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CHAPTER 58

Large Intestine

STRUCTURE AND FUNCTION

Robert J. Washabau

The large intestine of the dog and cat has evolved to serve two major functions: extraction of water and electrolytes from the fluid contents of the lumen and control of defecation. The large intestine accomplishes these functions by regulating fluid transport, bacterial fermentation, motility, immune surveillance, and blood flow. Sodium and water absorption serve to dehydrate the feces prior to defecation; mucus glycoproteins serve to trap bacterial pathogens and prevent bacterial translocation; epithelial cells, lymphocytes, plasma cells, macrophages, and dendritic cells serve to regulate the bacterial flora and the immune response to microbes; and motility serves to facilitate storage or defecation of feces. Perturbations in any of these functions may result in the problems of diarrhea, constipation, or systemic inflammatory response syndrome.

Structure

Macroscopic Anatomy

The large intestine consists of the cecum, colon, rectum, and anal canal (Figure 58-1). In dogs and cats, the ileum communicates directly with the colon, and what is referred to as the cecum in the dog and cat is actually a diverticulum of the proximal colon. The colon is further compartmentalized into ascending, transverse, and descending portions, each segment having slightly different functions and properties. The right colic or hepatic flexure separates the ascending and transverse colon, and the left colic or splenic flexure separates the transverse and descending colon. In dogs and cats, the large intestine contributes 20% to 25% of the total (small and large) intestinal length.[1,2]

The arterial blood supply to the colon is provided by the cranial and caudal mesenteric arteries, and venous return from the colon is transmitted to the main portal vein via the cranial and caudal mesenteric veins. Lymph is circulated from the colon to the right, middle, and left colic lymph nodes, and eventually into the cisterna chyli and thoracic duct. Parasympathetic innervation arises from the vagus nerve in the proximal colon, and from the pelvic nerves in the distal colon. Sympathetic innervation arises from the paravertebral ganglia and follows the lumbar splanchnic nerves and mesenteric arteries to the colonic mucosa and muscularis. Parasympathetic preganglionic fibers and sympathetic postganglionic fibers synapse on cell bodies and neurons of the enteric nervous system, respectively.

Microscopic Anatomy

As with the small intestine, the cross-sectional structure of the large intestine consists of four distinct layers, that is, mucosa, submucosa, muscularis, and serosa (Figure 58-2). The large intestine differs from the small intestine in the following important ways: villi are absent in the large intestine; the microvilli of the large intestine epithelial cells are much less abundant; goblet cells are more prominent in the large intestine; endocrine cells are less prominent in the large intestine; and crypt-to-epithelial migration is a much slower process in the large intestine.

The mucosa of the large intestine is a flat absorptive surface area differing from the small intestine in that villi are not present. However, numerous straight tubular glands (400 to 600 μm) are present in parallel cylinders and they extend from the muscularis mucosa to the mucosal surface.[3] The glands are lined by a continuous sheet of columnar epithelial cells, which are separated from the mesenchymal tissue of the lamina propria by a well-defined basement membrane. The epithelium in the lower half of the crypts is composed of proliferating undifferentiated columnar cells, mucus-secreting goblet cells, and at least three types of endocrine epithelial cells.[4] Cellular proliferation is predominantly in the lower part of the crypts in both dogs and cats. The epithelium of the upper half of the crypts consists of differentiating columnar cells, goblet cells, and a few endocrine cells. The flat absorptive surface is lined by many columnar cells as well as a moderate number of goblet cells (10 to 25 goblet cells per 100 epithelial cells),[3,5] most of which are largely depleted of their mucous granules. Intraepithelial lymphocytes are relatively sparsely distributed throughout the epithelium (one to seven lymphocytes per 100 epithelial cells),[3,5] and as in the small intestine, the predominant T cell subset is the cytotoxic-suppressor (CD8+) type.[6,7] The cellular elements of the lamina propria of the large intestine resemble closely those found in the small intestine and include lymphocytes, many plasma cells, mast cells, macrophages, eosinophils, enteric neurons, and fibroblasts.

The innermost layer of the mucosa is separated from the submucosa by the muscularis mucosae, a layer of smooth muscle cells roughly eight to 10 cells (or 70 to 80 μm) thick. The submucosa of the colon resembles the submucosa of the other tubular digestive organs. It contains many blood and lymph vessels, dense connective tissue sparsely infiltrated by cells (fibroblasts, lymphocytes, plasma cells, mast cells, macrophages, and eosinophils), and the unmyelinated nerve fibers and ganglion cells that form the submucosal plexus.

The muscularis is composed of an inner circular muscular layer forming a tight spiral circumferentially along the course of the colon and an incomplete outer longitudinal muscle layer. The ganglion cells of the myenteric plexus of Auerbach are found between the

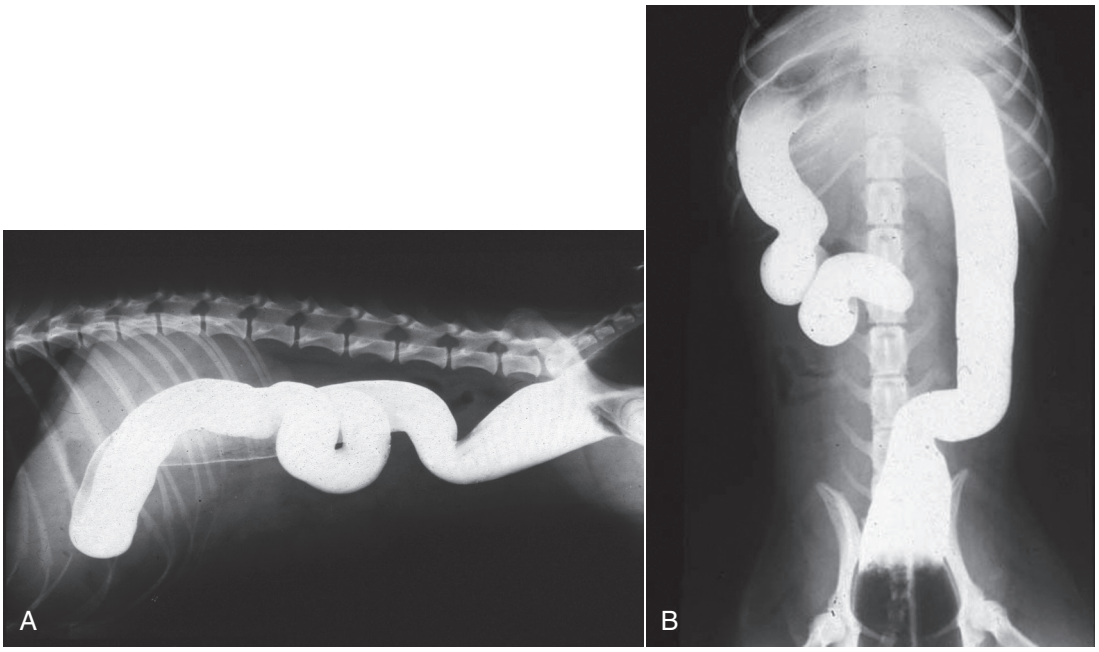

Figure 58-1 **A,** Gross anatomy of the feline colon—lateral projection, barium enema. **B,** Gross anatomy of the feline colon—ventrodorsal projection, barium enema. (Reprinted with permission from Washabau RJ: Diseases of the large intestine. In: Ettinger SJ, Feldman ED, editors: *Textbook of Veterinary Internal Medicine*, ed 6, Philadelphia, 2005, Saunders, p 1379.)

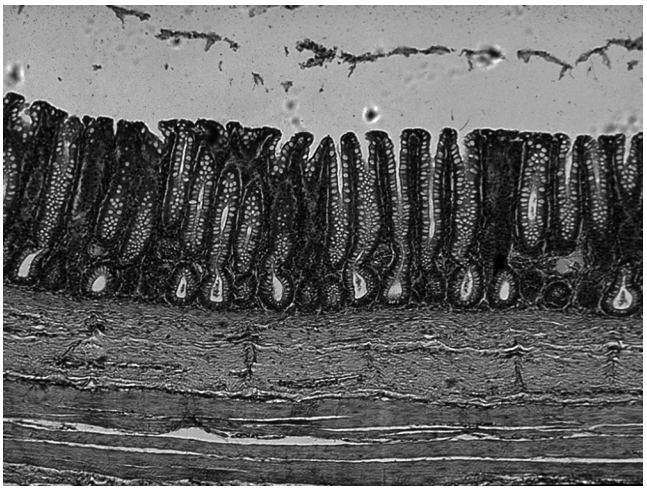

Figure 58-2 Microscopic anatomy of the canine colon. (Reprinted with permission from Washabau RJ: Diseases of the large intestine. In: Ettinger SJ, Feldman ED, editors: *Textbook of Veterinary Internal Medicine*, ed 6, Philadelphia, 2005, Saunders, p 1379.)

circular and longitudinal muscle layers. Unmyelinated postganglionic fibers are also found in the circular muscle layer and communicate with the submucosal (Meissner) plexus. The interstitial cells of Cajal, which are located on the submucosal surface of the circular smooth muscle, play a dual role as pacemaker cells and as mediators of neuromuscular transmission in the colon.[8-10]

The serosa is composed of mesothelial cells and covers only the portions of the large bowel that lay within the peritoneal cavity (cecum and colon).

