephaly, porencephaly	23	0.05 mg/kg PO SID, then taper to QOD
	Intracranial myiasis	23	0.1 mg/kg IV; repeat in 24-48 hr
	Canine chronic hepatitis/cirrhosis	37	Dog: 0.2-0.4 mg/kg PO SID
	Hyperparathyroidism, hypercalcemia	43, 127	a) 0.1-0.22 mg/kg IV, SC BID b) 0.25 mg/kg PO, SC QID
	Hypoadrenocorticism	45	2-4 mg/kg IV
	Anaphylaxis	76	1-2 mg/kg IV
	Feline plasma cell pododermatitis, eosinophilic granuloma complex	90, 91	Cat: 0.5 mg/kg PO SID, then taper
	Cutaneous immune-mediated diseases	90, 91	0.2-0.6 mg/kg PO SID or dd BID, then taper to QOD
	Envenomation with severe swelling	136	0.1-0.2 mg/kg IV once
Dexmedetomidine *(Precedex)*	Sedation, analgesia	1	Dog: 0.001-0.005 mg/kg SC, IM, IV Cat: 0.002-0.015 mg/kg SC, IM, IV

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DRUG (BRAND NAME OR ABBREVIATION)	PURPOSE OR USE	CHAPTERS WHERE CITED	DOSAGE
Dextran 70 (Macrodex, Gentran 70)	Hypovolemia from gastric dilatation-volvulus	32	Dog: 5 mL/kg IV over 5-15 min, combined with hypertonic (7%) saline
	Shock, hypotension, fluid loss from burns, hypoproteinemia, heat prostration	132, 134, 135	Dog: a) 10-20 mL/kg IV b) 20 mL/kg/day IV as CRI Cat: 5-10 mL/kg IV
Dextroamphetamine *(Adderall, Dexedrine)*	Narcolepsy	22	Dog: 5-10 mg PO BID-TID
	CNS stimulant	117	Dog: 0.2-1.3 mg/kg PO BID-TID
Dextrose 50%	Hyperkalemia	7, 48	a) 1 g/kg IV b) 1-2 g/U insulin IV quickly, then 1-2 g/U insulin IV over 4-6 hr
	Glycemic control	39	Dogs: Blood glucose <80 mg/dL: 2.5%-5% dextrose in isotonic fluids IV as CRI Blood glucose <50 mg/dL: 0.25-0.5 g/kg dextrose as IV bolus
	Hypoglycemia, xylitol toxicosis	45, 46, 126, 127, 135	a) 0.5 g/kg IV bolus, diluted 1:1 with sterile water b) 0.5-1 mL/kg slow IV bolus
Diazepam *(Valium)*	Preanesthetic, sedation, analgesia	1, 3, 4, 32, 71	0.1-0.5 mg/kg IV to effect, alone or in combination with other drugs
	Status epilepticus, cluster seizures, tremors, hyperesthesia from certain toxicoses	22, 23, 112, 125-128, 130, 135	Dog: a) 0.5-2 mg/kg IV, slowly to effect b) 0.5-2 mg/kg/hr IV in 0.9% NaCl as CRI × 4-6 hr; increase in increments of 0.5 mg/kg/hr Cat: a) 0.3-2 mg/kg IV slowly to effect b) 0.25-2 mg/kg PO BID for long-term use Rectal administration: Dog: 1-2 mg/kg Cat: 0.5-1 mg/kg
	Idiopathic tremor syndrome, muscle relaxant for spinal cord disorders	23, 24	Dog: 0.25 mg/kg PO BID-TID
	Urethral spasms, to decrease urethral sphincter tone	51, 52	Dog: a) 2-10 mg PO TID b) 0.1-0.25 mg/kg PO BID-TID, with dantrolene Cat: a) 0.2-0.5 mg/kg IV TID b) 2-5 mg PO TID
	Appetite stimulant	73, 122	Cat: a) 0.05-0.15 mg/kg IV, IM, PO SID-QOD or PRN b) 1 mg PO SID
	Muscle relaxant for exertional myopathy in greyhounds	82	Dog: 0.5 mg/kg IV
	Vertigo	108	Dog: 0.1-0.2 mg/kg PO SID-BID
	Certain behavioral disorders	117	Dog: 0.5-2 mg/kg PO q 4 hr Cat: 0.1-0.5 mg/kg PO q 4 hr
Diazoxide *(Proglycem)*	Hypoglycemia from insulinoma	46, 73	Dog: 5-13 mg/kg PO BID initially, then increase to 20 mg/kg PO BID (max)
Diclofenac 0.1% *(Voltaren)*	Anterior uveitis	99	Apply to affected eye BID-QID
Diethylcarbamazine citrate *(Hetrazan)*	Heartworm chemoprophylaxis	12	Dog: 6.6 mg/kg PO SID

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DRUG (BRAND NAME OR ABBREVIATION)	PURPOSE OR USE	CHAPTERS WHERE CITED	DOSAGE
Diethylstilbestrol (compounding pharmacies)	Hormone-responsive urinary incontinence	51	Dog: 0.1-1 mg PO × 3-5 days, then once weekly
	Induce estrus	61	Dog: 5 mg PO SID × 6-9 days
Difloxacin *(Dicural)*	Canine bacterial pyoderma	88	Dog: 5-10 mg/kg PO SID
Digoxin *(Lanoxin)*	Atrial fibrillation, dilated cardiomyopathy, mitral regurgitation	6, 9, 10	Dog: a) 0.003-0.005 mg/kg PO, IV BID b) 0.22 mg/m^2 PO BID Cat: a) <4 kg: 0.031 mg PO q 2-3 days b) >4 kg: 0.031 mg PO SID-QOD
Digoxin immune Fab *(Digibind)*	Cardiotoxic plant poisoning	131	1-2 vials IV over 30 min
Dihydrotachysterol (DHT; *Hytakerol*)	Hypoparathyroidism, hypocalcemia	43	0.02 mg/kg/day PO × 3 days, then 0.01 mg/kg/day PO SID-QOD × 1 wk
1,25-Dihydroxyvitamin D_3 *See* Calcitriol			
Diltiazem *(Cardizem)*	Acute atrial fibrillation/ flutter, orthodromic atrial reciprocating tachycardia	6, 10	Dog: a) 0.5 mg/kg PO TID, titrate to max dose of 1.5-2 mg/kg PO TID b) 0.1-0.2 mg/kg IV bolus, then 2-6 µg/kg/min IV as CRI c) *Cardizem-CD* or *Dilacor XR:* 3-4 mg/kg PO BID initially, then titrate Cat: a) 0.5-1 mg/kg PO BID-TID b) *Cardizem-CD:* 10 mg/kg PO SID c) *Dilacor XR:* 30-60 mg PO SID-BID
	Hypertrophic cardiomyopathy	10	Cat: a) 7.5 mg PO TID b) *Cardizem-CD:* 45 mg or 10 mg/kg PO SID
Dimenhydrinate *(Dramamine)*	Motion sickness, drug-induced vomiting	31, 126	2-4 mg/kg PO 30 min before giving D-penicillamine Dog: 4-8 mg/kg PO SID-TID Cat: 12.5 mg PO SID-TID
Dimethyl sulfoxide (DMSO)	Amyloidosis	48	90 mg/kg PO, SC 3 times/wk
Diminazene aceturate *(Berenil)**	*Babesia canis*	116	Dog: 3.5-5 mg/kg IM, SC once
	Cytauxzoon felis	116	Cat: 2 mg/kg IM, SC once
Diphenhydramine *(Benadryl)*	Rhinitis/sinusitis	14	Dog: 2-4 mg/kg PO TID Cat: 2-4 mg PO BID-TID
	Intracranial myiasis	23	4 mg/kg IM as pretreatment
	Drug-induced vomiting	31, 126	Dog: 2-4 mg/kg PO, IM TID 30 min before other drug
	Anaphylaxis, urticaria, angioneurotic edema, envenomation	71, 73, 76, 136	Dog: 1-2 mg/kg IV slowly, IM Cat: 2 mg/kg IM
	Atopic dermatitis, effects of mast cell tumors	85, 89	Dog: 2.2 mg/kg PO TID
Diphenoxylate *(Lomotil)*	Acute colitis	34	Dog: 0.05-0.1 mg/kg PO TID-QID Cat: 0.063 mg/kg PO TID
Dipivalyl epinephrine 0.5%-1% *(Dipivefrin)*	Glaucoma	100	Apply 1 drop to affected eye BID-QID, with other therapy

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Dobutamine *(Dobutrex)*	Acute sinus bradycardia, severe or refractory hypotension, shock, dilated cardiomyopathy	6, 37, 76, 132, 135, 136	Dog: 5-20 µg/kg/min IV as CRI Cat: 0.5-2 µg/kg/min IV as CR
	Inotropic agent	10, 32	Dog: 1-5 µg/kg/min IV as CRI
	Pulmonary hypertension	18	Dog: 5-7 µg/kg/min IV as CRI
Docusate sodium or dioctyl sodium sulfosuccinate *(Colace, Surfak, Docusate)*	Megacolon, stool softener	34	Dog: 50-100 mg PO SID-BID Cat: 50 mg PO SID-BID
Dolasetron *(Anzemet, Anemet)*	Serotonin 5-HT_3 receptor antagonist, refractory vomiting, GI ulceration	33, 36, 37, 39, 48, 135	Dog: 0.3-1 mg/kg PO, SC, IV SID-TID Cat: 0.6 mg/kg IV SID
Dopamine *(Inotropin)*	Vasopressor agent, refractory or severe hypotension, shock, dilated cardiomyopathy	1, 7, 37, 132, 135, 136	2-25 µg/kg/min IV as CRI
	Acute sinus bradycardia	6, 32	Dog: 1-3 µg/kg/min IV as CRI
	Pulmonary hypertension	18	Dog: 5-7 µg/kg/min IV as CRI
	Feline hypokalemic polymyopathy	82	Cat: 0.5 µg/kg/min IV as CRI
Dorzolamide 2% *(Trusopt)*	Glaucoma	100	Apply 1 drop to affected eye BID-TID
Doxapram *(Dopram-V)*	Respiratory stimulant		a) 1-10 mg/kg IV b) 0.1 mL IV into umbilical vein (neonate) c) 1-2 drops under tongue (neonate)
Doxepin *(Sinequan)*	Certain behavioral disorders	117	Dog: 3-5 mg/kg PO BID-TID; max = 150 mg BID Cat: 0.5-1 mg/kg PO BID
Doxorubicin *(Adriamycin)*	Chemotherapy for mammary tumors	60	Cat: 20-30 mg/m^2 IV slowly q 3 wk
	Chemotherapy for lymphoma	69, 72	Dog: a) Medium to large dogs: 30 mg/m^2 IV over 20 min q 3 wk b) Small dogs: 1 mg/kg or 25 mg/m^2 IV q 3 wk Cat: a) 25 mg/m^2 IV q 3 wk × 5 Rx b) 1 mg/kg IV q 3 wk, in a protocol
Doxycycline *(Vibramycin, Vibra-Tabs)*	Chronic endocarditis	9	Dog: 5 mg/kg PO SID
	Various bacterial and rickettsial infections	16, 23, 24, 48, 64, 80, 102, 113-116	Dog: 5-10 mg/kg PO SID-BID; may stain teeth of young dogs Cat: 5 mg/kg PO, IV BID
	Bronchiectasis, pneumonia	17, 18	Dog: 5-10 mg/kg PO BID Cat: 5 mg/kg PO BID
	Discospondylitis, osteomyelitis	24	Dog: 25 mg/kg PO SID; may cause vomiting
	Stomatitis, gingivitis, glossitis	27	5 mg/kg PO BID
	Chronic prostatitis	53	Dog: 4.4-11 mg/kg PO BID
	Feline plasma cell pododermatitis, eosinophilic granuloma complex	90, 91	Cat: 25 mg/day PO
	Cutaneous immune-mediated diseases	90	Dog: <10 kg: 100 mg PO SID, with niacinamide >10 kg: 100 mg PO BID, with niacinamide
Edrophonium Cl *(Tensilon, Enlon)*	Tensilon test	25	Dog: 0.2-5 mg IV; max = 5 mg Puppy: 0.1-0.5 mg IV
EDTA 1% ophthalmic (compounding pharmacies)	Calcium keratopathy	98	Administer to affected eye BID-TID

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DRUG (BRAND NAME OR ABBREVIATION)	PURPOSE OR USE	CHAPTERS WHERE CITED	DOSAGE
Enalapril *(Enacard, Vasotec)*	Chronic congestive heart failure, hypertension, to reduce left-to-right shunting	8-10	Dog: 0.5 mg/kg PO BID
	Glomerulonephritis, chronic renal failure	48	Dog: 0.25-1 mg/kg PO SID-BID
Enilconazole 1%-2% soln *(Imaverol)*	Nasal aspergillosis	14	Dog: Apply 120-200 mL intranasally; allow contact time of 45-60 min × 2-3 Rx
Enoxaparin *(Lovenox)*	Arterial thromboembolism	10	Cat: 1 mg/kg SC BID-TID
Enrofloxacin *(Baytril)*	Chronic endocarditis	9	Dog: 5-10 mg/kg PO BID
	Various bacterial and rickettsial infections	16, 23, 35, 50, 64, 80, 102, 112-115	Dog: 2.5-10 mg/kg PO, SC, IV, IM SID-BID; may cause cartilage deformation in young dogs Cat: 2.5 mg/kg PO, SC BID; doses >5 mg/kg/day associated with acute blindness
	Discospondylitis, osteomyelitis	24, 81	Dog: 5-15 mg/kg PO BID
	Stomatitis, gingivitis, glossitis, chronic prostatitis, canine pyoderma	27, 53, 88	Dog: 5-10 mg/kg PO SID Cat: 4 mg/kg PO SID; use with caution
	Chronic histiocytic ulcerative colitis	34	Dog: 5-15 mg/kg PO BID alone or with metronidazole and amoxicillin
	Hepatic abscess, feline acute cholangiohepatitis, canine chronic hepatitis/cirrhosis, acute abdominal syndrome	37, 39	Dog: 5-20 mg/kg IV SID Cat: 5 mg/kg IV SID; use with caution
Ephedrine *(Broncholate, Marax)*	Urinary incontinence	49	Dog: 2-4 mg/kg PO BID-TID Cat: 2-4 mg PO BID-TID
Epinephrine *(Adrenalin, EpiPen)*	Acute sinus bradycardia	6	0.05-0.2 mg IV
	Cardiopulmonary arrest	7	0.2 mg/kg IT
	Vasopressor	7	0.01-0.02 mg/kg IV q 3-5 min
	Anaphylaxis	76, 136	1:10,000 soln: 0.05-0.1 mL/kg IV; max = 2 mL
Epsiprantel *(Cestex)*	Tapeworms: *Dipylidium* spp., *Taenia* spp.	33	Dog: 5 mg/kg PO once Cat: 2.5 mg/kg PO once
Ergocalciferol *See* Vitamin D_2			
Erythromycin *(E-Mycin, Ery-Tab)*	Gastric motility disorders, megacolon	31, 34	Dog: 0.5-1 mg/kg PO, IV TID
	Campylobacter spp., *Helicobacter* spp. infections	33	Dog: 20 mg/kg PO BID-TID Cat: 10 mg/kg PO TID
	Chronic prostatitis, canine bacterial pyoderma	53, 88	Dog: 10-22 mg/kg PO TID
	Actinomycosis, nocardiosis	89	10 mg/kg PO TID
Erythromycin o.o. *(Erythromycin)*	Neonatal ophthalmia, conjunctivitis from *Chlamydophila* spp., *Mycoplasma* spp.	95, 96	Apply to affected eye TID-QID
Erythropoietin, human recombinant *(Epogen, Procrit)*	Anemia from renal failure, FeLV, or toxic plant poisoning	48, 112, 131	100 U/kg SC 3 times/wk, then 50-100 U/kg SC q 4-7 days
	Myelodysplastic syndrome	66	Dog: 100 U/kg SC QOD