Several classification systems for colonic mucosal architecture and cellularity have been proposed (see Chapter 29).[1,3,11] It should be emphasized that there are important age,[12] site,[1,3] diet,[13-16] and procedure-related[3] differences in the cellularity and architecture of the colonic mucosa, and these differences must be taken into account when interpreting colonic histology. For example, the protein and fiber content of the diet have significant effects on colonic mucosal morphology (e.g., crypt depth and cellularity).[14-16] The pathologist should always take these factors into account when interpreting colonic biopsy specimens. The method of biopsy also influences the architecture and cellularity of the mucosa. Compared to full-thickness biopsies, gland length is 25% to 30% shorter and goblet cell numbers are 70% to 75% less in endoscopic biopsies from the same animals. The shallow depth of the endoscopic biopsy apparently causes glandular collapse, and enema or cathartic preparative solutions are believed to cause discharge of mucous goblets.[3,11]

Function

Mucus Secretion

A lubricant layer of mucus forms a crucial physiologic barrier between the colonic mucosa and the luminal environment. Mucus is a constantly changing mix of secretions and exfoliated epithelial cells, the chief determinants of which are high-molecular-weight glycoproteins or mucins.[17] Gastrointestinal mucins are secreted from goblet cells as they ascend from their origin in the crypts up to the colonic epithelium. Mucin secretion is dependent upon the close integration of the cystic fibrosis transmembrane regulator (CFTR), chloride secretion, and granule exocytosis. In addition to their physiologic role as a mucosal barrier, mucins may also have a pathologic role in the metastases of epithelial tumors and enhanced susceptibility to infection.

Water Absorption

In health, approximately 2.7 L of fluid (oral intake, saliva, gastric fluid, bile, pancreatic fluid, and intestinal secretions) is presented each day to the small intestine of a 20-kg dog. Approximately 1.35 L

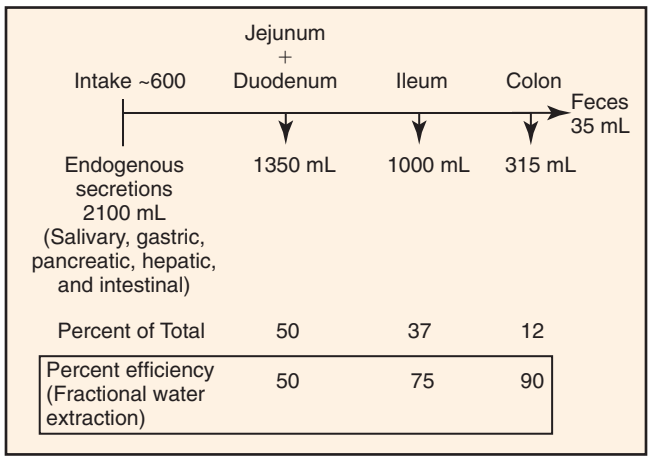

Figure 58-3 Regional daily net water turnover in the canine gastrointestinal tract. (Approximate figures: 20 kg dog, mL/24 h) (Reprinted with permission from Burrows CF: Chronic diarrhea in the dog. *Vet Clin North Am Small Anim Pract* 13:521, 1983.)

is absorbed in the jejunum, 1.0 L in the ileum, and 315 mL in the colon, leaving 35 mL in feces.[18] Thus, the jejunum absorbs 50%, the ileum 75%, and the colon 90% of fluid volume presented to it (Figure 58-3). This fluid absorptive capacity of the colon is largely determined by basal electrolyte (primarily sodium) transport and by the ability of several agonists (aldosterone and glucocorticoids) to augment electrogenic and electroneutral Na absorption. As long as ileocecal flow is less than the colonic absorptive capacity, significant alterations in small intestinal fluid movement may be present, but colonic absorption will prevent the development of diarrhea. On the other hand, when small intestinal absorption and ileocecal flow are normal, a relatively small decrease in colonic absorption (inflammatory bowel disease) will produce significant increases in fecal water output.

Electrolyte Transport

The large intestine regulates the electrolyte and water composition of the feces. There are distinct differences in the mechanisms of electrolyte transport between the ascending and descending colon,[19,20] but in general the canine and feline colon absorbs water, sodium, and chloride while secreting potassium and bicarbonate.

In many ways, the mechanisms of absorption and secretion in the large intestine are similar to those of the small intestine, but there are several important differences (Table 58-1). Active nutrient (glucose, amino acid, monoglyceride) transport is prominent in the small intestine, but there is no evidence of active glucose or amino acid absorption in the colon except during the early neonatal period. Sodium transport also differs in the colon. Glucose- and amino-acid–stimulated sodium transport is a well-established property of the small intestine, so much so that oral glucose-electrolyte solutions have been used to reduce the morbidity of cholera and other infectious diarrheal diseases of the small intestine. In contrast, glucose-coupled sodium transport does not take place in the colon and glucose-electrolyte solutions are of no benefit in diarrheal diseases of the large intestine. Sodium transport in the colon instead relies upon electrogenic transport.[20,21] The large intestine also differs in its response to mineralocorticoids. Aldosterone markedly increases sodium transport in the colon, but it has only a modest effect in the small intestine. Net sodium absorption ceases in the colon only when the luminal sodium concentration is reduced below 30 to 50 mEq/L, whereas net sodium absorption in the jejunum occurs only at luminal sodium concentrations above 130 mEq/L.[21]

Table 58-1 Special Features of Colonic Electrolyte Transport

	Small Intestine	Large Intestine
Water	Yes	Yes
Amino acid + glucose absorption	Yes	No
Lipid absorption	Yes	No
Glucose-stimulated Na absorption	Yes	No
Electrogenic Na absorption	No	Yes
Mineralocorticoid-stimulated Na absorption	Negligible	Significant

Chloride absorption in the colon has both passive and active properties. Passive chloride absorption primarily represents a potential–dependent process secondary to the electrical potential generated by electrogenic Na absorption.

Bicarbonate secretion is an important feature of colonic electrolyte function and helps to neutralize acids produced by bacterial fermentation. Chloride-bicarbonate ($Cl\text{-}HCO_3$) exchange is the primary cellular mechanism responsible for bicarbonate secretion.

The descending colon possesses both potassium absorptive and potassium secretory processes that are regulated by luminally and hormonally mediated mechanisms, and the overall net potassium movement represents the balance of these oppositely directed transport mechanisms.[20,21] The colon, therefore, has the potential to serve as an important regulatory system for the maintenance of overall potassium balance. Although renal potassium transport is critical in the overall control of potassium balance, the colon also contributes to the maintenance of potassium balance by modifying both potassium secretion and absorption, especially when kidney function is impaired.

Immune Surveillance

The colon contains a diverse array of immune cells, including T and B lymphocytes, plasma cells, macrophages, dendritic cells, antigen-presenting cells, mast cells, eosinophils, and neutrophils.[3,5-7,22-25] Immune cells are found in the epithelium, lamina propria, and submucosa of the colon. As in the small intestine, appropriate interactions between these different cell types are essential in generating either immune responsiveness or tolerance to the large array of luminal antigens.[26,27] Much less is known about colonic immunity, but some generalizations may be made. In the colon, CD8+ T cells are found primarily in the epithelium; very few CD8+ T cells are found in the lamina propria or submucosa. Most intraepithelial lymphocytes are CD3+/CD8+, a phenotype consistent with suppressor-cytotoxic functions. Lamina propria T cells on the other hand are predominantly of the CD4+ helper phenotype. Immunoglobulin (Ig) A-containing plasma cells are more prominent than IgG- or IgM-containing plasma cells in the lamina propria. Thus, in the normal colonic mucosa, a balance would appear to be maintained between helper and suppressor T-cell populations, which allows specific antigen responsiveness while avoiding hyperreactivity.[5,6,28] There are many similarities in the immune systems at both sites, but there are important differences in the immune response of the small and large intestine.

Motility

The colon has evolved to serve two important functions: extraction of water and electrolytes from the luminal contents in the ascending and transverse colon, and control of defecation in the descending colon. This specialization of function is attributed to regional differences in colonic motility patterns.[29-33] Electrical slow-wave frequency and rhythmic phasic contractions are slower in the proximal portion of the colon, thus facilitating extraction of water from the fecal mass by diffusion and active transport. Retrograde giant contractions (RGCs) and antiperistalsis further facilitate the mixing of contents in the proximal colon. In contrast to that of the proximal colon, motility of the distal colon is characterized primarily by migrating spike bursts and powerful giant migrating contractions (GMCs) that propagate the fecal mass toward the rectum.[4,33]

Colonic smooth muscle generates at least four different types of contractions to perform the complex motility functions of mixing and propulsion: (a) tone, (b) rhythmic phasic contractions (RPCs), (c) RGCs, and (d) GMCs. The time course, frequency, and force generated by each of these contractions are significantly different from each other.[30-33] The precise role of tone in circular muscle cells is not known, but the resulting decrease in the diameter of the colon may enhance the efficiency of the phasic contractions in mixing and propulsion. Tone is normally of small to moderate force and can last for prolonged periods of time (several minutes to hours). RPCs produce mixing and net slow distal propulsion of luminal contents in the postprandial and fasting state. Phasic contractions occur rhythmically at a few cycles per minute, last for approximately 3 to 5 seconds, and generate a moderate force (75 to 100 g). RGCs occur infrequently, last for approximately 20 seconds, generate a very strong force (>150 g), and are propagated from their point of origin into the ascending colon. RGCs facilitate mixing in the ascending colon. The GMCs are of a similar magnitude and frequency to the RGCs, but they generate mass movements from their point of origin to the anorectal junction. It has been suggested that different signal transduction pathways are used by smooth muscle cells to trigger different contractions.[34,35] It is remarkable that the same smooth muscle cells can generate so many different types of contractions using a limited number of second messengers.

Bacterial Fermentation

The colon contains the largest concentration of bacteria in the gastrointestinal tract, up to 10^{11} organisms per gram of feces. The colonic microflora play an important role in the nutrition of the animal primarily via the production of short-chain fatty acids (SCFAs).[36] Major fiber fermentation substrates include cellulose, hemicellulose, and pectin, substrates that typically are not digested by pancreatic or intestinal amylases. Acetate, propionate, and butyrate account for more than 85% of formed SCFAs, and they accumulate in concentrations up to 150 mmol/L in the colon of dogs.[37] SCFAs are rapidly absorbed by the colonic mucosa, are readily metabolized by colonic epithelial cells, and have various physiologic effects. Among their physiologic effects, SCFAs promote differentiation and proliferation of colonocytes,[38] stimulate absorption of water and electrolytes,[39] provide 7% to 10% of an animal's overall energy requirements,[37] and influence or modify motility of the gastrointestinal tract.[40]

The colonic flora is influenced by many factors, including host species, breed, developmental stage, dietary history, environmental conditions, geographic locale, colonic motility patterns, disease, and medication history.

In general, anaerobic bacteria (*Bacteroides* spp., *Bifidobacterium* spp., *Clostridium* spp., and *Lactobacillus* spp.) predominate in the canine colon, accounting for up to 90% of the colonic microflora. Most are facultative or aerotolerant anaerobes, not true obligate anaerobes.[41] Enterobacteria and streptococci are the predominant aerobic bacteria found in the canine colon. In the cat, approximately equal numbers of anaerobic and aerobic bacteria are found in the colonic lumen.[42]

The colonic flora changes significantly with developmental stages. The aging canine colon becomes more readily populated by *Clostridium perfringens* and other obligate anaerobes, and less populated by aerobes and aerotolerant anaerobes.[41,43] This change takes place in the ascending and descending colon, but is most significant in the descending colon where anaerobic conditions tend to predominate. Senescent changes in bacterial populations of the colon conform to the principles of successional ecology.[44] Over time, changes in pH, redox (oxidation-reduction) potential, bacterial competition, and nutrient availability facilitate the proliferation of anaerobic bacteria permitting them to eventually displace the aerotolerant forms.

The colonic flora may also be influenced by an animal's breeding and genetic background. For example, far fewer *Bifidobacterium* spp. are recovered from the feces of Beagle dogs than are recovered from other dog breeds.[43,45] This represents a problem for studies of colonic bacteriology because many of the reference studies have been generated from Beagle dogs.

Diet has a major impact on numbers and types of bacteria recovered from the colon. *Bacteroides* spp. appear to be particularly susceptible to changes in the diet.[45-47] The protein, carbohydrate, and fiber content of the diet all appear to influence the ability of bacteria to grow within the colon. Thus, dietary history should always be considered when interpreting results of fecal or colonic bacterial cultures.

Geographic locale and environmental conditions can also influence colonic bacteriology in the dog. *Bifidobacterium* spp. are readily isolated from dogs from Japan but they are inconsistently found in American dogs.[41,45] Housing conditions appear to be another confounding factor. Open housing environments[41] appear to facilitate colonization of a greater proportion of facultative anaerobic bacteria compared to closed facility conditions.[48]

Motility patterns of the colon influence the bacterial ecology of the colon. The antiperistaltic activity of the ascending and transverse colon particularly facilitates the mixing of fecal material with endogenous bacteria. Abnormalities in the motility patterns of this part of the colon lead to changes and proliferation of obligate anaerobes similar to that which is found in the descending colon.[29]

Disease and medical therapies, particularly antibiotics, alter the microbial characteristics of the colon. These changes are poorly understood in dogs and cats but they very likely contribute to clinical symptomatology (see Chapter 2).

DIAGNOSTIC EVALUATION

Robert J. Washabau

History and Physical Examination

Colitis

History

Inflammation is the most important pathophysiologic condition of the colon. Colitis is responsible for the major clinical signs of

Table 58-2 Clinical Signs Associated with Large Bowel Diarrhea

Signs	Small Bowel	Large Bowel
Weight loss	May be present	Uncommon
Vomiting	May be present	Uncommon
Flatulence	Present with malassimilation	Unusual
Defecation frequency	Normal to mild increase	Marked increased frequency
Fecal volume	Increased	Normal to mild increase
Urgency	Absent	Usually present
Tenesmus	Absent	Usually present
Mucous in feces	Usually absent	Frequently present
Hematochezia	Absent	Often present
Melena	Sometimes present	Absent
Steatorrhea	Present with malassimilation	Absent

hematochezia, mucus in the feces, dyschezia, abdominal discomfort, tenesmus, urgency, and increased frequency of defecation. The colon is an important target organ for inflammatory bowel disease (IBD) in the dog, whereas the upper gastrointestinal tract (stomach and small intestine) is more frequently involved in feline IBD. Clinical signs are useful in localizing the anatomic site of the diarrhea to the small or large bowel (Table 58-2), although some animals will have diffuse involvement of the small and large intestines.

The history should include specific questions about diet, parasite control, environment, travel history, concurrent medical disease, and drug history. Dietary sensitivity reactions[1] and parasitism are major causes of colitis in many pet populations. Dietary history should include information regarding type of diet, incidence of dietary indiscretion, supplements, snacks, and treats. Information concerning previous fecal examinations and anthelmintic usage may provide useful clues to the cause of the diarrhea. Environmental history should identify other pets in the household and the composition of their diets, and any behavioral interactions or hierarchies that might influence the development of clinical signs. The travel history may yield important information about exposure to histoplasmosis, pythiosis, and heterobilharziasis, all of which have regional distributions. Concurrent medical disease (e.g., Addison disease, IBD, pancreatitis) also helps to place the current episode of colitis in context. The drug history should include information about the use of alternative and complementary medicines that could contribute to clinical symptomatology.

Physical Examination

The physical examination may be normal in many cases of colitis. The most consistent physical examination findings are pain and irregularities of the colonic mucosa on digital rectal examination. The perineum should be examined carefully to exclude perineal diseases such as perineal hernia and perianal fistula. Physical examination may reveal other important findings, including *fever* (IBD, cecal or colonic perforation, fungal infection), *abdominal pain* (IBD, colonic neoplasia, cecal or colonic perforation), *abdominal mass* (colonic neoplasia, granulomatous colitis, intussusception), *small intestinal thickening* (concurrent small intestine IBD, small intestine lymphoma), *mesenteric lymphadenopathy* (small intestine IBD, small intestine lymphoma), *hepatosplenomegaly* (lymphoma, disseminated fungal infection), and *uveitis* (protothecosis, lymphoma). A scoring system has been developed to relate clinical signs with histologic findings in canine IBD.[2]

Constipation

History

Constipation is the second most important pathophysiologic condition of the colon. Clinical signs include reduced, absent, or painful defecation for a period of time ranging from days to weeks or months. Physical examination findings will depend on the severity and pathogenesis of constipation. Dehydration, weight loss, abdominal pain, and mild to moderate mesenteric lymphadenopathy are common findings in cats with idiopathic constipation.

Physical Examination

Physical examination might also reveal *abdominal mass* (cecal or colonic neoplasia, granulomatous colitis), *abdominal pain* (foreign bodies, colonic perforation), *autonomic neuropathy* (dysautonomia), *hind limb paresis* (lumbar spinal cord pathology), *pelvic fracture* (pelvic outflow obstruction), and *perineal hernia* (cause or complication of constipation).

For both inflammation (colitis) and constipation, the scope of the medical investigation is shaped by prior history, suspected etiology, chronicity, and signs of systemic illness (Figures 58-4 and 58-5).[3,4]

Laboratory Data

Complete blood count, serum chemistry, and urinalysis should be considered in animals with signs of colonic disease, particularly those with signs of systemic disease. These tests may provide evidence of *anemia* (chronic disease, GI blood loss), *leukocytosis* (IBD, neoplasia, cecal or colonic perforation), *eosinophilia* (parasitism, Addison disease, mast cell disease, hypereosinophilic syndrome), *thrombocytopenia* (concurrent immune thrombocytopenia), *hypoproteinemia* (protein-losing enteropathy), *hyperglobulinemia* (IBD, infection, neoplasia), *hypercalcemia* (neoplasia, fungal disease), *hypoglycemia* (leiomyosarcoma), and *hyponatremia/hyperkalemia* (Addison or pseudo-Addison disease). This minimum database is also useful to screen animals prior to anesthesia and colonoscopy. If fungal, oomycete, or algal infections are possible causes in the pet's geographic area, special serologic tests are available for the diagnosis of some of these diseases (Table 58-3). Feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) testing are warranted in cats with unexplained, chronic diarrhea.

Fecal Parasitic Evaluation

Direct fecal smears and fecal flotation studies should be performed to evaluate for helminth, protozoal, and some bacterial infections (see Table 58-3). Direct fecal smears may be useful in detecting *Giardia*, *Tritrichomonas*, and *Campylobacter* organisms. Zinc sulfate flotation is the most accurate and practical fecal flotation test available, and it may be more sensitive for the detection of *Giardia* and *Tritrichomonas* infections. Because some animals may have intermittent shedding of helminth ova and/or *Giardia* trophozoites and cysts, suspected infections should always be treated with anthelmintics or antiprotozoal agents before animals are subjected to colonoscopy.