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DRUG (BRAND NAME OR ABBREVIATION)	PURPOSE OR USE	CHAPTERS WHERE CITED	DOSAGE
Esmolol *(Brevibloc)*	Acute atrial fibrillation, flutter or tachycardia	6	a) 50-100 µg/kg IV slowly as bolus; repeat q 5 min, up to max dose of 500 µg/kg IV b) 50-200 µg/kg/min IV as CRI
Esomeprazole *(Nexium)*	GI ulceration	39	Dog: 0.5-1 mg/kg PO SID-BID
Essential fatty acids (*See also* Fish oil; Omega-3, Omega-6 Fatty Acid supplements)	Hepatocutaneous syndrome	37	Dog: 30-90 mg/kg PO SID
Ethanol 20%-30% (grade alcohol)	Ethylene glycol toxicosis	48, 128	20% soln: Dog: 5.5 mL/kg in 0.9% saline IV q 4 hr × 5 Rx, then QID × 4 Rx Cat: 5 mL/kg IV QID × 5 Rx, then TID × 4 Rx 30% soln: 1.3 mL/kg IV as loading dose, followed by 0.42 mL/kg/hr IV CRI × 48 hr
Ethyl lactate shampoo *(Etiderm)*	Staphylococcal pyoderma and folliculitis, impetigo, intertrigo, feline acne	88	Dog: Apply topically SID-QOD × 7-14 days Cat: Apply topically SID-QOD until resolution, then PRN
Etidronate disodium *(Didronel)*	Hypercalcemia	43	Dog: 10-40 mg/kg/day PO dd BID
Etodolac *(Etogesic)*	Musculoskeletal pain or inflammation	80, 127	Dog: 10-15 mg/kg PO SID
Etomidate *(Amidate)*	Anesthesia induction	1, 32	Dog: 1 mg/kg IV to effect, alone or with diazepam or fentanyl
Etretinate *(Tegison)*	Primary seborrhea, sebaceous adenitis	93	Dog: 1-2 mg/kg PO SID
	Vitamin A–responsive dermatoses	122	Dog: 0.75-1 mg/kg PO SID
Famciclovir *(Famvir)*	Feline herpesvirus keratitis	98	Cat: 1/4 of 125-mg tab PO BID × 8 days
Famotidine *(Pepcid)*	Esophagitis, GI tract ulceration, uremic gastritis, helicobacteriosis	15, 30-33, 37, 39, 48, 67, 73, 89, 112, 113, 124, 127, 128, 131, 135	a) 0.5-1 mg/kg IV, PO, SC, IM SID-BID b) 10-20 mg PO SID Do not give IV in cats
Felbamate *(Felbatol)*	Seizures	22	Dog: 15-70 mg/kg PO BID-TID; increase in 15 mg/kg increments up to 70 mg/kg/day PO
Fenbendazole *(Panacur)*	*Capillaria aerophila*, *Paragonimus kellicotti*, *Aelurostrongylus abstrusus*, *Oslerus osleri*	14, 16, 18	Dog: 25-50 mg/kg PO BID × 10-14 days Cat: 25-50 mg/kg PO BID × 14 days
	Parasitic gastritis: *Ollulanus* spp.	31	10 mg/kg PO SID × 3 days
	Strongyloides spp., *Giardia lamblia*, *Entamoeba histolytica*, *Balantidium coli*	31, 33, 34, 48, 50, 116	Dog: 50 mg/kg PO SID × 3-10 days
	Ascarids, hookworms, whipworms	33, 34	Dog: 50 mg/kg PO SID × 3 days; repeat in 3 wk and possibly 3 mo later
	Pancreatic fluke: *Euryterma procyonis*	36	Cat: 30 mg/kg PO SID × 6 days
	Mesocestoides spp. infections	38	Dog: 100 mg PO BID × 4-12 wk
	Renal parasite: *Capillaria felis cati*	48	Cat: 22 mg/kg PO BID × 3-10 days
Fentanyl transdermal patch *(Duragesic)*	Analgesia, pain control	81, 128	3-5 µg/kg q 3-4 days; apply 18-24 hr before surgery Dog: a) <10 kg: 25 µg/hr b) 10-20 kg: 50 µg/hr c) 20-30 kg: 75 µg/hr d) >30 kg: 100 µg/hr Cat: 25 µg/hr

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DRUG (BRAND NAME OR ABBREVIATION)	PURPOSE OR USE	CHAPTERS WHERE CITED	DOSAGE
Fentanyl citrate *(Sublimaze)*	Analgesia, pain control	1, 39, 134	Dog: a) 0.02 mg/kg IV, with midazolam b) 0.3-0.7 µg/kg/min IV as CRI c) 3-10 µg/kg IV initial bolus, then 0.5-1 µg/kg/min IV as CRI Cat: a) 0.01 mg/kg IV, with midazolam b) 0.3 µg/kg/min IV as CRI
	Anesthesia for gastric dilatation-volvulus surgery	32	Dog: 5-15 µg/kg/hr IV as CRI
Ferrous sulfate *(Feosol, Feratab)*	Chronic blood loss, iron deficiency anemia	64	10 mg/kg PO SID, with food
Filgrastim *(Neupogen)* *See* Granulocyte colony-stimulating factor			
Finasteride *(Propecia)*	Benign prostatic hyperplasia	53	Dog: 0.1-0.5 mg/kg PO SID
Fipronil *(Frontline Plus, Topspot)*	Flea control	85	Apply topically q 2-4 wk; wait 24-48 hr after bathing
	Otodectic mange, ear mites	85	Apply 2-3 drops in each ear; repeat in 7 and 30 days
	Cheyletiellosis	85	Apply topically q 4 wk × 2 Rx
	Sarcoptic mange	85	Apply topically q 2 wk × 3 Rx
Firocoxib *(Previcox)*	DJD	80	Dog: 5 mg/kg PO SID
Fish oil (eicosapentaenoic acid, docosahexaenoic acid) *See also* Omega 3 and 6 Fatty Acids	Hyperlipidemia	46	Dog: 200 mg/kg/day PO
	Primary seborrhea	93	Dog: 35 mg/kg PO SID
Fluconazole *(Diflucan)*	Nasal aspergillosis	14	Dog: 1.25-2.5 mg/kg PO BID
	Systemic and CNS mycotic or algal infections	14, 23, 24, 27, 50, 89, 102, 111	Dog: a) 5-15 mg/kg PO, IV SID b) 2.5-5 mg/kg PO, IV BID Cat: 25-50 mg PO BID
	Malassezia spp. dermatitis	85	Dog: 2.5 mg/kg PO SID
	Dermatophytosis	86	2.5-10 mg/kg PO SID-BID
Flucytosine *(Ancobon)*	Cryptococcosis	14, 89, 111	Dog: a) 25-50 mg/kg PO QID b) 50-75 mg/kg PO TID Cat: a) 100 mg PO QID b) 30 mg/kg PO QID c) 50 mg/kg PO TID
Fludrocortisone acetate *(Florinef)*	Hypoadrenocorticism	45	0.02 mg/kg PO SID
Flumazenil *(Romazicon)*	Benzodiazepine toxicosis	129	0.1 mg/kg IV
Fluocinolone (*Tri-Luma* cream)	Cutaneous or discoid lupus erythematosus, pemphigus erythematosus	90, 91	Dog: Apply topically BID × 5-7 days, then taper
Fluoxetine *(Prozac)*	Certain behavioral disorders	117	Dog: 1-2 mg/kg PO SID Cat: 0.5-1.5 mg/kg PO SID
Flurazepam *(Dalmane)*	Certain behavioral disorders	117	Dog: 0.1-0.5 mg/kg PO BID Cat: 0.1-1 mg/kg PO BID
	Appetite stimulant	122	0.2-0.4 mg/kg PO q 4-7 days
Flurbiprofen 0.03% *(Ocufen)*	Anterior uveitis	99	Apply to affected eye BID-QID

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DRUG (BRAND NAME OR ABBREVIATION)	PURPOSE OR USE	CHAPTERS WHERE CITED	DOSAGE
Fluticasone propionate *(Flovent)*	Chronic or allergic tracheobronchitis	16, 17	Dog: <20 kg: 110 µg BID >20 kg: 220 µg BID Cat: 110-220 µg BID Administer via spacing chamber/ metered dose inhaler and face mask; 1 puff = 110 µg
Fluvoxamine *(Fluvoxamine)*	Certain behavioral disorders	117	Dog: 1-2 mg/kg PO SID Cat: 0.5-1.5 mg/kg PO SID
Folic acid (Folic acid, Folate)	Dietary supplement, folate deficiency	33	1-5 mg PO, SC weekly × 1 mo
Fomepizole *(Antizol-Vet)*	Ethylene glycol toxicosis	48, 128	Dog a) 20 mg/kg IV as loading dose, followed by 15 mg/kg IV at 12 and 24 hr, then 5 mg/kg IV at 36 hr b) 3 mg/kg IV BID as additional doses if needed Cat: 125 mg/kg IV as loading dose, then 31.25 mg/kg IV at 12, 24, and 36 hr NOTE: Not approved for use and unknown efficacy in cats
Furazolidone *(Furoxone, Giarcid)*	*Giardia lamblia*, *Entamoeba histolytica*, *Balantidium coli*	33	4 mg/kg PO BID × 7 days
Furosemide *(Salix, Lasix)*	Enhanced diuresis	1, 73	1-2 mg/kg IV SID-BID
	Acute congestive heart failure	8-10	Dog: a) Moderate: 1-4 mg/kg IV, IM, SC, PO BID-TID b) Severe or fulminant: 4-8 mg/kg IV, IM, SC q 2-6 hr Cat: 1-2 mg/kg IV, IM, SC q 2-8 hr
	Chronic congestive heart failure	9, 10	Dog: a) Mild to moderate: 1-4 mg/kg PO SID-TID b) Moderate to severe: 2-4 mg/kg PO BID-TID Cat: a) Mild: 1 mg/kg PO SID-BID b) Moderate: 2-3 mg/kg PO BID c) Severe: 3-4 mg/kg IV, IM, SC, PO BID-TID
	Diuresis: pulmonary edema	18, 37, 133	a) 2-4 mg/kg IV once b) 2-4 mg/kg IM, PO q 4-12 hr
	Hydrocephalus, hydranencephaly, porencephaly	23	Dog: 1-2 mg/kg PO BID
	Diuresis: brain edema	23	0.7 mg/kg IV, 15 min after mannitol administration
	Diuresis: ascites from hepatic failure	37	Dog: 1 mg/kg PO BID
	Hypercalcemia, cholecalciferol toxicosis	1, 43, 73, 124, 127	a) 1-4.5 mg/kg IV, SC, PO, IM SID-QID b) 5 mg/kg IV initial dose, then 5 mg/kg/hr IV as CRI
	Diuresis: acute renal failure, certain toxicoses	48, 128	a) 1-2 mg/kg IV; double the dose if no response in 20-30 min b) Follow with 0.25-1 mg/kg/hr IV as CRI or 1-2 mg/kg IV QID
Gabapentin (*Neurontin)*	Seizures	22	Dog: 25-60 mg/kg PO BID-QID Cat: ≤30 mg/kg PO TID
	Neuropathic pain, paraesthesia	24	Dog: 10 mg/kg PO BID

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DRUG (BRAND NAME OR ABBREVIATION)	PURPOSE OR USE	CHAPTERS WHERE CITED	DOSAGE
Gamma globulin, human *(Iveegam)*	Immune-mediated hemolytic anemia	64	Dog: 0.5-1.5 g/kg IV as 12-hr CRI
	Pemphigus complex	91	Dog: 1 g/kg IV over 6-12 hr × 1-2 days
Gemfibrozil *(Lopid)*	Hyperlipidemia	46	Dog: 200 mg/day PO
Gentamicin *(Gentocin, Legacy)*	Infectious tracheobronchitis	16, 114	Dog: 3-5 mg/kg SID × 5 days as aerosolization or IT injection Cat: 6-8 mg/kg diluted 1:5 to 1:10 in 0.9% saline, delivered by face mask SID
	Serious bacterial infections, septic peritonitis, osteomyelitis	38, 50, 81, 112	6-6.6 mg/kg IV, IM, SC SID × 10-14 days
	Bacterial keratitis	98	20-40 mg applied subconjunctivally
	Brucellosis	113	5 mg/kg IM, SC SID, in a protocol with doxycycline or minocycline
Gingko biloba extract	Rodenticide toxicosis	124	100 mg/kg PO
Glipizide *(Glucotrol)*	Diabetes mellitus	44, 127	Cat: a) 2.5-5 mg PO BID b) 0.25-0.5 mg/kg PO BID
Glucagon *(Glucagon)*	Induce gastric hypomotility	4	Dog: 0.1-0.35 mg/kg IV, repeat PRN; max dose = 1 mg Cat: 0.1 mg IV, repeat PRN; max dose = 1 mg
	Hypoglycemia, neuroglycopenic crisis	46	50 ng/kg IV as initial bolus; then 10-15 ng/kg/min IV as CRI, PRN to maintain euglycemia
Glucosamine/chondroitin sulfate (*Cosequin DS, Cosequin* for cats)	Chronic feline idiopathic cystitis	50	Cat: 1 capsule PO SID
	DJD	80	Dog: 22 mg/kg PO SID
Glycerin *(Osmoglyn)*	Acute glaucoma	100	Dog: 1-2 g/kg PO × 1-2 Rx
Glycopyrrolate *(Robinul)*	Preanesthetic	1	Dog: 0.003-0.01 mg/kg SC, IM, IV Cat: 0.003-0.007 mg/kg SC, IM, IV
	Ptyalism	29	0.01 mg/kg SC PRN
Gonadotropin-releasing hormone *(Cystorelin, Factrel)*	Luteinize an ovarian follicular cyst	55, 62	Dog: 50-100 µg IM SID × 1-3 Rx Cat: 25 µg IM
	Vaginal edema	58	Dog: 2.2 µg/kg IM
	Poor libido in male dogs	61	Dog: 1-2 µg/kg IM 1 hr before breeding
	Induce ovulation	62	Cat: 25 µg IM; give 15-30 hr before artificial insemination
Granulocyte colony-stimulating factor or Filgrastim *(Neupogen)*	Bone marrow suppression (neutropenia, leukopenia)	65, 112, 127, 131	Dog: 1-10 µg/kg/day SC × 3-5 days Cat: 5 µg/kg/day SC for ≤ 2 wk
	Cyclic hematopoiesis, sepsis	65, 75	Dog: 5 µg/kg SC BID × 3-5 days
Griseofulvin *(Fulvicin-U/F, Gris-PEG)*	Dermatophytosis	86	Microsized product: Dog: a) 25 mg/kg PO BID b) 50 mg/kg PO SID Cat: 12.5-25 mg/kg PO BID Ultramicrosized product: Dog: 5-10 mg/kg PO SID Cat: 5-15 mg/kg PO SID
Growth hormone (Porcine GH)	Pituitary dwarfism, adult hyposomatotropism	41	Dog: 0.1 IU/kg SC 3 times/wk × 1-2 mo
Haloperidol *(Haldol)*	Vomiting, dopaminergic antagonist	31	Dog: 0.02 mg/kg PO BID