Fecal Bacterial Culture

Fecal cultures should be considered in animals with suspected bacterial infections of the intestine and colon. Risk factors for bacterial

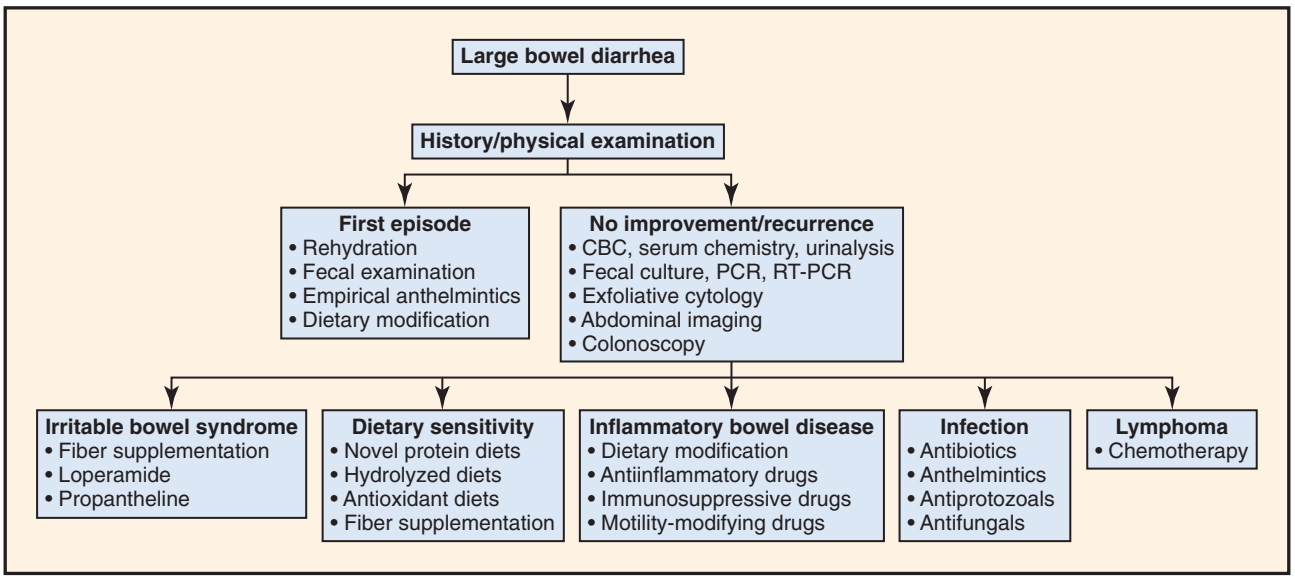

Figure 58-4 Diagnostic approach to large intestinal diarrhea. (Reprinted with permission from Washabau RJ: Diseases of the large intestine. In: Ettinger SJ, Feldman ED, editors: *Textbook of Veterinary Internal Medicine*, ed 6, Philadelphia, 2005, Saunders, p 1384.)

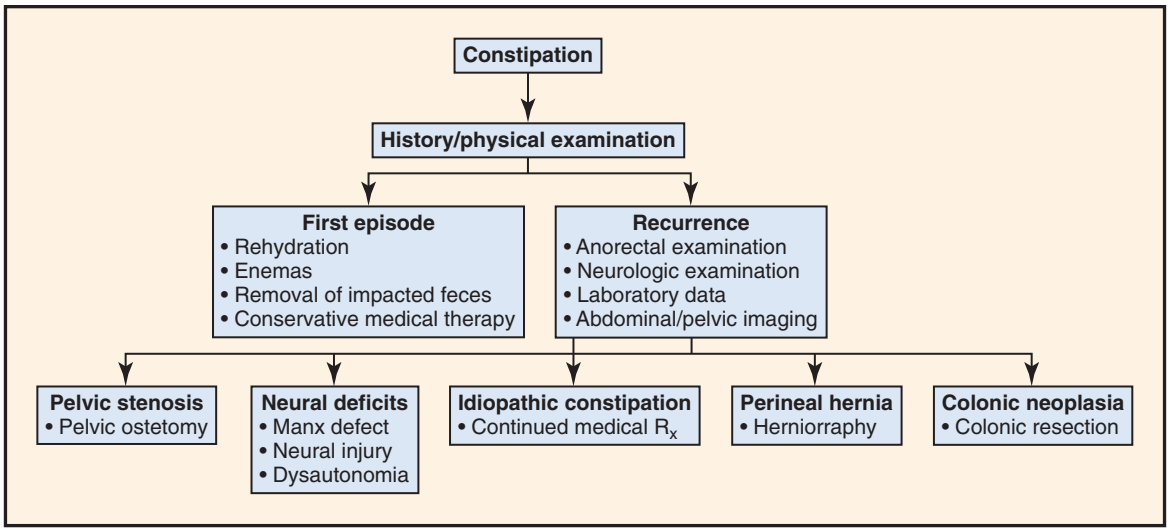

Figure 58-5 Diagnostic and therapeutic approach to constipation. (Reprinted with permission from Washabau RJ: Diseases of the large intestine. In: Ettinger SJ, Feldman ED, editors: *Textbook of Veterinary Internal Medicine*, ed 6, Philadelphia, 2005, Saunders, p 1384.)

colitis include young age, crowded or poor hygienic environmental conditions, coinfection with helminth or protozoal parasites, viral immunosuppression,[5] boarding or kenneling conditions, and multiple-pet households. Bacterial pathogens associated with colitis or enterocolitis lesions in dogs and cats have included *Brachyspira pilosicoli*, *Campylobacter* spp., *C. perfringens*, and *Clostridium difficile*, certain *Escherichia coli* (enterotoxigenic, enteroinvasive, enteropathogenic, enterohemorrhagic, enteroadherent), *Salmonella* spp., and perhaps *Yersinia enterocolitica* (see Table 58-3). The role of enteropathogenic bacteria in the pathogenesis of colitis-type diarrhea has been reviewed recently by Marks et al.[5a] Culture results should always be interpreted in light of clinical signs, other findings such as coinfections, and substantiating laboratory data such as serologies or polymerase chain reaction results. Fecal cultures should not be performed for the purpose of diagnosing small intestinal bacterial overgrowth.

Molecular Diagnosis

A number of polymerase chain reaction (PCR) and reverse transcriptase (RT)-PCR assays have been developed for gene amplification products and messenger RNAs of infectious organisms (see Table 58-3). Assays are now available for the molecular diagnosis of *Tritrichomonas foetus*, *Pythium insidiosum*, *Campylobacter jejuni*, *C. perfringens*, *C. difficile*, *E. coli*, *Salmonella* spp., and *B. pilosicoli*, and many more are likely forthcoming. Molecular detection is the standard for infectious disease diagnosis in many instances.[6]

Fecal Cytologic Examination

Exfoliative rectal or endoscopic cytology may be useful in identifying etiologic agents (e.g., fungal elements, neoplastic cells) and inflammatory cells (e.g., lymphocytes, eosinophils). Rectal smears

Table 58-3 Definitive, Suspected, and Unproved Pathogens of the Large Intestine of Dogs and Cats

Classification/Organism	Tissue Trophism	Evidence of Pathogenicity	Diagnosis
Helminths			
Trichuris vulpis–dogs	Colon	Good evidence	Fecal flotation
Trichuris serrata–cats	Colon	Weak evidence	Fecal flotation
Trichuris campanula–cats	Colon	Weak evidence	Fecal flotation
Ancylostoma caninum	Intestine, colon	Good evidence	Fecal flotation
Heterobilharzia americana	Colon	Good evidence	Fecal flotation, histology
Protozoa			
Balantidium coli	Colon	Weak evidence	Fecal flotation
Cryptosporidium parvum	Intestine, colon	Moderate to good evidence	Fecal flotation, PCR, serology
Entamoeba histolytica	Colon	Poor evidence	Fecal flotation
Giardia canis	Intestine, colon	Moderate to good evidence	Fecal flotation, PCR, serology
Isospora canis–dogs	Colon	Weak evidence	Fecal flotation
Toxoplasma gondii	Intestine, colon	Good evidence	Fecal flotation, PCR, serology
Tritrichomonas foetus–cats	Ileum, cecum, colon	Moderate to good evidence	Fecal flotation, culture, PCR
Fungi			
Histoplasma capsulatum	Intestine, colon	Good evidence	Exfoliative cytology, histology
Oomycetes			
Pythium insidiosum	Stomach, intestine, colon	Good evidence	Histology, immunohistochemistry, ELISA, PCR
Algae			
Prototheca zopfii, P. wickerhamii	Colon	Good evidence	Exfoliative cytology, histology
Bacteria			
Brachyspira pilosicoli	Ileum, colon	Weak to moderate evidence	Fecal culture, PCR, histology
Campylobacter coli, C. jejuni	Intestine, colon	Moderate evidence	Fecal culture, PCR
Clostridium perfringens	Colon	Weak to moderate evidence	Fecal culture, enterotoxin, PCR
Clostridium difficile	Colon	Weak to moderate evidence	Fecal culture, enterotoxin, PCR
Escherichia coli (EPEC, EI, EH)	Intestine, colon	Good evidence	Fecal culture, serotyping, PCR
Salmonella typhimurium	Intestine, colon	Good evidence	Fecal culture, serotyping, PCR
Salmonella krefeld	Intestine, colon	Good evidence	Fecal culture, serotyping, PCR
Yersinia enterocolitica	Colon	Poor evidence	Fecal culture

EH, Enterohemorrhagic; EI, enteroinvasive; EPEC, enteropathogenic *E. coli*. ELISA, enzyme-linked immunosorbent assay; PCR, polymerase chain reaction.

may be obtained with a cotton-tipped applicator or conjunctival spatula during anorectal examination, or with a cytology brush at the time of endoscopy. A good correlation (specificity, 97%; sensitivity, 93%) was shown between exfoliative cytology and subsequent endoscopic or surgical biopsy in one study.[7] Additional studies are still needed to verify the diagnostic value of this test.

Imaging

Survey abdominal radiographs may occasionally document colonic foreign objects, mesenteric or sublumbar lymphadenopathy, intussusception, and extraluminal compression, but survey radiographs are generally nonspecific in the diagnosis of colonic disease. Contrast studies (e.g., barium enema) are performed infrequently because of their poor sensitivity and requirement for general anesthesia. Ultrasonographic imaging has proved more useful in documenting mass lesions, lymphadenopathy, intussusceptions, and bowel thickening. Abdominal ultrasound may also be used to facilitate percutaneous aspiration of luminal masses, mucosal thickenings, and lymph nodes.[8,9] Computed tomography (CT) colonography, also known as virtual colonoscopy, has been successfully implemented in human medicine, and has been studied experimentally in the dog.[10]

Colonoscopy

Colonoscopy is indicated for the diagnosis of colitis-type diarrhea unresponsive to dietary modification and medical therapy, suspected colorectal neoplasia, chronic constipation, unexplained stricture, and evaluation of prior surgical or medical treatment.[11] Colonoscopy is performed after other noninvasive diagnostic tests (e.g., fecal parasitologic examination, fecal bacteriologic examination, exfoliative cytology, abdominal ultrasonography, survey ± barium-contrast radiography) have failed to diagnose the disease.

Rigid or flexible endoscopy may be performed, but flexible endoscopy provides better visualization and examination of the entire colon. The normal colonic mucosa is pink in color, smooth in texture, and glistening in appearance (Figure 58-6). Unlike the esophageal, gastric, and duodenal mucosa, submucosal blood vessels are readily apparent. The mucosa should not hemorrhage when abraded by the endoscope; active hemorrhage usually implies an underlying disorder such as inflammation or infection. The colonoscopic procedure should include examination of the more proximal structures—for example, ascending colon, cecum, ileocecal sphincter, and distal ileum—whenever possible. The proximal colon is an important site of inflammation, parasitism, ileocolic intussusception, cecal inversion, and neoplasia.

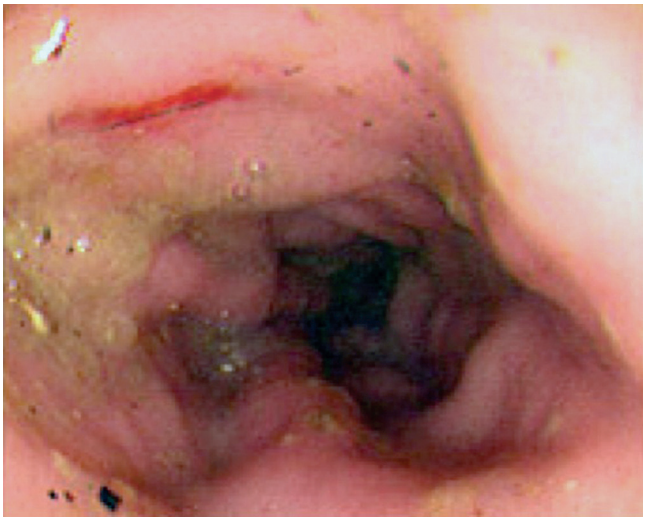

Figure 58-6 Endoscopic appearance of large intestinal inflammatory bowel disease. (Reprinted with permission from Washabau RJ: Diseases of the large intestine. In: Ettinger SJ, Feldman ED, editors: Textbook of Veterinary Internal Medicine, ed 6, Philadelphia, 2005, Saunders, p 1386.)

Box 58-1 Preparation and Patient Positioning for Colonoscopy

- Withhold food for 24 to 48 hours
- Lavage solutions → CoLyte, GoLYTELY
- 25 mL/kg, 24 and 12 hours before endoscopy
- Warm water enemas → 5 to 10 mL/kg,
- 24, 6, and 2 hours before endoscopy
- General anesthesia
- Left lateral recumbency

Fecal material must be completely evacuated before the colonic mucosa can be properly examined (Box 58-1). Incomplete bowel preparation is the major reason for an unsuccessful colonoscopic examination. Patient permitting, food should be withheld for 36 to 48 hours so that fecal material does not accumulate in the colon. The patient should also be given warm water enemas and/or gastrointestinal lavage solutions. Lavage solutions are preferable to warm water enemas,[12-14] but both may be given to facilitate successful colonoscopy. Polyethylene glycol solutions are isosmotic, are administered orally, and induce a diarrhea that rapidly removes fecal material from the bowel. Large volumes may be administered without inducing significant changes in water or electrolyte balance.[12] Electrolyte solutions should be given at a dose of 25 mL/kg at 24 and 12 hours prior to colonoscopy. Warm-water enemas should be performed gently, without irritating substances, at 24, 6, and 2 hours before colonoscopy. The combination of a 36- to 48-hour food fast, gastrointestinal lavage solution, and enemas usually results in a colon that is free of fecal fluids and solids.

Endoscopic examination of the colon has been described in detail.[11] General anesthesia is induced and the patient is placed in left lateral recumbency. The tip of the endoscope is introduced into the anorectal canal, and air is insufflated to dilate the anorectal and colonic lumen. As with upper gastrointestinal endoscopy, the tip of the endoscope should never be advanced unless the lumen is in full view. While inspecting the colonic mucosa, the endoscope is advanced through the descending colon to the splenic flexure. To facilitate passage of the endoscope through the splenic flexure, the tip of the endoscope is deflected slightly upward, and the endoscope is pushed into the transverse colon. The transverse colonic mucosa is now more visible as the endoscope enters the short, straight segment of the transverse colon. At the hepatic flexure, the tip of the endoscope is deflected caudally to enter the ascending colon. While keeping the tip of the endoscope in the center of the lumen, the endoscope is advanced the full length of the ascending colon into the cecum and ileocecal sphincter. The cecum is easily inspected, and the endoscope is then advanced through the ileocecal sphincter to evaluate the distal ileum. Endoscopic biopsies may be obtained at each sequential site or during withdrawal of the endoscope at the end of the study (see Chapter 27).

Diseased tissue, nondiseased tissue, and the transition zone between diseased and nondiseased tissue should be biopsied during colonoscopic procedures. This standard helps to verify the extent of the disease, ensures that disease in the submucosa has not been missed, and provides representative tissue samples to the pathologist to diagnose the disease.[15] In some cases of severe IBD or colonic neoplasia, advanced tissue necrosis may prevent the diagnosis of the disease process in the central part of the lesion. In the absence of gross mucosal abnormalities, three to five biopsy specimens should be obtained from each of the mid-ascending, mid-transverse, and mid-descending colonic regions (see Chapter 29).

INFLAMMATION

Frédéric P. Gaschen and Karin Allenspach

Inflammatory diseases of the colon are frequently encountered in dogs, but appear to be less common in cats. In many instances, acute nonspecific colitis may be self-limiting. However, chronic colitis is often associated with a long, sometimes waxing and waning clinical course and specific treatment is required to resolve clinical signs. Depending on patient signalment and history, dietary indiscretion, parasite infestation, and bacterial infection are common causes that need to be ruled out. The diseases discussed in this section are classically associated with noninfectious inflammation, although it appears that bacteria may play a role in multifactorial pathophysiology.

Acute Colitis

Acute colitis is characterized by a sudden onset of sometimes explosive watery diarrhea associated with the typical clinical signs of large bowel inflammation. Affected animals may also present with vomiting and lethargy. The disease often follows ingestion of toxins (e.g., spoiled food) as a component of "garbage can enterocolitis." However, intestinal parasites and bacterial infections must be ruled out systematically (or treated empirically) if deemed a likely cause based on signalment, history, and clinical signs. Acute nonspecific colitis is usually self-limiting and carries a good prognosis; most cases respond well to symptomatic treatment, which may include fluids, use of antimicrobials such as metronidazole, and a 24-hour fast followed by feeding an easily digestible, hypoallergenic diet over the following few days. Mild cases may be self-limiting. In the absence of exposure to toxins, hemorrhagic gastroenteritis should be considered as a possible differential diagnosis for dogs with bloody diarrhea of large bowel origin.

Inflammatory Bowel Disease

Definition

IBD is an idiopathic inflammatory disorder affecting the gastrointestinal (GI) tract of dogs and cats. Canine and feline IBD can be defined on the basis of clinical and histopathologic criteria. Clinically, IBD is diagnosed in animals with chronic (longer than 3 weeks' duration) GI signs such as anorexia, vomiting, diarrhea (small and/or large bowel in origin), and weight loss for which no other known cause of gastroenterocolitis can be documented. Therefore, affected animals fail to respond to symptomatic treatment, including parasiticides, antibiotics, and diet.[1] In addition, histopathologic evaluation reveals inflammatory infiltration of the colonic mucosa with predominantly round cells (lymphocytic plasmacytic colitis), eosinophils (eosinophilic colitis), neutrophils (suppurative or neutrophilic colitis), macrophages (granulomatous colitis), or a combination thereof. The inflammatory process can solely involve the colon (colitis) or affect the whole GI tract (enterocolitis).

Pathophysiology and Mechanism

Immunologic Basis of IBD

IBD is a complex disease that can affect any part of the GI tract in dogs and cats. Although the exact pathogenesis of IBD in small animals has not been elucidated, research on human and experimental IBD, as well as several studies performed recently in dogs and cats, has led to the formulation of current hypotheses.

In people, IBD encompasses two main disorders: Crohn's disease can occur anywhere in the GI tract and is characterized by a transmural inflammation, whereas ulcerative colitis is restricted to the colon and is characterized by a mucosal inflammation. IBD is clearly a multifactorial disease in which physiologic interactions of the innate and adaptive immune system with luminal microbial antigens are disrupted.[2,3] Overall, three factors are thought to be required for the development of IBD: (a) the presence of bacteria in the intestinal lumen with potential dysbiosis in the luminal microbiome; (b) defective mucosal barrier function that allows bacterial and/or food antigens to come in contact with the innate and adaptive immune cells in the lamina propria; and (c) an aberrant innate and adaptive mucosal immune response to bacterial antigens.[2,3]

In some human IBD patients, genetic alterations affecting the expression of important molecules of the innate immunity (e.g., polymorphisms in the gene encoding the nucleotide oligomerization domain 2 [NOD2]) are responsible for the abnormal recognition and response to luminal microbiota.[2] NOD2 is an intracellular pattern recognition receptor that binds to muramyl dipeptide derived from peptidoglycan common to both Gram-positive and Gram-negative bacteria.