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DRUG (BRAND NAME OR ABBREVIATION)	PURPOSE OR USE	CHAPTERS WHERE CITED	DOSAGE
Heparin (Heparin sodium)	Arterial thromboembolism, DIC	10, 18, 38, 64, 68	Dog: a) 200 U/kg IV, then 75-200 U/kg SC TID-QID b) 15-20 IU/kg/hr IV as CRI Cat: 50-100 U/kg SC QID
	Pyothorax	19	1500 U/100 mL lavage soln
	Thrombosis prevention	68	a) 100-200 U/kg SC QID b) 200-300 U/kg SC TID
Hetastarch *(Hetastarch)*	Shock, hypoalbuminemia, severe fluid loss from burns	1, 32, 33, 37, 112, 132, 134, 135	Dog: a) 5-20 mL/kg IV bolus, then 1 mL/kg/hr IV b) 20-30 mL/kg/day IV as CRI Cat: a) 5-10 mL/kg IV bolus b) 20-30 mL/kg/day IV as CRI
Human gamma globulin *See* Gamma globulin, human *(Iveegam)*			
Hydralazine *(BiDil)*	Severe hypertension, reduce left-to-right shunting	8-10, 48	Dog: 0.25-2 mg/kg PO BID
Hydrochlorothiazide *(Aldoril)*	Chronic, refractory congestive heart failure	9, 10	Dog: 2-4 mg/kg PO BID Cat: 1-2 mg/kg PO BID
	Nephrogenic diabetes insipidus	41	0.5-1 mg/kg PO BID
	Chronic calcium oxalate urolithiasis	50	Dog: 2 mg/kg PO BID
Hydrocodone bitartrate *(Hycodan)*	Cough suppressant	9, 15-17, 114	Dog: a) 0.22-0.25 mg/kg PO SID-QID b) 2.5-10 mg PO BID-QID
Hydrocortisone 1% *(Resicort)*	Flea allergic, atopic, contact, and acute moist dermatitides	85	Apply conditioner 1-2 times/wk after bathing; do not rinse
Hydrogen peroxide 3%	Emesis, decontamination	123, 130	0.5-2 mL/kg PO; may repeat once; max = 45 mL
Hydromorphone *(Dilaudid, Hydromorphone)*	Analgesic, preanesthetic, sedation	1, 10, 15, 32, 39, 81, 133, 134, 136	Dog: 0.05-0.2 mg/kg SC, IM, IV q 4-6 hr Cat: 0.02-0.2 mg/kg IV, SC, IM QID
Hydroxyurea *(Hydroxyurea)*	Primary polycythemia vera, chronic myelogenous leukemia	64, 66, 72	Dog: a) 15 mg/kg PO SID until PCV normalizes b) 80 mg/kg PO q 3 days c) 500 mg/m^2 PO per day × 3 wk, then increase to 2000 mg/m^2 PO per day if needed; use with vincristine Cat: 25 mg/kg PO 3 times/wk
	Chronic granulocytic leukemia, basophilic leukemia	66	a) 20-25 mg/kg PO BID, then taper to 10-12 mg/kg PO SID or to 50 mg/kg PO q 3-4 days b) 50 mg/kg PO SID × 14 days, then taper to QOD and then q 3 days
	Eosinophilic leukemia	66	Cat: 40 mg/kg/day PO × 7 days, then QOD or q 3 days, with prednisone
Hydroxyzine *(Hydroxyzine)*	Atopic dermatitis, allergic blepharitis	85, 95	Dog: 2.2 mg/kg PO BID-TID Cat: 10 mg PO BID-TID
Hyperimmune plasma (from recovered dogs)	Canine herpesvirus protection in puppies, canine parvovirus	112	Dog: a) 1-2 mL IP b) 1.1-2.2 mL/kg IV slowly
Hypertonic saline (7%-7.5%)	Cerebral edema	23	1-5 mL/kg IV over 10-15 min
	Acute abdominal syndrome	39	4-5 mL/kg IV over 10-15 min
Idoxuridine 0.1% soln (compounding pharmacies)	Ocular herpesvirus infection	96, 98, 114	Cat: Apply soln to affected eye q 5 min for 30 min, then 5-6 times daily

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DRUG (BRAND NAME OR ABBREVIATION)	PURPOSE OR USE	CHAPTERS WHERE CITED	DOSAGE
Ifosfamide *(Ifex)*	Chemotherapy, in a protocol	72	Dog: 350 mg/m^2 IV q 2-3 wk, with mesna Cat: 900 mg/m^2 IV q 3 wk, with mesna
Imidacloprid *(Advantage, Advantix)*	Flea control	85	Dog: Apply topically q 2-4 wk
Imidocarb dipropionate *(Imizol)*	Babesiosis	64, 116	Dog: 5-7.5 mg/kg IM once; may repeat in 14 days
	Cytauxzoonosis, ehrlichiosis, hepatozoonosis	64, 115, 116	Dog: 5 mg/kg IM; repeat in 1-3 wk Cat: 2-5 mg/kg IM once, or repeat in 14 days
Imipenem *(Primaxin)*	Endocarditis	9	Dog: 10 mg/kg IV, SC TID
	Septicemia, endotoxemia, peritonitis	33, 38	Dog: 2-10 mg/kg IV, IM TID
Imipramine *(Imipramine, Tofranil)*	Cataplexy	22	Dog: 0.5-1 mg/kg PO BID-TID
	Urinary incontinence, increase urethral sphincter tone	51	Dog: 5-15 mg PO BID Cat: 2.5-5 mg PO BID
	Certain behavioral disorders	117	Dog: 0.5-2 mg/kg PO BID-TID
Insulin, intermediate *(NPH: Humulin N, Novolin N; Vetsulin)*	Diabetes mellitus	44	0.5 U/kg SC BID
Insulin, PZI *(PZI Vet)*	Diabetes mellitus	44	0.5 U/kg SC BID
Insulin, regular *(Humulin R, Novolin R)*	Diabetes mellitus	44	0.5 U/kg SC BID or PRN
	Diabetic ketoacidosis, transient hyperglycemia	39, 44, 46	a) 0.2 U/kg IM, then 0.1 U/kg IM hourly until glucose <250 mg/dL b) 2.2 U/kg in 250 mL 0.9% NaCl IV as CRI
	Severe hyperkalemia	6, 7, 45, 48, 49	0.06-0.5 U/kg IV, with 4 mL of 50% dextrose/unit insulin
Interferon-α *(Intron A, Roferon-A)*	Immune modulator, antiviral therapy for FeLV, FIP, herpesvirus	112, 114, 122	Cat: a) 30 U PO SID on alternating wk b) 10^6 U/kg/day SC for 5 days, beginning on days 0, 14, and 60
Interferon omega	Canine parvovirus	112	Dog: 2.5 million U/kg IV SID × 3 days
Iodine	Stabilization prior to feline hyperthyroidism surgery	42	Cat: 30-100 mg PO SID or dd BID Use in combination with β-adrenergic blocking agent 10-14 days before surgery
Ipecac syrup *(Ipecac)*	Emetic	123	Dog: 1-2.5 mL/kg PO diluted 50:50 with water Cat: 3.3 mL/kg PO diluted 50:50 with water Not routinely recommended in animals
Ipodate *(Solu-Biloptin)*	Feline hyperthyroidism in methimazole-intolerant cats	42	Cat: 100 mg PO SID or dd BID
Iron dextran complex (*INFeD* injection)	Chronic blood loss, iron deficiency anemia	64	50 mg iron/mL: max dose = 2 mL IM SID
Isoproterenol *(Isuprel)*	Acute sinus bradycardia	6	0.01-0.2 μg/kg/min IV as CRI
Isotretinoin *(Accutane)*	Severe feline acne	88	Cat: 2 mg/kg PO SID
	Vitamin A–responsive dermatoses	122	Dog: 1-3 mg/kg/day PO

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Itraconazole *(Sporanox)*	Systemic mycotic and algal infections	14, 23, 33, 89, 102, 111	Dog: 5-10 mg/kg PO BID Cat: a) 25-50 mg PO SID-BID b) 5-10 mg/kg PO SID
	Mycotic stomatitis, gingivitis, glossitis; gastric pythiosis	27, 31	5-10 mg/kg PO SID
	Fungal cystitis, *Malassezia* spp. otitis and dermatitis, dermatophytosis	50, 85, 86, 90, 107, 108	5 mg/kg PO SID-BID
Ivermectin *(Heartgard Plus, Tru-Heart Plus)*	Heartworm prophylaxis	12	Dog: 6-12 µg/kg PO once monthly Cat: 24 µg/kg PO once monthly
	Elimination of heartworm microfilariae	12	Dog: 50 µg/kg PO, may repeat in 2 wk; do not exceed 200 µg/kg; do not use in ivermectin-sensitive breeds Cat: 24 µg/kg PO
	Nasal capillariasis, *Pneumonyssoides caninum, Oslerus osleri*, *Strongyloides* spp., *Aelurostrongylus abstrusus*	14, 16, 18, 33	Dog: 0.2-0.4 mg/kg PO, SC once; do not use in ivermectin-sensitive breeds Cat: 0.2 mg/kg SC, PO
	Intracranial myiasis	23	400 µg/kg SC; repeat in 24-48 hr; do not use in ivermectin-sensitive dog breeds
	Renal parasite: *Capillaria plica*	48, 50	Dog: 0.2 mg/kg PO once; do not use in ivermectin-sensitive breeds
	Cheyletiellosis, notoedric and sarcoptic mange, demodectic blepharitis	85, 95	0.2-0.3 mg/kg PO, SC q 2 wk × 3 Rx; do not use in ivermectin-sensitive dog breeds
Ivermectin (*Ivomec* 1%)	Otodectic mange	85	0.2-0.4 mg/kg PO, SC q 2 wk × 3 Rx Not approved in United States for this use; do not use in ivermectin-sensitive dog breeds
	Canine demodicosis	86	Dog: 0.1 mg/kg PO SID × 7 days; then increase to 0.2-0.6 mg/kg PO SID × 3-9 wk; do not use in ivermectin-sensitive breeds
Ivermectin 0.01% otic soln *(Acarexx)*	Otodectic mange, ear mites	85	Apply 0.5 mL in each ear once; repeat in 2 wk
Ketamine *(Ketaject, Ketaset)*	Anesthesia	1	Dog: a) 3-5 mg/kg IV, IM, in combination with other drugs b) 0.01-0.02 mg/kg/min IV as CRI Cat: a) 3-5 mg/kg IV, IM, in combination with other drugs b) 0.01 mg/kg/min IV as CRI
	Restraint, sedation	3, 4, 71	Cat: 1-4 mg/kg IV, with acepromazine or diazepam and atropine
	Anesthesia induction	32	Dog: 6.6 mg/kg IV to effect, with diazepam
Ketoconazole *(Nizoral, Ketoconazole)*	Systemic mycotic infections	14, 27, 89, 111	Dog: a) 5-15 mg/kg PO BID b) 30 mg/kg PO SID Cat: a) 5-10 mg/kg PO BID b) 10-20 mg/kg PO
	CNS fungal infections	24	Initial dose: 15-20 mg/kg PO BID × 2-3 mos Maintenance dose: 10 mg/kg PO SID

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DRUG (BRAND NAME OR ABBREVIATION)	PURPOSE OR USE	CHAPTERS WHERE CITED	DOSAGE
Ketoconazole *(Nizoral, Ketoconazole)—cont'd*	Pituitary-dependent hyperadrenocorticism, pre-adrenalectomy therapy	45	Dog: 7.5 mg/kg PO BID; increase over 3 wk to 15 mg/kg PO BID
	Fungal cystitis	50	Dog: 10-20 mg/kg PO SID or dd BID Cat: 10 mg/kg PO BID
	Malassezia spp. dermatitis and otitis, dermatophytosis	85, 86, 90, 107, 108	Dog: 5-10 mg/kg PO SID-BID Cat: 5-10 mg/kg PO SID-BID; use with caution
Ketoconazole shampoo *(Nizoral, KetoChlor)*	*Malassezia* spp. dermatitis, seborrhea oleosa	85	Use 1-2 times/wk until resolution
Ketoprofen *(Anafen, Ketoprofen)*	Pain, inflammation	1, 24, 127	Dog: 2 mg/kg PO, SC, IM, IV once, then 1 mg/kg PO SID × 4-5 days Cat: 1 mg/kg SC, IM, IV
Ketorolac 0.5% *(Acular)*	Allergic conjunctivitis	96	Apply soln to the affected eye BID-QID
Ketotifen fumarate 0.025% *(Zaditor)*	Conjunctivitis	96	Apply soln to the affected eye BID-TID
Lactulose *(Kristalose, Lactulose)*	Megacolon, laxative therapy	34	2-10 mL PO TID; titrate to produce soft stools
	Congenital portosystemic shunts, hepatic encephalopathy, canine chronic hepatitis/cirrhosis	37	Emergency Rx: 100 mL in 200 mL water, given as an enema at 5-15 mL/kg QID Long-term Rx: 0.5-1 mL/kg PO TID; titrate to produce soft stools
Lansoprazole *(Prevacid)*	Severe gastric ulceration	73	Dog: 1-2 mg/kg PO SID; max = 20 mg/day
Latanoprost 0.005% *(Xalatan)*	Glaucoma	100	Emergency Rx (dog): Apply 1 drop to affected eye; repeat in 5-10 min Maintenance Rx (dog): Apply 1 drop to affected eye SID-BID
Leflunomide *(Arava)*	Cutaneous histiocytosis	77	Dog: 2-4 mg/kg PO SID
Levamisole *(Levasol, Tramisol)*	*Capillaria aerophila*	14, 18	Dog: a) 8-10 mg/kg PO SID × 5 days; repeat in 9 days b) 8-10 mg/kg PO SID × 10-20 days
	Parasitic cystitis, epidermolysis bullosa	50, 91	2.5 mg/kg PO SID-QOD × 5 days
Levetiracetam *(Keppra)*	Seizures	22	Dog: a) 5-30 mg/kg PO BID-TID, as an add-on therapy b) 25-60 mg/kg PO BID-TID
Levocabastine 0.05% *(Livostin)*	Conjunctivitis	96	Apply soln to affected eye QID
Lidocaine *(Lidocaine, Xylocaine)*	Local, regional blockade anesthesia	1	Dog: 2-5 mg/kg SC, perilesional or perineural infiltration Cat: 2-3 mg/kg SC, perilesional or perineural infiltration
	Analgesia	1	Dog: 0.05 mg/kg/min IV as CRI Cat: 0.005 mg/kg/min IV as CRI
	Topical anesthesia, nasal cannulation	3	2% soln: 0.1-1 mL instilled into nares/nostril
	Cardiopulmonary arrest, premature ventricular arrhythmias	6, 7, 32, 126, 130, 135	Dog: a) 1-2 mg/kg IV bolus; repeat up to 3 ×; then 25-100 µg/kg/min IV as CRI or PRN b) 4 mg/kg IT Cat: 0.2-1 mg/kg IV bolus; use with extreme caution in cats

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DRUG (BRAND NAME OR ABBREVIATION)	PURPOSE OR USE	CHAPTERS WHERE CITED	DOSAGE
Lime sulfur suspension *(LymDyp)*	Sarcoptic and notoedric mange, dermatophytosis, cheyletiellosis, pruritus, itching	85, 86	2%-3% dip (4 oz lime dip/gal water): apply to skin 1-2 times/wk × 6-8 wk until resolution
Lincomycin *(Lincocin)*	Canine bacterial pyoderma	88	Dog: a) 22 mg/kg PO BID b) 15.4 mg/kg PO TID
	Bacterial blepharitis	95	20 mg/kg PO BID
Lisinopril *(Prinivil)*	Chronic congestive heart failure	9, 10	Dog: 0.5 mg/kg PO SID
Lithium carbonate *(Eskalith, Lithobid)*	Marrow hypoplasia with pancytopenia or neutropenia, cyclic hematopoiesis	65, 75	Dog: 11 mg/kg PO BID
Lomustine (CCNU; CeeNU)	Mast cell tumor, CNS tumors, lymphoma rescue protocol	72, 89	Dog: Medium to large dogs: 70-80 mg/m^2 PO q 4-6 wk Small dogs: 50-60 mg/m^2 PO q 4-6 wk Cat: 50-60 mg/m^2 PO q 4-6 wk
	Cutaneous T cell lymphoma	91	10 mg/kg PO q 3 wk
Loperamide *(Imodium)*	Noninfectious diarrhea, acute colitis	33, 34	Dog: 0.08-0.2 mg/kg PO BID-QID Cat: 0.04 mg/kg PO SID-BID; use with caution
Lorazepam *(Lorazepam)*	Certain behavioral disorders	117	Dog: 0.02-0.5 mg/kg PO TID Cat: 0.03-0.08 mg/kg PO BID
Lufenuron *(Program, Sentinel)*	Inhibit flea growth	85	Dog: 10 mg/kg PO monthly Cat: 30 mg/kg PO monthly
	Coccidioidomycosis	89	Dog: 5 mg/kg PO SID
L-Lysine *(Viralyis, Enisyl)*	Ocular herpesvirus infection	96, 98, 114	Cat: 250-500 mg PO SID-BID
Lysine-8 vasopressin *(Diapid)*	Central diabetes insipidus	41	1-2 sprays in a nostril SID-TID to effect
Magnesium hydroxide *(Milk of Magnesia, Maalox)*	Iron toxicosis	123, 127	30-90 mg/kg PO; repeat in 6 hr
Magnesium sulfate	Ventricular arrhythmias	7, 32	Dog: a) 50 mg/kg IV bolus over 5 min, followed by 100 μg/kg/min IV as CRI for 6 hr b) 20 mg/kg in 5% D/W over 5 min IV
	Serum magnesium deficit	44	1 mEq/kg/day IV
Mannitol 20% *(Am-Vet Mannitol, Mannject)*	Cerebral edema, acute renal failure, diuresis	1, 23, 37, 48, 128, 135	0.25-1.5 g/kg IV slowly over 10-20 min q 4-6 hr or BID-TID
	Acute glaucoma	100	1-2 g/kg IV over 20-40 min; repeat in 2-4 hr if needed
Marbofloxacin *(Zeniquin)*	Hepatic abscess	37	Dog: 5 mg/kg PO BID
	Bacterial pyoderma	88	2.75-5.5 mg/kg PO SID
Mechlorethamine *(Mustargen)*	Lymphoma, lymphoid leukemia rescue chemotherapy	72	Dog: 3.0 mg/m^2 IV, in a protocol
Meclizine *(Bonine, Antivert)*	Vertigo	108	0.5 mg/kg PO BID
Medetomidine *(Domitor)*	Sedative	1	Dog: 0.001-0.01 mg/kg SC, IM, IV, alone or in combination with other drugs Cat: 0.005-0.03 mg/kg SC, IM, IV, alone or in combination with other drugs
Medium-chain triglycerides (MCT Oil; *Liprocil*)	Exocrine pancreatic insufficiency	36	1-2 mL/kg/day PO, with low-fat diet
Medroxyprogesterone acetate *(Amen, Depo-Provera, Provera)*	Pituitary dwarfism	41	Dog: 2.5-5 mg/kg PO q 3 wk; taper to q 6 wk
	Galactorrhea	60	Dog: 5-11 mg/kg SC, IM; max = 3 doses per yr

Continued

DRUG (BRAND NAME OR ABBREVIATION)	PURPOSE OR USE	CHAPTERS WHERE CITED	DOSAGE
Megestrol acetate *(Ovaban, Megace)*	Lymphoplasmacytic stomatitis, eosinophilic granuloma complex	27	Cat: 0.25 mg/kg PO SID-QOD × 3 doses, then 1-2 times/wk PRN Use with caution
	Galactorrhea, pseudocyesis	60	Dog: 2-2.5 mg/kg PO SID × 5-8 days
	Feline eosinophilic keratitis, conjunctivitis	96, 98	Cat: 0.5 mg/kg PO SID × 7-14 days Use with caution
Meglumine antimonate *(Glucantime)*	Leishmaniasis	89, 90, 116	a) 20-50 mg/kg SC BID b) 200-300 mg/kg IV QOD c) 75 mg/kg SC BID, with allopurinol
Melarsomine HCl *(Immiticide)*	Heartworm disease	12	Dog with class 1 and 2 disease: 2 injections of 2.5 mg/kg IM, 24 hr apart Dog with class 3 disease: 1 injection of 2.5 mg/kg IM; wait 30 days, then give 2 injections of 2.5 mg/kg IM, 24 hr apart (split-dosing regimen) Cat: 2.5 mg/kg IM
Melatonin *(Melatonin)*	Growth hormone deficiency-related alopecia	41	Dog: 3-6 mg PO BID
	Color dilute alopecia, pattern baldness, cyclical flank alopecia, alopecia X	87	Dog: <10 kg: 3 mg PO SID-BID >10 kg: 6 mg PO SID-BID
Meloxicam *(Metacam)*	Pain, inflammation	1, 80-82, 99, 127	Dog: a) 0.2 mg/kg SC, PO, IM, IV once, then 0.1 mg/kg PO SID b) 0.1 mg/kg PO SID × 3-4 days Cat: 0.2-0.3 mg/kg SC, IM, IV once, then 0.1 mg/kg PO q 2-3 days
Melphalan *(Alkeran)*	Essential (primary) thrombocythemia	66	Cat: 0.5 mg PO SID × 4 days, then QOD
	Multiple myeloma	72, 77	0.1 mg/kg PO SID × 10 days, then 0.05 mg/kg PO SID
2-Mercaptopropionyl glycine or Tiopronin *(Thiola)*	Cystine urolithiasis	50	Dog: 15-20 mg/kg PO BID
Methazolamide *(Neptazane)*	Glaucoma	100	Dog: 2-4 mg/kg PO BID-TID Cat: 1-2 mg/kg PO BID
Methimazole *(Tapazole)*	Feline hyperthyroidism	42	Cat: a) 2.5-5 mg PO BID b) 1.25-2.5 mg PO BID if renal insufficiency present c) Transdermal gel form: 2.5-5 mg on ear pinna BID
Methocarbamol *(Robaxin)*	Urine retention disorders, decrease urethral sphincter tone	51	Dog: 15-20 mg/kg PO TID Cat: 33 mg/kg PO TID initially, then 20 mg/kg PO TID
	Muscle relaxation from certain toxicoses	124-126, 128	Dog: 50-220 mg/kg IV slowly to effect; repeat PRN; max = 330 mg/kg/day
Methoprene *(Frontline Plus)*	Inhibit flea growth	85	Apply to the skin once monthly, as directed
Methotrexate *(Trexall, Rheumatrex)*	Chemotherapy for lymphoma, in a protocol	69, 72	Dog: 0.6-0.8 mg/kg IV q 3 wk Cat: 0.5-0.8 mg/kg IV q 4 wk
	SLE, refractory erosive/nonerosive arthritis	80	Dog: 2.5 mg/m^2 PO SID, with prednisone

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DRUG (BRAND NAME OR ABBREVIATION)	PURPOSE OR USE	CHAPTERS WHERE CITED	DOSAGE
Methylene blue *(Methylene blue)*	Severe methemoglobinemia	64	Cat: 0.2 mg/kg IV once slowly
Methylphenidate *(Ritalin)*	Narcolepsy	22	Dog: 0.25 mg/kg PO BID-TID
	CNS stimulant	117	Dog: 2-4 mg/kg PO BID-TID
Methylprednisolone *(Medrol)*	Inflammatory bowel disease	33	Cat: 1 mg/kg PO BID
	Severe canine acne	88	Dog: 0.5 mg/kg PO SID × 7 days, then taper
Methylprednisolone acetate *(Depo-Medrol)*	Feline allergic bronchitis	17	Cat: 10-20 mg IM q 2-8 wk
	Lymphoplasmacytic stomatitis	27	Cat: 2-4 mg/kg IM q 2-6 wk
	Hypoadrenocorticism	45	Cat: 10 mg IM q 3-4 wk
	Tenosynovitis of biceps brachii tendon, mosquito bite hypersensitivity, reactive fibrohistiocytic nodule	82, 88, 89	Dog: 10-40 mg sublesional injection Cat: 20 mg IM q 2-4 wk PRN
	Feline eosinophilic granuloma complex, idiopathic facial dermatitis	91, 93	Cat: 4 mg/kg or 20 mg IM, SC q 2-3 wk, then taper to q 2-3 mo PRN
	Pannus, anterior uveitis	98, 99	Apply 4-8 mg subconjunctivally
Methylprednisolone sodium succinate *(Solu-Medrol)*	Intervertebral disc disease, fibrocartilaginous embolic myelopathy, spinal cord trauma	24	30 mg/kg IV, then 15 mg/kg IV at 2 and 6 hr, then continued QID for max of 48 hr
4-Methyl-pyrazole *See* Fomepizole			
Methyltestosterone *(Estratest)*	Galactorrhea	60	Dog: 1-2 mg/kg PO × 5-7 days; max = 25 mg/kg
Methyltestosterone plus estradiol *(Sesoral)**	Galactorrhea	60	Dog: 0.7 mg/kg PO SID × 5-10 days
Metoclopramide *(Reglan)*	Esophagitis, gastric acid reflux, GI ulceration, delayed gastric emptying	15, 30, 31, 33, 36, 37, 39, 48, 112, 126-128, 131, 135	Dog: a) 0.1-0.4 mg/kg PO, IV, SC, IM TID-QID b) 1-2 mg/kg/day IV as CRI c) 0.01-0.02 mg/kg/hr IV as CRI Cat: a) 0.1-0.2 mg/kg PO, IV, SC, IM TID b) 0.01-0.02 mg/kg/hr IV as CRI
	Increase milk production	60	Dog: 0.2-0.5 mg/kg IM, SC, PO BID-TID
Metoprolol *(Metoprolol)*	Cardiac arrhythmias from Guarana toxicosis	130	0.02-0.06 mg/kg IV slowly
Metronidazole *(Flagyl)*	Bacterial meningoencephalitis, anaerobic bacterial CNS infections	23, 24	Dog: 10-15 mg/kg PO, IV TID Cat: 8-15 mg/kg PO, IV BID
	Stomatitis, gingivitis, glossitis	27, 126	5-15 mg/kg PO BID-TID, then taper to SID
	GI tract bacterial overgrowth, clostridial enterocolitis	33, 36	5-15 mg/kg PO BID
	Giardia lamblia, *Entamoeba histolytica*, *Balantidium coli* infections, trichomoniasis, *Helicobacter* spp.	33, 116	Dog: a) 15-25 mg/kg PO BID × 5-7 days b) 25-50 mg/kg PO SID × 5 days Cat: 10 mg/kg PO BID
	Acute and chronic colitis, pancreatic insufficiency, acute abdominal syndrome, septic peritonitis, perianal fistula, various chronic liver diseases	34-39, 113	10-15 mg/kg PO, IV BID
	Hepatic abscess	37	20-30 mg/kg IV, PO SID
	Osteomyelitis	81	15 mg/kg IV, PO BID

*Not available in the United States.