Toll-like receptors (TLRs) are a family of transmembrane receptors with a ligand-binding extracellular domain that recognize microbe-associated molecular patterns. They are an important component of the innate immune system. In the GI tract, specific TLRs are found located on epithelial cells, macrophages, and dendritic cells. TLR2 recognizes bacterial lipopeptides, TLR4 is activated by lipopolysaccharides, and unmethylated cytosine-phosphate diester–guanine Cpg DNA found in prokaryotic genomes and DNA viruses act as ligand for the intracellular receptor, TLR9.[4,5] Once activated, TLRs elicit an intracellular signaling cascade leading to the production of proinflammatory cytokines. However, the physiologic function of TLRs in the GI tract includes maintaining hyporesponsiveness to innocuous luminal commensals, inhibition of allergic responses to food allergens and protection of mucosal barrier function.[4,5] Polymorphisms in the genes encoding TLR1, TLR2, TLR4, and TLR6 are associated with an increased risk for development of IBD in human patients and in murine animal models.[4,5]

NOD and TLRs are also a focus of attention in canine chronic enteropathies. Cultured primary canine colonocytes can express NOD2, TLR2, and TLR4 when stimulated by their respective ligands.[6] In a study investigating TLR expression profiles in endoscopic biopsies, it was found that dogs with chronic enteropathies that needed steroid treatment to keep their symptoms controlled had increased levels of TLR2, TLR4, and TLR9 messenger RNA (mRNA) expression compared with healthy dogs.[7] However, no difference in TLR expression was detected between biopsies sampled before and after clinically successful therapy, regardless of whether dogs had been treated with diet or steroids.[7,8] Another study identified a correlation between clinical severity of disease and expression of TLR mRNA. Duodenal mucosal mRNA expression of TLR2 was markedly increased in dogs with clinically severe IBD when compared with healthy controls, and TLR2 expression was correlated with clinical severity of diseases in a linear fashion.[8] Breed differences in TLR expression profiles have been reported in dogs with IBD. German Shepherd Dogs (GSD) with IBD have increased levels of TLR4 mRNA and decreased levels of TLR5 mRNA in the intestine compared to healthy greyhounds.[8a] Differences in TLR expression mimic those reported in people with Crohn's disease and have prompted genetic investigations into polymorphisms of pattern recognition receptors in dogs with IBD. In GSDs, single-nucleotide polymorphisms (SNPs) in TLR4 and TLR5 have been associated with an increased incidence of IBD.[8b] SNPs in TLR5 are associated with increased risk of development of IBD in 38 other breeds, and have been shown to be functionally hyper-responsive in GSD. This particular mutation may play a role in the pathogenesis of IBD in dogs in general.[8b] Finally, although it does not appear that food antigens play a direct role in the pathogenesis of human IBD, various dietary components can exert deleterious or beneficial effects on the intestinal microflora and on the intestinal mucosa, making it plausible that dietary changes could influence the inflammatory process in the mucosa of dogs with IBD.[9] To date, the effects of dietary antigens on canine and feline IBD have not been studied in detail. However, dietary treatment is viewed by most as an integral part of the therapeutic approach to chronic inflammatory GI diseases.

A number of studies have investigated the inflammatory process associated with canine and feline colitis. Immunohistochemical studies have shown T and B lymphocytes, as well as IgG-positive plasma cells to be increased in the colonic mucosa of dogs with IBD.[9-11] Semiquantitative RT-PCR has been used to evaluate cytokine mRNA expression in colonic mucosal biopsies. Human ulcerative colitis patients typically show a Th2 dominated inflammatory response.[2] In one study the prevailing cytokine mRNA expression pattern in dogs was that of a Th1 immune response.[12] Nevertheless, the accuracy of these results has since been questioned, at least in the duodenal mucosa, where the more reliable quantitative real-time RT-PCR showed a lack of difference in cytokine mRNA expression between healthy dogs and dogs with IBD.[13] However, colonic cytokine mRNA expression has not been investigated again using the more accurate amplification techniques, and it is prudent not to overinterpret the results from the initial study. To date there are no published data about cytokine expression in feline colitis, but duodenal mucosa of cats with IBD revealed a complex pattern of cytokine mRNA expression with a possible increase in Th1 cytokine mRNA expression.[14,15]

Table 58-4 Efficacy of Various Treatments for Chronic Colitis in Dogs and Cats Based on Published Case Series

Source	Number of Animals	Treatment Evaluated	Success Rate
Cats			
Nelson et al., 1984[29]	6 Cats	Homemade diet (boiled lamb and rice), then switched to highly digestible commercial diet. SS × 3 weeks in 1 cat with NR to commercial diet.	CR in 6 cats fed homemade diet. Rec in 2 cats when switched to highly digestible diet. Both controlled with homemade diets, 1 required SS for 3 wk.
Dennis et al., 1993[30]	13 Cats available for follow up	F (high F diet or addition of F to diet) in 8 of 10 cats with CR or PR, highly digestible diet in 2/7. CR cats received T and/or P initially, which was then d/c. All cats with CR maintained on diet alone. Cats with PR on P or SS as needed.	CR in 7 cats within 6 to 50 mo. PR in 3 cats. No change in one cat. Two cats with severe disease euthanized without treatment.
Dogs			
Nelson et al., 1988[39]	13 Dogs	Diet, initially homemade (cottage cheese and rice), followed by commercial novel antigen or low-residue diet. No medication.	CR to homemade diet in all dogs within 3 days to 6 wk. Rec in 2 of 13 after switch to commercial novel antigen or low-residue diet. Rec in 9 of 11 after exposure to pretreatment diet.
Simpson et al., 1994[40]	11 Dogs	Diet (commercial restricted antigen), initially SS in 9 dogs, d/c after resp of clinical signs. No F supplementation.	SS could be d/c after 1 mo in 3 of 9, 2 mo. in 8 of 9 but had to be resumed in 1 dog. Improvement in stool consistency, fecal mucus, and fecal blood, but not in frequency of defecation in all dogs.
Leib, 2000[31]	27 Dogs available for follow up	F (psyllium) added to various commercial or homemade (low-fat, low-residue or novel protein) diet.	Response excellent in 17, very good in 6, good in 3, and poor in 1 dog. Fiber could be d/c in 5 of 11 dogs, and special diet could be d/c in 5 of 7 dogs.
Allenspach et al., 2007[28]	30 Dogs	Diet (commercial novel antigen), P if NR to diet after 10 days.	CR in 28, NR or PR in 2. No data about resp to P in these 2 dogs.

CR, complete remission; D, diet; d/c, discontinued; F, fiber; NR, no response; P, prednisone; PR, partial remission; rec, recurrence; resp, response; SS, sulfasalazine; T, tylosin

Influence of Diet

A high proportion of dogs and cats with colitis respond to dietary therapy alone (Table 58-4); however, it is important to distinguish the various reasons for diet-responsive colitis. In humans, as well as in dogs and cats, adverse reactions to food can result from immunologic (food allergy) and nonimmunologic (food intolerance) mechanisms.[16] So far, in small animals, the clinical differentiation between food allergy and food intolerance relies heavily on restricted antigen dietary trials.[17,18] All dogs and cats with GI manifestations of adverse reaction to food get better when fed a novel diet, especially if it is designed to avoid antigens from their original diet. When challenged with their original food, they all show a relapse of GI signs. However, only food-allergic dogs and cats also relapse when their low-allergen diet is supplemented with proteins from a single source such as beef, chicken, milk, or any protein that was part of their original offending food.[17] Finally, a number of animals with colitis may simply benefit from being fed a highly digestible diet. These dogs and cats may have mild IBD that responds to the novel diet, which usually also offers additional benefits, such as an improved ratio of n6-to-n3 fatty acids or the presence of prebiotics. These animals usually do not experience a relapse when fed their original diet.

Effects of Inflammation on Colonic Function

The main functions of the colon include absorption of water and electrolytes (proximal colon) and storage of feces (distal colon). Colonic inflammation disrupts these normal events. It may decrease the total absorptive capacity of the mucosa through loss of functional colonocytes, increased epithelial permeability and disturbance of sodium and chloride transport.[19] Additionally, colitis has direct effects on colonic motility. The colon exhibits three types of contractions: While the individual phasic contractions and the migrating and nonmigrating motor complexes produce extensive mixing and kneading of fecal material and slow net distal propulsion, the giant motor complexes (GMCs) produce mass movements and expel feces during defecation.[20] In an experimental model, dogs with acute colitis had a decrease in nonpropulsive motility and an increase in GMCs, resulting in frequent defecation and tenesmus.[21] Decreased nonpropulsive motility may be explained by disturbances of the circular colonic smooth muscle cells associated with inflammation. These include impairment of calcium mobilization,[22-24] changes in expression of key signaling molecules for excitation–contraction coupling,[25] inhibition of muscarinic signaling,[26] and increased transcription of nuclear factor kappa B (NF-κB).[27] Finally, absorptive and motility disorders may change the composition of the luminal commensal flora, which plays an important role in the maintenance of colonic function, and therefore contribute to further deterioration.

Differential Diagnoses

Other colonic diseases that may lead to similar clinical signs include infectious diseases (e.g., parasite infestation with nematodes or

protozoa), infections with systemic fungi, oomycetes, algae, and bacteria. Histiocytic ulcerative colitis (HUC), another chronic inflammatory disease, can only be distinguished from lymphoplasmacytic IBD histologically. Moreover, lymphoma or other neoplasia can infiltrate the large intestine and cause identical clinical signs to those of inflammatory diseases. Finally, cecal intussusception, although rare, is another differential diagnosis of chronic noninfectious colitis. In cats with clinical signs of colitis, it is generally recommended to search for concomitant involvement of the small bowel as enterocolitis appears to occur more frequently than isolated colitis in that species.