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DRUG (BRAND NAME OR ABBREVIATION)	PURPOSE OR USE	CHAPTERS WHERE CITED	DOSAGE
Mexiletine *(Mexitil)*	Ventricular tachycardia	6	Dog: 4-8 mg/kg PO TID, with other drugs
Mibolerone *(Cheque Drops)*	Galactorrhea	60	Dog: 16 µg/kg PO SID × 5 days
Miconazole 1% shampoo/ conditioner *(Miconazole, Resizole)*	*Malassezia* spp. dermatitis	85	Apply topically 1-2 times/wk
Midazolam *(Versed)*	Preanesthetic, sedation, analgesia	1, 32	Dog: 0.1-0.5 mg/kg SC, IM, IV, alone or with other drugs
	Status epilepticus, cluster seizures	22	Dog: a) 0.07-0.22 mg/kg IV, IM, intranasally, rectally b) 0.5-2 mg/kg/hr IV as CRI × 4-6 hr; increase in 0.5 mg/kg/hr increments
Milbemycin oxime *(Interceptor)*	Elimination of heartworm microfilariae, chemoprophylaxis of roundworm, hookworm, whipworm, heartworm infections	12, 34	500 µg/kg PO monthly
	Pneumonyssoides caninum infection	14	0.5-1 mg/kg PO once weekly × 3 wk
	Sarcoptic mange	85, 95	2 mg/kg PO q 7-14 days × 3 Rx
	Canine demodicosis	86	Dog: 1-2 mg/kg PO SID × 60 days; may double dosage if needed
Milk thistle *(Silymarin)*	Antioxidant, liver protectant, hepatic necrosis/failure, amanita mushroom poisoning	37, 124	20-50 mg/kg PO SID
Minocycline *(Dynacin)*	Actinomycosis, nocardiosis	89	Dog: 5-25 mg/kg PO, IV BID
	Brucellosis, ehrlichiosis	113, 115	Dog: 12.5 mg/kg PO BID
	Q Fever	115	5 mg/kg PO SID
Misoprostol *(Arthrotec)*	Hemorrhagic gastroenteritis, GI protectant	31, 39, 124, 127	Dog: 1-5 µg/kg PO BID-QID Do not use in pregnant animals; should not be handled by pregnant women
Mitotane *(Lysodren)*	Pituitary-dependent hyperadrenocorticism	45	Dog: a) Normal induction protocol: 25-50 mg/kg/day PO × 5-10 days b) Slow induction protocol: 25 mg/kg PO weekly × 1 mo c) Maintenance dose: 50 mg/kg/wk PO dd into 2 doses, 3-4 days apart
	Functional adrenocortical tumors	72	Dog: a) Induction protocol: 25 mg/kg PO BID b) Maintenance protocol: 50 mg/kg PO per wk, dd into 2-3 doses
Mitoxantrone *(Novantrone)*	Chemotherapy, in a protocol	72	Dog: 5.5-6 mg/m^2 IV q 3 wk Cat: 5-6.5 mg/m^2 IV q 3 wk
Montelukast sodium *(Singular)*	Pulmonary effects of chronic heartworm disease	12	Cat: 5 mg PO SID
Morphine *(Infumorph, Astramorph)*	Analgesia	1, 39, 81, 107, 134, 136	Dog: a) 0.1-1.0 mg/kg SC, IM, IV q 3-6 hr b) 0.002 mg/kg/min IV as CRI c) 1.5 mg/kg/24 hr as CRI in 0.9 % saline

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DRUG (BRAND NAME OR ABBREVIATION)	PURPOSE OR USE	CHAPTERS WHERE CITED	DOSAGE
Morphine *(Infumorph, Astramorph)—cont'd*			Cat: a) 0.05-0.5 mg/kg SC, IM b) 0.002 mg/kg/min IV as CRI
	Local, regional blockade anesthesia (epidural)	1, 81	Dog: 0.1-0.05 mg/kg, with bupivacaine Cat: a) 0.07 mg/kg (pelvic limb fracture) b) 0.1 mg/kg, with 0.9% saline (thoracic limb fracture)
Morphine, oral sustained-release *(MS-Contin)*	Narcotic analgesic	72	Dog: 1.5-3 mg/kg PO BID
Moxidectin *(ProHeart-6);* currently unavailable	Heartworm chemoprophylaxis	12	Dog: 0.17 mg/kg SC q 6 mo
Mupirocin *(Bactroban)*	Staphylococcal pyoderma and folliculitis, impetigo, intertrigo, canine acne, mucocutaneous pyoderma	88, 91	Dog: Apply topically SID-BID × 1-4 wk or until lesions resolve
Mycophenolate mofetil *(Cellcept)*	Acquired myasthenia gravis	25	Dog: 20 mg/kg PO BID
Naloxone *(Narcan)*	Cardiopulmonary arrest	7	0.04 mg/kg IT
	Reverse CNS effects of apomorphine	123	Dog: 0.04 mg/kg IV, IM, SC Cat: 0.05-0.1 mg/kg IV
	Antidote for opioid drug toxicosis	129	0.1-0.2 mg/kg IV; repeat PRN
Nandrolone decanoate *(Deca-Durabolin)*	Bone marrow stimulant, chronic idiopathic myelofibrosis	66	Dog: 2 mg/kg IM weekly × 3 wk, then q 3 wk; max = 200 mg/wk Cat: 15 mg IM once weekly
	Appetite stimulant	122	Dog: 5 mg/kg IM weekly; max = 200 mg/wk
Naphazoline 0.027%/ pheniramine 0.315% *(Opcon-A)*	Allergic conjunctivitis	96	Apply soln to affected eye BID-QID
Neomycin *(Neomycin, Neo-fradin)*	Congenital portosystemic shunts, hepatic encephalopathy	37	20 mg/kg PO BID-TID × 10-14 days
Neomycin-polymyxin B-dexamethasone (ophthalmic)	Blepharitis, conjunctivitis	95, 96, 103	Apply to affected eye TID-QID
Neostigmine *(Prostigmin)*	Acquired myasthenia gravis	25	Dog: 0.04 mg/kg IM QID
Niacin	Hyperlipidemia	46	Dog: 100 mg/day PO
Niacinamide *(Nicotinamide)*	Immune-mediated diseases, episcleritis	90, 98	Dog: <10 kg: 250 mg PO TID, with tetracycline >10 kg: 500 mg PO TID, with tetracycline
	Sebaceous adenitis	93	Dog <10 kg: a) 250 mg PO TID, with tetracycline b) 250 mg PO in morning, then 500 mg PO in evening, with tetracycline Dog >10 kg: a) 500 mg PO TID, with tetracycline b) 500 mg PO in morning, then 1000 mg PO in evening, with tetracycline
Nitenpyran *(Capstar)*	Flea adulticide		Dog or cat 1-11.4 kg: 11.4 mg Dog 11.5-57 kg: 57.0 mg

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DRUG (BRAND NAME OR ABBREVIATION)	PURPOSE OR USE	CHAPTERS WHERE CITED	DOSAGE
Nitrofurantoin *(Macrodantin, Furadantin)*	Resistant bacterial cystitis, UTI prevention	50	4.4 mg/kg PO TID
Nitrofurazone *(Furacin)*	Enteric coccidiosis	116	8-20 mg/kg PO SID-BID × 5 days; decrease dose by 50% when used with sulfonamides
Nitroglycerin 2% ointment *(Nitro-Bid)*	Vasodilator for acute congestive heart failure	9, 10	Dog: a) 1/8-1/2 inch topically QID on ear pinna or inguinal area b) 4-12 mg topically on ear pinna BID-TID Cat: 1/8-1/4 inch topically q 4-6 hr
Nitroprusside *(Sodium Nitroprusside, Nitropress)*	Arterial vasodilator for acute heart failure	8-10	Dog: 0.5-5 µg/kg/min IV as CRI, titrate to effect; max = 10 µg/kg/min IV
Nizatidine (Axid)	Megacolon	34, 73	Cat: a) 2-5 mg/kg PO SID b) 1-3 mg/kg SC, IM, IV TID
	Gastric ulcers	31	Dog: 5 mg/kg PO SID
Norepinephrine bitartrate *(Levophed)*	Vasopressor for hypotension	7, 136	Dog: 0.01-0.5 µg/kg/min IV as CRI
Olopatadine 0.1% *(Patanol)*	Allergic conjunctivitis	96	Apply soln to affected eye BID-TID
Olsalazine *(Dipentum)*	Chronic idiopathic colitis	34	Dog: 5-10 mg/kg PO BID × 3-4 wk, then taper to lowest effective dose Use with caution in cats
Omega-6, Omega-3 fatty acid supplements (*Heska F.A.* granules, *Derma-Form*)	Atopic dermatitis	85	1 capsule per 10 kg PO SID
	Immune-mediated diseases, symmetrical lupoid onychodystrophy	90	Give at twice the manufacturer's dosage instructions × 3-4 mo
Omeprazole *(Prilosec)*	Severe reflux esophagitis, GI ulceration	30, 31, 33, 39, 48, 73, 127, 135	Dog: 0.5-2 mg/kg PO, SC SID-BID; max = 20 mg/day Cat: 0.7 mg/kg PO SID
Ondansetron *(Zofran)*	Antiemetic	31, 33, 36, 37, 39, 48, 127	Dog: a) 0.5-1 mg/kg PO, IV slowly SID-BID or 30 min before chemotherapy b) 0.1-1 mg/kg PO, IM, SC BID-TID c) 0.1-0.3 mg/kg PO, IV slowly TID-QID
Orbifloxacin *(Orbax)*	Bacterial pyoderma	88	2.5-7.5 mg/kg PO SID
Ormetoprim-sulfadimethoxine *(Primor)*	Protozoal CNS diseases	24	Dog: 15 mg/kg PO BID
	Canine bacterial pyoderma	88	Dog: 55 mg/kg PO on day 1, then 22 mg/kg PO SID
	Enteric coccidiosis	116	Dog: 66 mg/kg PO SID
Oseltamivir phosphate *(Tamiflu)*	Parvoviral enteritis	112	Dog: 2 mg/kg PO BID × 5 days
Oxacillin (oxacillin sodium)	Perioperative antibiotic	81	22 mg/kg IV q 2 hr
	Canine bacterial pyoderma	88	Dog: 22 mg/kg PO TID
Oxazepam *(Serax)*	Appetite stimulant	48, 111, 122	Dog: 0.2-1 mg/kg PO SID-BID Cat: 2-3 mg PO SID-BID
	Certain behavioral disorders	117	Dog: 0.04-0.5 mg/kg PO QID Cat: 0.2-1 mg/kg PO BID
Oxibendazole *(Anthelcide EQ)*	*Trichuris vulpis* infection	34	Dog: 6 mg/kg PO SID

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DRUG (BRAND NAME OR ABBREVIATION)	PURPOSE OR USE	CHAPTERS WHERE CITED	DOSAGE
Oxybutynin chloride *(Ditropan)*	Urinary incontinence, decrease detrusor muscle contraction	51	Dog: 1.25-5 mg PO BID-TID Cat: 0.5 mg PO BID
Oxyglobin, purified bovine hemoglobin *(Oxyglobin)*	Red blood cell substitute	71	Dog: 10-30 mL/kg IV at max rate of 10 mL/kg/hr IV
Oxymorphone *(Numorphan)*	Analgesia, sedation	1, 15, 36, 81	Dog: 0.025-0.2 mg/kg SC, IM, IV q 4-6 hr Cat: 0.025-0.05 mg/kg SC, IM q 4-6 hr
	Anesthesia induction	61	Dog: 0.1-1 mg/kg IV to effect
Oxytetracycline *(Medamycin, Biomycin)*	Ehrlichiosis, hemoplasmosis	115	Dog: 20-25 mg/kg PO, IV TID × 21-28 days Cat: 22 mg/kg PO TID × 21 days
	Salmon poisoning disease	115	Dog: 7 mg/kg PO, IV TID × 3-5 days
Oxytetracycline-polymyxin o.o. *(Terramycin)*	Neonatal ophthalmia, conjunctivitis *Cytauxzoon felis*, *Mycoplasma* spp.–associated conjunctivitis	95, 96 114	Apply to affected eye TID-QID Cat: Apply to affected eye TID
Oxytocin *(Pitocin, Syntocinon)*	Uterine prolapse	57	Dog: 5-10 U SC once
	Stimulate milk letdown	60	Dog: 2-20 IU SC, IM Cat: 1-10 IU SC, IM
	Dystocia from uterine inertia; not to be used unless cervix is open	61, 62	Dog: 2-5 IU SC, IM; may repeat in 20-30 min, up to 3 doses Cat: 1-3 IU SC, IM; may repeat in 20-30 min
	Metritis, evacuate uterine contents	61	Dog: 1 IU/kg IM
Pamidronate *(Aredia)*	Hypercalcemia, cholecalciferol toxicosis, calcipotriene toxicosis	43, 124, 127	Dog: 1-2 mg/kg in 0.9% NaCl IV over 2-4 hr; repeat in 5-7 days
Pancreatic enzymes, powdered *(Viokase-V, Pancrezyme)*	Exocrine pancreatic insufficiency	36	Dog: 2 tsp/20 kg initially with each meal BID, then taper slowly Cat: 0.5 tsp/5 kg initially with food, then taper slowly
Pantoprazole *(Protonix)*	GI tract ulceration	15, 39, 135	Dog: 0.7-1 mg/kg IV, PO SID-BID
Paromomycin *(Humatin)*	Cryptosporidiosis	33, 116	125-165 mg/kg PO SID-BID × 5 days Use with extreme caution
Paroxetine *(Paxil)*	Certain behavioral disorders	117	Dog: 1-1.5 mg/kg PO SID Cat: 0.5-1.5 mg/kg PO SID
D-Penicillamine *(Cuprimine)*	Copper hepatopathy, canine chronic hepatitis/cirrhosis	37	Dog: 10-15 mg/kg PO BID
	Lead poisoning	126	Dog: 30-50 mg/kg/day PO dd QID × 7 days; wait 7 days, then repeat Cat: 125 mg PO BID × 5 days
Penicillin G (Penicillin G potassium = IV; Crysticillin procaine = SC, IM)	Infectious meningomyelitis, bacterial infections	24	10-30 mg/kg IV, IM BID-QID
	Leptospirosis	48, 113	Dog: 25,000-40,000 U/kg IM, SC, IV BID × 2 wk
	Actinomycosis	89, 113	a) 60,000 U/kg SC, IM, IV TID b) 40 mg/kg PO TID
	Tetanus	113	a) 20,000 U/kg IV QID × 10 days b) 20,000-100,000 U/kg IV, SC, IM BID-TID × 10 days
Penicillin V *(Veetids)*	Actinomycosis	89, 113	a) 60,000 U/kg PO TID b) 40 mg/kg PO TID
Pentamidine (Phenamidine) isethionate*	*Babesia canis* infection	116	Dog: 15-20 mg/kg SC SID × 2 days

*Not available in the United States.

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DRUG (BRAND NAME OR ABBREVIATION)	PURPOSE OR USE	CHAPTERS WHERE CITED	DOSAGE
Pentobarbital (sodium pentobarbital)	Status epilepticus, cluster seizures	22	2-15 mg/kg IV over several min, then 0.5 mg/kg/hr IV as CRI × 4-6 hr
Pentosan polysulfate sodium *(Elmiron, Cartrophen-Vet)*	Chronic feline idiopathic cystitis	50	Cat: 50 mg PO BID on food
Pentoxifylline *(Trental)*	Dermatomyositis	82	Dog: 25 mg/kg PO BID
	Contact dermatitis	85	Dog: 15-20 mg/kg PO TID
	Vasculitis, ischemic dermatopathy, vesicular cutaneous lupus erythematosus, pinnal seborrhea	86, 90, 91, 93	Dog: 10-20 mg/kg PO BID-TID
Permethrin 2% *(Long-Acting Knock Out)*	Flea adulticide, repellant	85	Dog: Apply 1-2 times/wk to dry hair coat
Phenobarbital (*Luminol Sodium, Phenobarbital* injection; *Solfoton* tablets)	Seizures, tremors	22, 23, 112, 126-128, 130	1-6 mg/kg PO, IV, IM BID-TID Dog: 3-30 mg/kg IV slowly to effect Cat: 2.5 mg/kg PO SID
	Status epilepticus, cluster seizures	22	Loading dose: 12-15 mg/kg IV dd into 2-4 mg/kg doses q 1-2 hr × 24 hr Emergency Rx: 2 mg/kg PO, IV, IM BID, with diazepam or midazolam
	Necrotizing sialometaplasia, sialadenosis	29	Dog: 2 mg/kg PO BID
Phenoxybenzamine *(Dibenzyline)*	Hypertension from pheochromocytoma	45	Dog: 0.2-1.5 mg/kg PO BID
	Urine retention disorders, urethral spasms, to decrease urethral sphincter tone	51, 52	Dog: a) 0.5 mg/kg PO BID b) 2.5-30 mg PO TID c) 2.5-7.5 mg PO SID-BID, with prazosin Cat: 1.25-5 mg PO SID-BID
Phenylephrine injectable *(Neo-Synephrine)*	Vasopressor	7	Dog: 1-10 µg/kg/min IV
Phenylephrine topical 1.25% *(Neo-Synephrine)* or ophthalmic 2.5%-10% *(Ak-Dilate)*	Rhinitis/sinusitis	14	Apply as nose drops BID-TID
	Anterior uveitis, hyphema	99	Apply to affected eye 2-6 times/day, with atropine
Phenylpropanolamine *(Proin)*	Urinary incontinence, increase urethral sphincter tone	49, 51, 116	Dog: a) 12.5-50 mg PO TID b) 1 mg/kg PO TID Cat: 12.5 mg PO TID
Physostigmine 0.25% o.o. *(Eserine)*	Dysautonomia	105	Apply to affected eye BID-TID
Phytomenadione, Phytonadione *See* Vitamin K_1			
Pilocarpine ophthalmic *(Piloptic)*	Neurogenic KCS	97	1%-2% soln: 1-4 drops on food PO BID-TID
	Glaucoma	100	2% soln: Apply 1 drop to affected eye TID-QID
	Dysautonomia	105	0.1%-1% soln: Apply 1 drop to both eyes BID-TID
Pimobendan	Dilated cardiomyopathy, congestive heart failure	9, 10	Dog: 0.25-0.5 mg/kg PO BID Cat: 0.3 mg/kg PO BID
Piroxicam *(Feldene)*	Transitional cell carcinoma, pain, inflammation	50, 52, 53, 72, 97, 127	Dog: 0.3 mg/kg PO SID-QOD
Plasma, fresh frozen	Protein-losing enteropathy, hypoproteinemia	33, 134, 135	Dog: 10-20 mL/kg IV
	Platelet disorders, von Willebrand disease, clotting factor deficiencies, thrombosis	37, 67, 68	6-15 mL/kg IV over 0.5-2 hr or BID; repeat q 8-12 hr PRN

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DRUG (BRAND NAME OR ABBREVIATION)	PURPOSE OR USE	CHAPTERS WHERE CITED	DOSAGE
Polymyxin-neomycin cream *(Neosporin)*	Mucocutaneous pyoderma	91	Dog: Apply topically BID × 2-4 wk
Polysulfated glycosaminoglycan *(Adequan)*	Chronic feline idiopathic cystitis	50	Cat: 1.1-4.8 mg/kg IM q 4 days × 6 doses
	DJD		Dog: 5 mg/kg IM once weekly × 6-8 wk
Potassium bromide (compounding pharmacies)	Seizures	22, 23	Dog: Loading dose: total = 400-600 mg/kg PO or rectally, dd into 6 doses given over 1-5 days Maintenance dose: 20-40 mg/kg PO SID, slowly increased to effect; max = 60 mg/kg PO SID Use with caution in cats
Potassium chloride injectable (KCl)	Severe electrolyte loss, hypokalemia	33, 37, 44, 46	Dog: 10-40 mEq/L of crystalloid soln; not to exceed 0.5 mEq/kg/hr IV
	Feline hypokalemic polymyopathy	82	Cat: 0.4 mEq/kg/hr IV in lactated Ringer's soln; reduce dose when serum potassium is >3.5 mEq/L
Potassium citrate *(Nutrived, Citrolith)*	Hypokalemia, metabolic acidosis	48	Cat: 40-75 mg/kg PO BID
	Urine alkalization	50	Dog: 50-75 mg/kg PO BID
Potassium gluconate *(Tumil-K)*	Hypokalemia	48	Cat: 0.45 mEq/kg/day PO
	Feline hypokalemic polymyopathy	82	Cat: 5-8 mEq PO dd BID if serum potassium is <3 mEq/L Maintenance dose: 2-6 mEq PO SID-BID
Potassium iodide (*Thyroblock;* SSKI soln)	Stabilization before feline hyperthyroidism surgery	42	Cat: 30-100 mg PO SID or dd BID, with β-adrenergic blocking agent 10-14 days before surgery
	Sporotrichosis	89	Dog: 40 mg/kg PO TID Cat: 20 mg/kg PO BID
Potassium phosphate (Potassium phosphate injection)	Hypophosphatemia	44, 64	0.01-0.03 mmol/kg/hr IV; max = 0.06 mmol/kg/hr
Povidone iodine (Betadine soln)	Congenital portosystemic shunts, hepatic encephalopathy	37	Emergency Rx: 1:10 dilution with water, give as enema at 20 mL/kg QID
Pralidoxime, 2-PAM chloride *(Protopam)*	Organophosphorus and carbamate toxicoses	125	10-15 mg/kg IM, SC BID
Praziquantel *(Droncit, Drontal Plus)*	Ascarids, whipworms, tapeworms (*Dipylidium* spp., *Taenia* spp.)	33, 116	Dog: 5-7.5 mg/kg PO once Cat: 5 mg/kg PO once
	Giardia lamblia	33	Dog: Use at labeled dose PO × 3-5 days Cat: Give 2 small dog tabs PO SID × 5 days
	Pancreatic, biliary duct flukes	36, 37	Cat: 20-40 mg/kg PO SID × 3 days
	Salmon poisoning disease	115	Dog: 10-30 mg/kg PO, SC once
Prazosin *(Minipress)*	Urine retention disorders, urethral spasm, to decrease urethral sphincter tone	51, 52	Dog: a) 1 mg/15 kg PO BID-TID b) 0.25 mg PO SID-BID, with phenoxybenzamine Cat: 0.25-0.5 mg PO SID-BID
Prednisolone, prednisone *(Deltasone)*	Pulmonary parenchymal inflammation from heartworm disease	12	1-2 mg/kg PO BID, then taper over 7-14 days
	Laryngitis, laryngeal edema, tracheitis, acute/allergic bronchitis, airway inflammation	15, 16	Dog: 0.5-2 mg/kg PO SID-BID, then taper Cat: 0.5-1 mg/kg PO BID, then taper

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DRUG (BRAND NAME OR ABBREVIATION)	PURPOSE OR USE	CHAPTERS WHERE CITED	DOSAGE
Prednisolone, prednisone *(Deltasone)—cont'd*	Pulmonary eosinophilic diseases	18	1-2 mg/kg PO BID
	Hydrocephalus, hydranencephaly, porencephaly	23	0.25-0.5 mg/kg PO BID, then taper to QOD
	FIP, meningoencephalitis, for palliative relief	23	Cat: 2-4 mg/kg PO SID-BID
	Granulomatous meningoencephalomyelitis, necrotizing meningoencephalitis and leukoencephalitis, eosinophilic meningoencephalitis, canine meningeal polyarteritis	23, 24	Dog: 1-4 mg/kg PO BID × 1 mo, then slowly taper over 3-6 mo to 0.5 mg/kg PO SID-QOD
	Idiopathic tremor syndrome	23	Dog: 1-2 mg/kg PO SID × 4 wk, then taper to 0.5-1 mg/kg PO q 24-72 hr
	Caudal occipital malformation, syringohydromyelia, spinal intraarachnoid cysts, intervertebral disk disease, cervical spondylomyelopathy, spinal stenosis, distemper myelitis, demyelinating neuropathy	23-25	Dog: 0.5-1 mg/kg PO, IV SID-QOD, then taper
	Acquired myasthenia gravis	25	Dog: 0.5 mg/kg PO SID-BID initially, then 2-4 mg/kg PO SID-BID × 7-10 days
	Lymphoplasmacytic stomatitis	27	Cat: 2 mg/kg PO SID-BID, then taper
	Sialadenitis, necrotizing sialometaplasia	29	Dog: 0.5-2.2 mg/kg PO SID-BID
	Chronic idiopathic gastritis, atrophic gastritis, hypertrophic gastritis	31	Dog: 1-2 mg/kg PO SID, then slowly taper Cat: 2-4 mg/kg PO SID, then slowly taper Dog/cat: Chronic low dose: 0.5-1 mg/kg PO QOD
	Small cell GI lymphoma	31, 34	Cat: 5 mg PO BID, with chlorambucil
	Inflammatory bowel disease	33	Dog: 1-2 mg/kg PO BID, then taper Cat: 2-3 mg/kg PO BID, then taper
	Chronic lymphocytic-plasmacytic colitis, eosinophilic and granulomatous colitis, chronic histiocytic ulcerative colitis	34	Dog: 2-4 mg/kg PO SID or dd BID, then slowly taper
	Perianal fistula	35	Dog: 3-4 mg/kg PO SID, then slowly taper to 1 mg/kg SID-QOD
	Exocrine pancreatic insufficiency, canine chronic hepatitis/cirrhosis	36, 37	Dog: 1-2 mg/kg PO SID, then taper
	Feline chronic cholangiohepatitis	37	Cat: 2-4 mg/kg PO SID, then slowly taper
	Hypoadrenocorticism, hypopituitarism, postadrenalectomy	41, 45	Dog: a) 0.1-0.2 mg/kg, with DOCP b) 0.2-0.4 mg/kg PO SID-QOD, with fludrocortisone
	Hyperparathyroidism, hypercalcemia	43, 73, 124, 127	a) 1-3 mg/kg PO SID-BID b) 0.25 mg/kg PO, SC QID
	Insulinoma, hypoglycemia	46, 73	0.5-2 mg/kg/day PO
	Granulomatous urethritis	52	Dog: 1.1 mg/kg PO BID, then taper to 0.07 mg/kg PO BID
	Immune-mediated hemolytic anemia	64	1-2 mg/kg PO BID, then taper

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DRUG (BRAND NAME OR ABBREVIATION)	PURPOSE OR USE	CHAPTERS WHERE CITED	DOSAGE
Prednisolone, prednisone *(Deltasone)—cont'd*	Chronic lymphocytic leukemia	65	Dog: 30 mg/m^2 PO SID × 7 days, then 20 mg/m^2 SID, then 10 mg/m^2 QOD, with chlorambucil Cat: 1 mg/kg PO SID, with chlorambucil
	Myelodysplastic syndrome, chronic idiopathic myelofibrosis	66	Dog: 2-3 mg/kg PO SID, then taper to QOD Cat: 1-4 mg/kg PO, IM SID, in a protocol
	Eosinophilic leukemia	66	Cat: 2 mg/kg PO BID, with hydroxyurea
	Immune-mediated thrombocytopenia	67	Dog: 1-3 mg/kg PO BID, then taper
	Lymphoma	69, 72	Dog: a) 2 mg/kg/day PO alone b) 40 mg/m^2 PO SID, in a protocol c) 20 mg/m^2 PO SID × 1 wk, then QOD × 7 wk, in a protocol d) 20 mg/m^2 PO BID for 6 wk, in a protocol e) 1-2 mg/kg PO SID × 1-3 wk, then 0.5 mg/kg QOD × 1 wk; in a protocol Cat: a) 2 mg/kg PO SID, in a protocol b) 50 mg/m^2 PO SID × 1 yr, in a protocol c) 1-2 mg/kg PO SID × 1-3 wk, then 1 mg/kg QOD; in a protocol
	Mast cell tumors	72, 73	1-2 mg/kg PO SID-BID × 30 days, then QOD, in a protocol
	Primary seborrhea, angioneurotic edema, urticaria	73, 76, 93	1-2 mg/kg PO SID-BID, then taper
	Cutaneous histiocytosis	77	Dog: 1-2 mg/kg PO BID until remission, then taper
	Multiple myeloma, in a protocol	77	0.5 mg/kg PO SID × 10 days, then 0.5 mg/kg PO QOD
	Nonerosive and erosive arthritis, SLE	76, 80	1-2 mg/kg PO BID, then taper slowly to 1 mg/kg PO QOD
	Hypertrophic osteopathy	81	Dog: 0.25-0.5 mg/kg PO SID
	Masticatory myositis, polymyositis, dermatomyositis, extraocular myositis	82, 103	Dog: 1-2 mg/kg PO SID-BID, then taper over 2-6 mo
	Flea allergic, atopic, and contact dermatitides; mosquito bite hypersensitivity	85, 88	Dog: 1 mg/kg PO SID × 5 days, then 0.5 mg/kg PO QOD Cat: 2-5 mg/kg PO SID × 5 days
	Severe canine acne, enhance zinc absorption	88, 93	Dog: 0.5 mg/kg PO SID
	Juvenile cellulitis, sterile eosinophilic pustulosis, sterile granuloma, pyogranuloma	88, 89	Dog: 1-2 mg/kg PO SID-BID
	Immune-mediated skin diseases, nodular panniculitis, uveodermatologic syndrome, blepharitis	89-92, 95, 99	Dog: 2-4 mg/kg PO SID-BID, then taper
	Feline plasma cell pododermatitis, eosinophilic granuloma complex	90, 91	Cat: 4.4 mg/kg PO SID-BID, then taper
	Idiopathic facial dermatitis	93	Cat: 1-3 mg/kg PO SID × 4 wk; then 1-3 mg/kg PO QOD

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DRUG (BRAND NAME OR ABBREVIATION)	PURPOSE OR USE	CHAPTERS WHERE CITED	DOSAGE
Prednisolone, prednisone *(Deltasone)—cont'd*	Jack Russell terrier vasculopathy	93	Dog: 1 mg/kg PO SID, alone or with dapsone and vitamin E
	Ligneous conjunctivitis, episcleritis	96, 98	0.5-2 mg/kg PO SID-BID, then taper
	Feline eosinophilic keratitis	98	Cat: 5-10 mg PO SID or dd BID × 7-14 days
	Anterior uveitis, chorioretinitis, optic neuritis, retinal detachments	99, 102	Antiinflammatory dose: 0.25-0.5 mg/kg PO BID Immunosuppressive dose: 1-2 mg/kg PO SID-BID
	Otitis externa, media	107, 108	Dog: 0.25-2.2 mg/kg PO SID-BID, then taper over 1-3 wk
	FIP	112	Cat: 2-4 mg/kg PO BID
	Appetite stimulant	122	0.2-0.5 mg/kg PO SID-QOD
	Envenomation with severe swelling	136	0.5-1 mg/kg PO SID, tapered over 5-7 days
Prednisolone acetate 1% *(Econopred-Plus, Pred Forte)*	Conjunctivitis	96, 103	Apply soln to affected eye BID-QID
	Anterior uveitis, hyphema, pannus, episcleritis, eosinophilic keratitis	98, 99	Apply soln to affected eye 1-8 times/day, taper slowly
Prednisolone sodium succinate *(Solu-Delta-Cortef)*	Feline allergic bronchitis	17	Cat: 10-20 mg/kg IV
	Hypoadrenocorticism, glucocorticoid replacement	45	15-20 mg/kg IV
	Shock, anaphylaxis	45, 76, 136	5-25 mg/kg IV
	Envenomation with severe swelling	136	0.5-1 mg/kg IV once
Prednisolone-Trimeprazine *(Temaril-P)*	Allergic dermatitis	85	Capsules/Tablets = 2 mg prednisone and 5 mg trimeprazine Dog: a) <5 kg: 1 capsule PO SID × 4 days or ½ tab PO BID × 4 days, then reduce dose by 50% b) ≥5-10 kg: 2 capsules PO SID × 4 days or 1 tab PO BID × 4 days, then reduce dose by 50% c) ≥10-20 kg: 4 capsules PO SID × 4 days or 2 tabs PO BID × 4 days, then reduce dose by 50% d) ≥20 kg: 6 capsules PO SID × 4 days or 3 tabs PO BID × 4 days, then reduce dose by 50%
Primaquine phosphate *(Primaquine)*	*Babesia felis* infection	116	Cat: a) 0.5 mg/kg PO SID × 3 days b) 1 mg IM q 36 hr × 2-3 doses Caution: 1 mg/kg = lethal to cats
Proanthozone nutrient and antioxidant supplement	Antioxidant	64	Cat: 10 mg/day PO
Procainamide *(Procan)*	Acute ventricular arrhythmias and/or tachycardia	6, 32	Dog: a) 10-20 mg/kg PO TID-QID b) 6-15 mg/kg IV bolus over 2-5 min c) 25-50 µg/kg/min IV as CRI in 5% D/W d) 8-20 mg/kg IM QID Cat: a) 2-5 mg/kg PO BID-TID b) 1-2 mg/kg IV bolus slowly c) 10-20 µg/kg/min IV as CRI in 5% D/W