Evaluation of the Patient

History

Dogs with IBD tend to be middle-aged (mean age: 6 to 6.5 years with a wide age range)[1,28] and older than those with diet-responsive enterocolitis (mean age: 3.5 years; range: 0.6 to 7.6).[28] In cats with lymphoplasmacytic colitis, the mean age of onset of clinical signs is similar (around 5.2 years; range: 0.5 to 10 years).[29,30] A predilection for purebred cats was noticed in one study,[30] but no canine breed appeared more frequently affected. There is no sex predilection. Signs of chronic colitis are characterized by large bowel diarrhea with frequent defecation of small volumes of soft to watery stool, often mixed with mucus and/or fresh blood (hematochezia). Urgency to defecate and tenesmus are often noticed by the owners, especially in dogs. Although occasional vomiting is often reported, abdominal pain, weight loss, anorexia, and/or lethargy are infrequently part of the history. They may occur during severe episodes, in severely affected animals, or in those with concurrent involvement of stomach and/or small intestine.[31] Clinical signs are often intermittent, although they may be continuous in some animals.[31] A gradual deterioration to more severe disease may be observed over weeks to months.

Physical Examination

Most dogs and cats with large intestinal IBD are in good general condition. Their nutritional status is unchanged by the disease. However, low body condition score and lethargy may be present in severe cases, or in animals with gastroenterocolitis. Without small intestinal involvement, abdominal palpation is often unrewarding, but may help ruling out space-occupying lesions affecting the colon (e.g., intussusception, neoplasia). Rectal palpation may be painful because of anal and rectal inflammation associated with colitis. The rectum may appear empty, or contain blood, mucus, and/or diarrheic stool. Abnormal surface of the rectal wall may be noticeable on rectal palpation.

Ancillary Tests and Laboratory Investigation

Generally, complete blood cell count, serum biochemistry, and urinalysis do not reveal significant abnormalities in dogs and cats with large intestinal IBD. This may be different in animals with generalized GI inflammation: leukocytosis with neutrophilia and left shift, hypoproteinemia with hypoalbuminemia and hypoglobulinemia, and mildly to moderately increased liver enzymes can all be present in such patients. Evaluation of acute phase reactants such as C-reactive protein in the serum has delivered mixed results,[1,28,32] and is not specific for GI inflammation. The precise clinical relevance of serum markers of autoimmunity such as perinuclear antineutrophil cytoplasmic antibodies still remains to be determined in dogs with IBD, but they may be suggestive of diet-responsive disease.[33] A parasitologic examination of one or several fecal samples is necessary to rule out parasite infestation. Alternatively, empirical treatment with broad-spectrum parasiticides such as fenbendazole (50 mg/kg PO daily for 3 days) will eliminate most GI nematodes and protozoa. Cytologic examination of rectal scrapings can reveal the presence of *Histoplasma capsulatum*, large numbers of neutrophils, a sign of inflammation, or increased numbers of Gram-positive rods (suggestive of overgrowth with *C. perfringens*).[34] Usually, diagnostic imaging (radiographs and ultrasonography) is not very helpful in cats and dogs with colitis. It may however yield useful information if the disease extends to the small intestine.

When the diagnostic elimination process confirms the possibility of large intestinal IBD, evaluation of the disease severity is desirable and best performed by colonoscopy (preceded by gastroduodenoscopy in cases with small and large bowel involvement). Full endoscopic examination of the colon requires general anesthesia but remains a safe diagnostic procedure.[35] Flexible colonoscopy allows full visualization of the rectum and descending and ascending colon, as well as cecum and ileocolic junction. Additionally, it is often possible to pass the endoscope into the ileum. Changes noticed during colonoscopy may include an increase in friability, granularity, or hyperemia; changes in the numbers of lymphoid follicles; decreased visualization of submucosal blood vessels; localized colonic spasms; and localized erosions.[31] Significant edema and inflammatory infiltrate may give the mucosa a honeycomb appearance (Figure 58-7); however, the colonic mucosa may also appear normal.[31] The endoscopic procedure also makes it possible to collect mucosal biopsies to evaluate the histopathologic appearance of the mucosa. As the colon can usually be easily distended, it is advisable to use an endoscope with a large-bore biopsy channel that makes the use of large biopsy forceps possible (≥2.8 mm diameter). Rigid proctoscopy/colonoscopy is an alternative method for procuring good size colonic mucosal samples.

Histopathology allows identification of neoplastic processes and differentiation between the various types of colonic inflammation. Recently, criteria for the scoring of colonic inflammation in dogs and cats have been proposed[36]; however, there is currently no universally approved grading system. Consequently, various pathologists may give different interpretations when evaluating the same mucosal sample.[37] Lymphoplasmacytic colitis is the most common form of chronic colitis. It may occur in young dogs (often associated with diet-responsive disease) as well as in older dogs (often associated with IBD). Eosinophilic inflammation may occur in association with IBD, or result from parasite infestation. Pyogranulomatous colitis is uncommon and associated with proliferative masses (millimeters to centimeters in diameter) visible during colonoscopy or palpable rectally. Affected dogs show severe clinical signs.[38] Suppurative colitis has been reported as a probable variant of IBD in cats and often responds to the empirical treatment of colitis.

Treatment and Management

In many instances, treatment of colonic IBD can be initiated after known causes of large intestinal disease have been ruled out. Empirical treatment should focus on a dietary approach and the use of several drugs with limited side effects. A precise assessment of the disease with colonoscopy and histopathologic evaluation of mucosal samples is required prior to using glucocorticoids or other immunosuppressive drugs. These drugs can have multiple side effects and may also hamper the success of further diagnostic efforts.

Several clinical reports describe the dietary approach to dogs and cats with histologically documented chronic colitis and large intestinal IBD (see Table 58-4).[28-31,39,40] Diets recommended for patients with chronic colitis include elimination diets (based on a novel

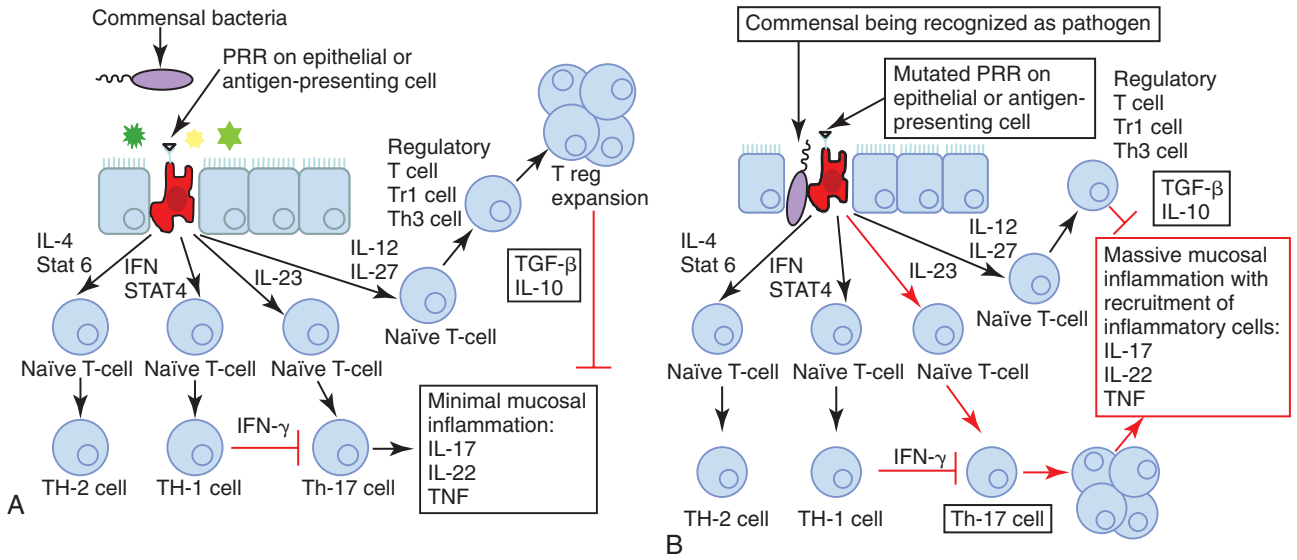

Figure 58-7 Proposed mechanism of oral tolerance against commensal organisms and pathogenesis of IBD. **A,** The pathogenesis of IBD involves three factors: the mucosal barrier, including an intact epithelial cell lining; the host immune system consisting of innate immunity and adaptive immunity; and microbes and food antigens in the intestinal lumen. The interplay of these three factors is important to maintain intestinal homeostasis. In the normal case scenario, antigen-presenting cells continuously sample antigens from the intestinal lumen through pattern recognition receptors (PRRs). Depending on the nature of these antigens, the signals elicited by the antigen-presenting cells drive the adaptive immune response in the appropriate direction to eradicate a pathogen. For example, in the case of a parasite, naive T cells are preferentially driven to differentiate into T-helper (Th) 2 cells that recruit eosinophils, basophils, and mast cells to kill the parasites. In the case of a pathogenic virus, the naive T cells preferentially differentiate into Th1 cells that produce cytokines such as interferon (IFN)-γ. These cytokines recruit macrophages that phagocytose and kill intracellular viruses. In the case of pathogenic bacteria being recognized, naive T cells preferentially differentiate into Th17 cells to produce proinflammatory cytokines such as interleukin (IL)-17 and IL-22. This recruits T cells and neutrophils to kill extracellular bacteria. In the case of commensal bacteria being recognized through PRRs, naive T cells preferentially differentiate into T-regulatory cells that counteract the effect of proinflammatory cytokines produced by Th17 cells. **B,** In the case of IBD, a primary defect in the recognition of commensals or certain pathogens by innate immune receptors may play a causative role. Mutations in PRRs lead to misrepresentation of commensals as pathogens, leading to the massive production of IL-23, driving naive T cells to differentiate into Th17 cells. These Th17 cells then produce large amounts of proinflammatory cytokines, such as IL-17, IL-22, and tumor necrosis factor (TNF). This leads to tissue destruction and epithelial cell injury, letting even more antigens pass through to the lamina propria. This inflammatory response cannot be counterregulated by regulatory T cells, leading to the characteristic inflammatory pattern seen in IBD.

protein or on hydrolyzed peptides),[28,40] and highly digestible, low-residue diets.[29,39] Most dogs and cats with colitis respond within 2 weeks to a diet change, some however may require up to 6 weeks. It is important to communicate the importance of exclusive feeding of the diet to the animal's owner, especially if an elimination diet is chosen. Recommendations regarding the required duration of dietary therapy after clinical remission diverge significantly. Although in one study most dogs relapsed after being fed their original pretreatment diet again,[39] many of the dogs could be switched again to their pretreatment diet after varying time periods in another study.[28] Consequently, it is important to discuss the risks and benefits of a reexposure to the regular diet with the patient's owners in each case to enable them to make an informed decision about their pet.