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DRUG (BRAND NAME OR ABBREVIATION)	PURPOSE OR USE	CHAPTERS WHERE CITED	DOSAGE
Procarbazine *(Matulane)*	Chemotherapy, in a protocol	72	Dog: 50 mg/m^2 PO SID × 14 days q 4 wk
Prochlorperazine *(Compazine)*	Antiemetic	31, 33, 39, 112	Dog: 0.1-0.5 mg/kg IM, SC BID-QID Cat: 0.125 mg/kg IM BID
Progesterone in oil	Hypoluteoidism	61	Dog: 2 mg/kg IM q 3 days
Proligestone *(Delvosteron)**	Pituitary dwarfism	41	Dog: 10 mg/kg SC q 3 wk
	Galactorrhea	60	Dog: 20-30 mg/kg SC
Propantheline bromide *(Pro-Banthine)*	Sinus bradycardia	6	0.25-0.5 mg/kg PO BID
	Urinary incontinence, decrease detrusor muscle contraction	51	Dog: a) 0.2 mg/kg PO TID-QID b) 5-30 mg PO TID
Propofol *(PropoFlo, Rapinovet)*	Anesthesia induction	1	3-6 mg/kg IV to effect
	Status epilepticus, seizures, tremors	22, 127	a) 4-8 mg/kg IV to effect b) 0.1-0.6 mg/kg/min IV as CRI × 4-6 hr
Propranolol *(Inderal)*	Tetralogy of Fallot, pulmonic stenosis	8	Dog: 0.25 mg/kg PO TID initially, then increase over 4 wk to 1 mg/kg PO TID
	Refractory idiopathic tremor syndrome	23	Dog: 1 mg/kg PO TID
	Tachycardia, severe hypertension from pheochromocytoma	45	Dog: 0.15 mg/kg PO TID, with phenoxybenzamine
	Tachycardia, especially from certain toxicoses; serotonin antagonism	48, 126, 129, 130	Dog: a) 0.02-0.06 mg/kg IV slowly b) 5-80 mg PO BID-TID Cat: 2.5-10 mg PO BID-TID
	Urine retention disorders, enhance detrusor muscle contraction	51	Dog: 2.5-20 mg PO BID-TID Cat: 2.5-5 mg PO BID-TID
Prostaglandin $F_{2\alpha}$ *(Lutalyse)*	Open-cervix pyometra/metritis, evacuate uterine contents	57, 61, 62	Dog: 0.1-0.25 mg/kg SC SID × 5-7 days Cat: 0.1 mg/kg SC SID Limit use to healthy animals ≤6-8 yr of age
	Cystic endometrial hyperplasia	62	Cat: 0.1-0.25 mg/kg SC SID-TID
Protamine sulfate *(Protamine sulfate)*	Antagonize heparin overdose	18	1 mg IV slowly per 100 U of heparin to be inactivated; reduce dose by 50% q 30 min
Protriptyline *(Vivactil)*	Cataplexy	22	Dog: 5-10 mg/kg PO SID
Pseudoephedrine *(Sudafed)*	Rhinitis/sinusitis	14	Dog: 15-50 mg PO BID-TID; max = 4 mg/kg Cat: 2-4 mg/kg PO BID-TID
	Retrograde ejaculation	61	Dog: 4-5 mg/kg PO, 1 and 3 hr before breeding
Psyllium *(Metamucil)*	Chronic histiocytic ulcerative colitis, fiber-responsive colitis, irritable bowel syndrome	34	Dog: 0.5-3 tbsp/day PO
	Bulk cathartic	123	Dog: 3-10 g PO SID-BID mixed with food Cat: 3 g PO SID-BID mixed with food
Pyrantel pamoate *(Nemex, Strongid-T)*	Parasitic gastritis: *Physaloptera* spp.	31	5 mg/kg PO q 3 wk × 2 Rx
	Ascarids, hookworms	33	Dog: 5 mg/kg PO; repeat in 3 wk Cat: 10 mg/kg PO; repeat in 3 wk
Pyrethrin otic soln	Otodectic mange	85	Apply in each ear SID × 7 days; repeat in 7 days
Pyrethrin spray	Mosquito bite hypersensitivity, mosquito repellant	88	Cat: Apply spray topically SID to affected areas
Pyridostigmine bromide *(Mestinon)*	Acquired myasthenia gravis	25	Dog: 0.5-3 mg/kg PO BID-TID; begin with low dose, then increase PRN

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DRUG (BRAND NAME OR ABBREVIATION)	PURPOSE OR USE	CHAPTERS WHERE CITED	DOSAGE
Pyrimethamine *(Daraprim)*	*Toxoplasma gondii,* protozoal CNS diseases and myositis, *Hepatozoon americanum*	23, 24, 82, 116	Dog: 0.25-0.5 mg/kg PO SID, with sulfonamides Cat: 0.25-0.5 mg/kg PO SID, with trimethoprim-sulfadiazine
	Protozoal polyradiculoneuritis, chorioretinitis, *Neospora caninum*	25, 102, 116	Dog: 1 mg/kg PO SID, with sulfonamides
Ramipril *(Altace)*	Chronic congestive heart failure	9, 10	Dog: 0.25-0.5 mg/kg PO SID Cat: 0.5 mg/kg PO SID
Ranitidine *(Zantac)*	Esophagitis, gastric reflux, GI tract ulceration, chronic gastritis, megacolon	15, 30-34, 39, 48, 73, 112, 135	Dog: 0.5-2 mg/kg PO, SC, IV BID-TID Cat: 0.1-2.5 mg/kg IV, PO, SC BID-TID
Remifentanil *(Ultiva)*	Preanesthetic, anesthetic agent	1	Dog: a) 0.001-0.003 mg/kg IV b) 0.01-0.03 µg/kg IV as CRI Cat: a) 0.001-0.003 mg/kg IV b) 0.01-0.03 µg/kg IV as CRI
Rifampin *(Rimactane, Rifadin)*	CNS fungal infections, tuberculosis	24	Dog: 10-20 mg/kg PO TID
	Feline leprosy	113	Cat: 10-15 mg/kg PO SID, with clofazimine or clarithromycin
	Brucellosis	113	Dog: 10 mg/kg PO BID-TID, with doxycycline
Ronidazole*	*Tritrichomonas foetus* infection	33, 116	Cat: 10-50 mg/kg PO BID × 14 days CAUTION: Can be neurotoxic
Rotenone ointment *(Goodwinol)*	Canine demodicosis	86	Dog: Apply topically SID-BID to alopecic regions
Rutin	Lymphedema, chylothorax	19	Dog: 50 mg/kg PO TID
S-Adenosyl-L-methionine (SAMe; *Denosyl*)	Antioxidant for canine chronic hepatitis/cirrhosis, feline chronic cholangiohepatitis, hepatic necrosis/failure, acetaminophen and Saint John's Wort toxicoses	37, 124, 126, 127, 130, 131	Dog: 17-20 mg/kg PO SID, on an empty stomach Cat: a) 200 mg PO SID, on an empty stomach b) 20 mg/kg PO SID, on an empty stomach
Selamectin *(Revolution)*	Heartworm chemoprophylaxis	12	6 mg/kg applied topically once monthly
	Flea adulticide; cheyletiellosis; sarcoptic, notoedric, and otodectic mange; *Pneumonyssoides caninum*	85, 95	Apply 6-15 mg/kg topically q 30 days or q 2 wk × 2-3 Rx
	Linognathus setosus		8 mg/kg applied topically
Selegiline *(Anipryl)*	Narcolepsy	22	Dog: 1 mg/kg PO SID
	Pituitary-dependent hyperadrenocorticism	45	Dog: 1 mg/kg/day PO
	Cognitive dysfunction	117	Dog: 0.5-1 mg/kg PO SID
Selenium	Nutritional myodegeneration	82	Dog: 100-400 IU PO BID
Selenium sulfide 1% shampoo *(Selsun Blue)*	*Malassezia* spp. dermatitis	85	Dog: Use 1-2 times/wk until resolution
Sertraline *(Zoloft)*	Certain behavioral disorders	117	Dog: 0.5-4 mg/kg PO SID Cat: 0.5-1.5 mg/kg PO SID
Sildenafil *(Viagra)*	Pulmonary hypertension, polycythemia	8, 18	Dog: 0.5-3 mg/kg PO BID-TID
Sodium bicarbonate	Cardiopulmonary arrest, metabolic acidosis, hyperkalemia	7, 45, 48	1 mEq/kg IV initially, then 0.5 mEq/kg IV q 10 min Cat: 10 mg/kg PO BID
	Hypercalcemic crisis	43	1 mEq/kg IV slow bolus infusion
	Urine alkalinization	127	10-90 gr/day PO

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DRUG (BRAND NAME OR ABBREVIATION)	PURPOSE OR USE	CHAPTERS WHERE CITED	DOSAGE
Sodium bicarbonate—*cont'd*	Certain toxicoses Shock, metabolic acidosis	128 132	1-2 mEq/kg per L of crystalloid soln IV Administer half of bicarbonate deficit slowly IV over 4-6 hr
Sodium nitrite injectable	Cyanogenic glycoside plant poisoning	131	Dog: 16 mg/kg IV, followed by sodium thiosulfate CAUTION: Use only in cyanide poisoning cases
Sodium phosphate injectable	Severe hypophosphatemia	64	Cat: 0.01-0.03 mmol/kg/hr IV; max = 0.06 mmol/kg/hr
Sodium stibogluconate *(Pentostam)*	Leishmaniasis	116	Dog: 30-50 mg/kg SC SID × 3-4 wk, with allopurinol
Sodium sulfate (Glauber's salts; compounding pharmacy)	Osmotic cathartic	123	250 mg/kg PO added to activated charcoal slurry
Sodium thiosulfate *(Sodium thiosulfate)*	Cyanogenic glycoside plant poisoning	131	Dog: 30-40 mg/kg IV following sodium nitrite CAUTION: Use only in cyanide poisoning cases
Sorbitol 70% soln *(Toxiban with Sorbitol, Sorbitol Solution)*	Osmotic cathartic	123	1-2 mL/kg, with activated charcoal soln
Sotalol *(Betapace)*	Atrial fibrillation or flutter, supraventricular and ventricular arrhythmias	6	Dog: 0.5-2.5 mg/kg PO BID Cat: 10 mg PO BID
Spironolactone *(Spironolactone)*	Chronic heart failure, ascites from hepatic failure	9, 37	Dog: 1-2 mg/kg PO SID-BID
Stanozolol *(Winstrol-V)*	Appetite stimulant	122	Dog: a) 1-4 mg PO BID b) 25-50 mg IM q 7 days Cat: a) 1-2 mg PO BID b) 25 mg IM q 7 days
Streptokinase *(Streptase)*	Arterial thromboembolism	10	Cat: 90,000 U IV over 30 min, then 45,000 U/hr IV × 3 hr
Streptomycin *(Streptomycin)*	Brucellosis	61	Dog: 20 mg/kg IM SID × 14 days
Streptozocin *(Zanosar)*	Insulinoma	46	500 mg/m^2 mixed with 0.9% NaCl, given at 18.3 mL/kg/hr IV × 2 hr
Succimer *(Chemet)*	Lead poisoning	126	Dog: 10 mg/kg PO TID × 10 days Cat: 10 mg/kg PO TID × 5 days, then 10 mg/kg PO or rectally BID × 10 days
Sucralfate *(Carafate)*	Esophagitis, GI tract ulceration, uremic gastritis	30, 31, 33, 37, 39, 45, 48, 73, 124, 126-128, 130, 131, 135	Dog: a) 250 mg/15 kg PO TID-QID b) 0.5-1 g/25 kg PO BID-QID c) 0.25-1 g PO BID-QID (as slurry) Cat: 0.125-0.5 g PO BID-TID Give 30-60 min after Histamine$_2$ blockers
Sulfadiazine *See also* Trimethoprim-sulfadiazine	Nocardiosis Toxoplasmosis, neosporosis	89 102, 116	Dog: a) 80 mg/kg PO TID b) 110 mg/kg PO BID Dog: 15-20 mg/kg PO BID × 2-4 wk, with pyrimethamine
Sulfadimethoxine *(Albon)*	Coccidiosis	33, 116	55 mg/kg PO once, then 27.5 mg/kg PO SID × 10-14 days
Sulfadimethoxine-Ormetoprim *(Primor)* *See* Ormetoprim			

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DRUG (BRAND NAME OR ABBREVIATION)	PURPOSE OR USE	CHAPTERS WHERE CITED	DOSAGE
Sulfamethazine *(Sulmet Soluble Powder)*	Coccidiosis	33	100 mg/kg PO once, then 50 mg/kg PO BID × 14 days
	Nocardiosis	89	50 mg/kg PO TID
Sulfasalazine *(Azulfidine)*	Chronic idiopathic colitis	34	Dog: 15-20 mg/kg PO TID; max = 3 g/day Use with caution in cats
	Chronic histiocytic ulcerative colitis, vasculitis	34, 91	Dog: 20-40 mg/kg PO TID; doses >3 g/day potentially toxic
Sulfisoxazole *(Gantrisin)*	Nocardiosis	89	Dog: 50 mg/kg PO TID
Suprofen 1% *(Profenal)*	Anterior uveitis	99	Apply 1 drop to affected eye BID-QID
Tacrolimus 0.1% cream *(Protopic)*	Cutaneous or discoid lupus erythematosus, pemphigus erythematosus, KCS	90, 91, 98	Apply topically SID-BID × 14 days, then taper to 2-3 times/wk
Tacrolimus 0.02%-0.03% (compounding pharmacies)	Tear stimulation, KCS	97	Apply soln to affected eye BID-TID
Taurine	Taurine deficiency, dilated cardiomyopathy	10, 122	Dog: 500-1000 mg PO BID-TID Cat: 250-500 mg PO SID-BID
	Feline central retinal degeneration	102	Cat: 250-500 mg PO SID-BID
Tepoxalin *(Zubrin)*	Musculoskeletal pain and inflammation	80, 127	Dog: 10-20 mg/kg PO once, then 10 mg/kg PO SID
Terbinafine *(Lamisil)*	Gastric pythiosis, oomycosis	31, 111	Dog: 5-10 mg/kg PO SID
	Malassezia spp. dermatitis	85	Dog: 15-30 mg/kg PO SID
Terbutaline *(Brethine, Terbuatline)*	Sinus bradycardia	6	Dog: 0.2 mg/kg PO BID-TID
	Bronchodilator	16-18, 133	Dog: a) 1.25-5 mg PO BID-TID b) 0.01 mg/kg SC, IM BID-QID Cat: a) 0.625-1.25 mg PO BID b) 0.01 mg/kg SC, IM BID-QID
Testosterone cypionate *(Depo-Testosterone)*	Hormone-responsive urinary incontinence	51	Dog (male): 2.2 mg/kg IM monthly
	Decrease milk production in pseudocyesis	61	Dog: 0.5-1 mg/kg IM
Testosterone propionate *(Testosterone propionate)*	Hormone-responsive urinary incontinence	51	Cat: 5-10 mg IM PRN
Tetanus antitoxin (equine)	Tetanus treatment	113	Test dose: 0.1-0.2 mL SC, ID; observe for 30 min for signs of anaphylaxis Treatment dose: 100-1000 U/kg IV or IM, SC near the wound site, once
Tetracycline *(Achromycin)*	Rickettsial diseases, leptospirosis carrier state, canine hemoplasmosis	24, 48, 102, 115	Dog: 22-30 mg/kg PO TID Cat: 15 mg/kg PO TID
	GI bacterial overgrowth, bacterial cystitis or arthritis	33, 50, 80	Dog: 10-22 mg/kg PO TID
	Brucellosis	61	Dog: 30 mg/kg PO BID × 28 days
	Immune-mediated dermatological diseases, nodular panniculitis, sterile granuloma, sebaceous adenitis, episcleritis	77, 89-91, 93, 98	Dog: <10 kg: 250 mg PO TID, with niacinamide >10 kg: 500 mg PO TID, with niacinamide
	Salmon poisoning disease	115	Dog: 22 mg/kg PO, IV TID × 3-5 days

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DRUG (BRAND NAME OR ABBREVIATION)	PURPOSE OR USE	CHAPTERS WHERE CITED	DOSAGE
Theophylline *(Theolair, Aquaphyllin)*	Bronchodilator	6, 12, 16-18	Dog: 10–20 mg/kg PO BID Cat: 25 mg/kg PO SID *Theochron-Extended Release:* Dog: 10 mg/kg PO BID *Theo-Dur tablets:* Dog: 20 mg/kg PO BID Cat: 20-25 mg/kg PO SID in evening *Slo-Bid Gyrocaps:* Dog: 25 mg/kg PO BID Cat: 25 mg/kg PO SID in evening
Thiabendazole *(Mintezol)*	Nasal aspergillosis *Oslerus osleri*	14 16	Dog: 10 mg/kg PO BID Dog: 32-140 mg/kg/day PO × 10-23 days
Thiabendazole *(Tresaderm)*	Otodectic mange	85	Apply to the ears SID × 7 days; repeat in 7 days
Thiamine HCl (Vitamin B_1)	Adjunctive therapy for seizures Thiamine deficiency, malabsorption	22 23, 33	25-50 mg IM, IV Dog: 25-50 mg IM SID Cat: 10-20 mg IM SID
Thiopental *(Pentothal)*	Anesthetic induction	1, 61	4-10 mg/kg IV, to effect
Tiopronin *(Thiola)* *See* 2-Mercaptopropionyl glycine			
Thymosin fraction 5	Growth hormone deficiency	75	Dog: 1 mg/kg SC SID × 7 days (in the puppy)
L-Thyroxine, T_4 *(Soloxine, Synthroid)*	Hypothyroid-related neuropathy Hypothyroidism Myxedema stupor or coma	25 41, 42, 61, 87 42	Dog: 0.02 mg/kg PO BID Dog: 0.02-0.04 mg/kg PO BID initially, then possibly SID Cat: 0.05-0.1 mg/cat PO SID-BID Dog: 1-5 µg/kg IV BID
Ticarcillin/clavulanate *(Timentin)*	Acute endocarditis, bartonellosis Septicemia, endotoxemia, acute abdomen syndrome Feline acute cholangiohepatitis	9 33, 39 37	Dog: 50 mg/kg IV QID, with amikacin Dog: 40-50 mg/kg IV TID-QID Cat: 33-50 mg/kg IV QID
Tiletamine/zolazepam *(Telazol)*	Short-duration anesthesia		Dog: 6-13 mg/kg IM Cat: 9-12 mg/kg IM
Timolol maleate 0.5% *(Timoptic)*	Glaucoma	100	Apply 1 drop to affected eye BID
Tissue plasminogen activator, alteplase *(Activase)*	Intraocular fibrinous clots	99	Inject 25 µg (0.1 mL of 250-µg/mL soln) in anterior chamber of affected eye
Tobramycin *(Nebcin)*	Resistant *Pseudomonas* spp. infections		1-2 mg/kg IM, SC, IV TID
Tocopherol *See* Vitamin A			
Tramadol *(Ultracet, Tramadol)*	Pain relief	72, 81	Dog: 1-4 mg/kg PO BID-QID Cat: 12.5 mg PO BID
Transfusion therapy *See also* Cryoprecipitate	Platelet disorders, von Willebrand disease, severe anemia	37, 67	a) Whole blood: 10-20 mL/kg IV SID PRN b) Platelet-rich plasma: 6-10 mL/kg IV; repeat BID-TID PRN c) Platelet concentrate: 1 U/10 kg IV; repeat BID-TID PRN d) Fresh or fresh-frozen plasma: 6-12 mL/kg IV; repeat BID-TID PRN

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DRUG (BRAND NAME OR ABBREVIATION)	PURPOSE OR USE	CHAPTERS WHERE CITED	DOSAGE
Travoprost 0.004% *(Travatan)*	Glaucoma	100	Dog: Apply 1 drop to affected eye SID-BID
Tretinoin *(Retin-A Micro Cream)*	Vitamin A-responsive dermatoses	122	Apply topically SID-BID
Triamcinolone *(Vetalog)*	Feline immune-mediated cutaneous diseases, plasma cell pododermatitis, eosinophilic granuloma complex	90, 91	Cat: 0.4-0.8 mg/kg PO SID, then taper
	Appetite stimulant	122	0.11-0.22 mg/kg PO SID, then quickly taper to 0.028-0.055 mg/kg PO SID
Triamcinolone injectable suspension *(Kenalog)*	Pannus, feline eosinophilic keratitis, anterior uveitis, episcleritis	98, 99	Apply 4-8 mg subconjunctivally to affected eye
Triamcinolone 0.0125% *(Genesis Spray)*	Flea allergic, atopic, contact, and acute moist dermatitides	85	Apply topically SID × 7 days, then QOD
	Severe canine acne	88	Dog: Apply topically SID × 14 days
Trientine *(Syprine)*	Copper hepatopathy	37	Dog: 10-15 mg/kg PO BID
Trifluridine 1% *(Viroptic)*	Ocular herpesvirus infection	96, 98	Apply soln to affected eye 5-8 times daily
Trilostane*	Alopecia associated with adult-onset growth hormone deficiency	41, 87	Dog: <2.5 kg: 20 mg PO SID 2.5-5 kg: 30 mg PO SID 5-10 kg: 60 mg PO SID
	Pituitary-dependent hyperadrenocorticism	45	Dog: a) 6 mg/kg PO SID b) 3 mg/kg PO BID
Trimethoprim/sulfadiazine *(Tribrissen)*	Bacterial upper respiratory infections and pneumonia, nocardiosis, toxoplasmosis, neosporosis, coccidiosis, *Pneumocystis carinii* and *Cyclospora cayetanensis* infections	18, 89, 113, 114, 116	15-30 mg/kg PO BID
	Protozoal polyradiculoneuritis, bacterial and protozoal CNS diseases	23-25	Dog: 15-30 mg/kg PO, SC BID
	Routine infections, bacterial cystitis, prostatitis and pyoderma	33, 50, 53, 88, 90, 91	15 mg/kg PO, SC BID
	Protozoal myositis	82	Dog: 30 mg/kg PO BID, with pyrimethamine Cat: 30 mg/kg PO BID
	Hepatozoon americanum infection	116	15 mg/kg PO BID, with other drugs
	Acanthamoeba castellani, Acanthamoeba culbertsoni infections	116	Dog: 30 mg/kg PO BID
Trimethoprim/sulfamethoxazole *(Bactrim, Septra)*	Canine bacterial pyoderma	88, 90	Dog: 15 mg/kg PO BID
Trypan blue 1% *(Trypan Blue 1X Solution)*	*Babesia canis*	116	Dog: 10 mg/kg IV once, followed by imidocarb
Tylosin tartrate powder (*Tylan,* 2.27 g of tylosin per teaspoon)	GI bacterial overgrowth, histiocytic ulcerative colitis	33, 34	Dog: 40-80 mg/kg PO SID-BID in food
	Cryptosporidiosis	33, 116	Dog: 11 mg/kg PO BID-TID in food Cat: 11 mg/kg PO BID in food
	Acute colitis, chronic lymphocytic-plasmacytic colitis	34	10-20 mg/kg PO BID in food
	Exocrine pancreatic insufficiency	36	Dog: 25 mg/kg PO BID in food

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*Not available in the United States.

DRUG (BRAND NAME OR ABBREVIATION)	PURPOSE OR USE	CHAPTERS WHERE CITED	DOSAGE
Ursodiol *(Actigall)*	Improve bile flow, reduce toxic bile acids in chronic hepatitis/cirrhosis, cholangiohepatitis, gallbladder mucocele	37	10-15 mg/kg PO SID
Vanadium *(Super Vanadyl Fuel)*	Diabetes mellitus	44	Cat: 45 mg PO SID, with insulin
Vasopressin *See* Desmopressin and Lysine-8-vasopressin			
Vidarabine (compounding pharmacies)	Ocular herpesvirus infection	96	Apply ointment to the affected eye 5-8 times daily
Vinblastine *(Velban)*	Mast cell tumor, lymphoma	72	2-3 mg/m^2 IV q 1-3 wk, in a protocol
Vincristine *(Oncovin)*	Transmissible venereal tumor	58, 72, 89	Dog: a) 0.5-0.6 mg/m^2 IV once weekly b) 0.025 mg/kg IV once weekly
	Myelodysplastic syndrome, essential (primary) thrombocythemia	66	Dog: 0.7 mg/m^2 once IV, with hydroxyurea Cat: 0.025 mg/kg IV weekly, with other drugs
	Immune-mediated thrombocytopenia	67	Dog: 0.02 mg/kg IV once, with prednisone
	Lymphosarcoma	69, 72	Dog: 0.5-0.75 mg/m^2 IV once weekly, in a protocol Cat: a) 0.5-0.75 mg/m^2 IV once weekly, in a protocol b) 0.025 mg/kg IV once weekly, in a protocol
Vinorelbine *(Navelbine)*	Rescue chemotherapy for lymphoma, lung tumors	72	Dog: 15-18 mg/m^2 IV q 1-2 wk, in a protocol
Vitamin A *(Visutein)*	Dietary supplement	33	Dog: 100-500 IU PO, IM SID, with food
	Severe feline acne	88	Cat: 8000 IU PO SID
	Vitamin A–responsive dermatitis	93	Dog: 10,000 IU PO SID × 8-10 wk, with a fatty meal
	Primary seborrhea	93	Dog: 400 IU/kg/day PO indefinitely (max dose)
Vitamin B_1 *See* Thiamine			
Vitamin B_{12} *See* Cyanocobalamin			
Vitamin C *See* Ascorbic acid			
Vitamin D_2, ergocalciferol *(Drisdol, Calciferol)*	Hypoparathyroidism, hypocalcemia	43	1000-2000 U/kg PO SID, taper to once weekly
Vitamin D_3 *See* Calcitriol			
Vitamin E *(E-Gems Soft Gels)*	Nutritional myodegeneration	82	Dog: 100-400 IU PO BID
	Dermatomyositis, vitamin E deficiency	82, 122	200-800 IU PO BID-TID
	Symmetrical lupoid onychodystrophy, discoid lupus erythematosus	90	Dog: a) 400 IU PO BID b) 800 IU PO SID
	Jack Russell terrier vasculopathy	93	Dog: 200-400 IU PO SID, alone or with prednisolone and dapsone
D-Alpha-tocopheryl-1000-polyethylene glycol succinate *(Liqui-E)*	Antioxidant for canine chronic hepatitis/cirrhosis, feline chronic cholangiohepatitis, hepatic necrosis/failure, pansteatitis	37	25 IU/kg PO BID

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DRUG (BRAND NAME OR ABBREVIATION)	PURPOSE OR USE	CHAPTERS WHERE CITED	DOSAGE
Vitamin K_1 *(AquaMEPHYTON, Mephyton)*	Vitamin K deficiency	33, 68	1-5 mg/kg SC, PO SID
	Vitamin K–dependent multifactor coagulopathy	68	Dog: 1 mg/kg PO SID Cat: 5 mg PO SID initially
	Anticoagulant rodenticide toxicosis	124	1-1.5 mg/kg PO TID × 2-6 wk
Warfarin *(Coumadin)*	Prevent thromboembolism	10, 18	Dog: 0.1 mg/kg PO SID Cat: 0.25 mg PO SID
Xylazine hydrochloride *(Rompun)*	Emetic	123	Cat: 0.44 mg/kg IM
Yohimbine *(Yobine)*	Reverse effects of xylazine, amitraz toxicosis	123, 125	Dog: 0.1-0.2 mg/kg IV slowly; repeat if needed
	Coma, general CNS stimulant	128	Dog: 0.1 mg/kg IV
Zinc acetate or gluconate	Canine chronic hepatitis/cirrhosis, copper storage hepatopathies, hepatocutaneous syndrome, hepatic encephalopathy	37	Dog: a) 5-10 mg/kg PO SID of elemental zinc 1 hr before or 2 hr after a meal b) Medium- and large-breed dogs: 50-100 mg SID
	Zinc-responsive dermatoses	90, 93	Dog: 5 mg/kg PO SID
Zinc methionine *(Zin Pro, Nutrived Chewable Zinpro)*	Zinc-responsive dermatoses	93, 122	1.7-2 mg/kg elemental zinc PO SID Do not give with food
Zinc sulfate *(Zinc-220, Zinca-Pak)*	Zinc-responsive dermatoses	93, 122	a) 10-15 mg/kg/day PO; crush tab, mix with food b) 10-15 mg/kg IM weekly × 4 wk
Zonisamide *(Zonegran)*	Seizures	22	Dog: 10 mg/kg PO BID

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