Dietary fiber consists of nondigestible complex carbohydrates. The addition of soluble fiber to the diet has provided additional benefits in clinical studies of canine and feline chronic colitis.[30,31] Fermentable fibers are metabolized to short-chain fatty acids by the large intestinal flora and provide a useful source of energy to the colonocytes. Overall, they enhance structure and function of the intestinal epithelium.[41] Examples of fermentable fibers include beet pulp, psyllium, and fructooligosaccharides. Fructooligosaccharides are oligosaccharides that resist digestion in the small intestine and are fermented by the colonic bacterial flora. Their beneficial effects on the large intestine include proliferation of colonocytes by increasing blood flow to the colonic mucosa and promotion of epithelial cell differentiation into fully functional colonocytes.[41] Additionally, fructooligosaccharides are prebiotics and therefore are able to influence the composition of the large bowel commensal flora. In cats, they were reported to increase colonic fecal concentrations of *Bacteroides* and *Lactobacillus* spp. and decrease those of *E. coli* and *C. perfringens*.[42] Finally, dietary fibers also have beneficial effects on colonic motility. As a tradeoff, addition of fiber to the diet may have a negative impact on nutrient digestibility, depending on the specific fiber type. Some fibers may also delay gastric emptying time and slow small intestinal transit time.[41] Psyllium is a soluble fiber derived from the seed of *Plantago ovata*. It has great water-holding capacities and forms gels in water, two properties that can contribute to improvement of fecal consistency. Psyllium was very efficient when added to a highly digestible diet in the treatment of chronic idiopathic colitis using the following initial daily dosage: 0.5 tablespoons (T) for toy breeds, 1 T for small dogs, 2 T for medium dogs, and 3 T for large dogs.[31] The fiber supplement should be administered with each meal, and the dose adapted to effect.

Probiotics are live microorganisms that may be beneficial to the host GI tract. Canine- and feline-specific probiotic cocktails are available commercially. However, the achievable benefits of modification of the large intestinal flora by administration of probiotics are subject to controversy. To date, no clinical study has been able to document positive effects of probiotics in dogs and cats with chronic GI diseases,[43] even though in vitro experiments yielded promising results.[44]

Table 58-5 Pharmaceutical Therapy of Large Bowel Inflammation

Drug Category and Name	Dosage Recommendation	Indication
Antimicrobials		
Enrofloxacin	5 mg/kg PO once daily (D)	HUC
Metronidazole	10 to 15 mg/kg PO BID (D, C) to TID (D) For metronidazole benzoate increase above dose by approximately 50%	Acute and chronic colitis
Antiinflammatory Drugs		
Sulfasalazine	10 to 30 mg/kg PO TID for 4 to 6 weeks, max 1 g total dose (D) 5 to 12.5 mg/kg PO TID for 2 to 4 weeks (C) Administer with food; slowly decrease in 10- to 14-day steps to BID, then half the dose BID, then once daily; regularly measure tear production	Colonic IBD refractory to diet and metronidazole
Immunosuppressive Drugs		
Prednisone	1 to 2mg/kg PO bid for 10 to 14 days, then slow tapering over several weeks	Colonic IBD refractory to diet and antibiotics
Azathioprine (D)	Starting dose 2 mg/kg PO once daily for 2 weeks, then 2 mg/kg every other day for 2 to 4 weeks, then 1 mg/kg PO every other day May take 2 to 4 weeks to take effect	Steroid-refractory colonic IBD
Chlorambucil (C)	Cats weighing >4 kg: 2 mg per cat PO every other day for 2 to 4 weeks then tapered to the lowest effective dose (2 mg/kg PO per cat every 3 to 4 days) Cats weighing <4 kg are started at 2 mg/kg per cat every third day	Refractory or severe feline IBD, combined with prednisolone
Cyclosporine (D)	5 mg/kg PO once daily for 10 weeks	Steroid-refractory chronic colonic IBD

C, cat; D, dog.

Pharmacologic intervention (Table 58-5) is required if dietary therapy fails to control clinical signs or may be initiated simultaneously to dietary changes in severe cases. Among antimicrobials, metronidazole is frequently used in the initial management of dogs and cats with colitis. Beside its antimicrobial effects against a variety of obligate anaerobic bacteria, metronidazole is also effective against *Giardia* spp. Furthermore, metronidazole has immunomodulatory effects.[45] It is used in dogs and cats with colitis to modify the intestinal flora (decrease in obligate anaerobes) and decrease inflammation. If a suspension is administered to a cat, metronidazole HCl is not a palatable formulation and may elicit ptyalism and anorexia. Metronidazole benzoate is the preferable formulation for feline patients, but it contains only 62% metronidazole and therefore requires a dose adjustment. Other side effects of metronidazole are rare, although cats may be more susceptible because of the probable increased half-life of the drug, and include vomiting and diarrhea. Hepatotoxicity and neurotoxicity have been reported at higher dosages.[45]

Sulfasalazine consists of 5-aminosalicylic acid (5-ASA; also called mesalamine [United States] or mesalazine [Europe]) linked by an azo bond to sulfapyridine, a sulfonamide compound.[46] Most of the orally administered sulfasalazine reaches the distal small intestine and colon unchanged. There, the microbial flora breaks the azo bond and liberates both molecules. Sulfapyridine is essentially a carrier molecule and is not thought to unfold any therapeutic effect. It is absorbed, metabolized in the liver, and filtered through the kidneys. The antiinflammatory effects of 5-ASA on the colonic mucosa are associated with inhibition of cyclooxygenase and a decrease in prostaglandin and leukotriene synthesis. Moreover, 5-ASA is an activator of peroxisome proliferator-activating receptor (PPAR)-γ.[46] In dogs, PPAR-γ are expressed at a high level in gastric, duodenal, and colonic mucosal epithelial cells.[47] They inhibit pathways leading to increased NF-κB transcription and hence to production of inflammatory cytokines and chemokines.[46] However, recent data do not support a decrease in PPAR in the colonic mucosa of dogs with colitis.[48] The main side effect of sulfasalazine is keratoconjunctivitis sicca (KCS). Although the exact mechanism of action is unknown, sulfapyridine is likely responsible for damaging lacrimal glands.[49] Early detection followed by treatment discontinuation is necessary to prevent the onset of irreversible KCS. Consequently, tear production must be measured at regular intervals in all dogs receiving sulfasalazine. Vomiting may also occur, and can be prevented if the drug is administered with food. Other drugs with the same mechanism of action are available and include olsalazine (two molecules of mesalamine linked by an azo bond) and other formulations of mesalamine coated with an acrylic resin that release the compound in the distal small bowel or colon. Although these drugs have not been extensively tested in small animals, KCS has been reported with their use in dogs.

Glucocorticoids are used as a second line of treatment in dogs with colonic IBD that are refractory to dietary modifications and treatment with metronidazole and sulfasalazine. Their antiinflammatory effects are partly a result of the lipocortin-mediated inhibition of phospholipase A that inhibits the cascade leading to formation of proinflammatory prostaglandin and leukotriene synthesis. Their therapeutic interest also relies on the multiple effects they have on both the innate and adaptive immune response.[50] However, because of their multiple side effects, immunosuppressive doses of prednisone should be reserved for dogs that have undergone colonoscopy, and for which a histologic diagnosis confirms the existence and type of the inflammatory infiltrate. Cats do not appear to develop as many side effects from glucocorticoid therapy as dogs. Additionally, cats may not tolerate TID medication with sulfasalazine, and are more susceptible to mesalamine toxicity. Moreover, many cats with colitis also have lesions in the small intestine (enterocolitis) on which sulfasalazine has no effect. This combination of facts makes glucocorticoids a treatment option that is often considered earlier in feline than in canine colitis patients.

In cases refractory to immunosuppressive doses of glucocorticoids, additional immunosuppressive drugs such as azathioprine (dogs only), chlorambucil (cats), and cyclosporine[51] may be helpful. Because of potential side effects and financial considerations, these drugs should be reserved for patients with well-documented colonic inflammatory disease that showed no response to any other treatment.

Prognosis

The prognosis for IBD is generally better when only the colon is affected. However, one retrospective study of dogs with IBD failed to find any association between localization of disease and outcome.[52] Nevertheless, the various clinical studies summarized in Table 58-4 demonstrate that a majority of dogs and cats with colitis will respond completely to dietary modification and/or to sulfasalazine treatment. If sulfasalazine is used, it can often be discontinued after a few weeks. However, there is a risk of recurrence when the animals are switched back to their original diet or a commercial diet. Therefore, the owners of dogs and cats with colitis should be prepared to feed their pets a special diet in the long-term, and consider the financial implications of the prolonged treatment. In a few cases, colitis may be refractory to treatment. This is probably most common in cats showing predominantly large bowel diarrhea, while in reality they have a general involvement of their GI tract (enterocolitis). In dogs with IBD, several negative prognostic factors have been identified that all reflect severe involvement of the small intestine, including hypoalbuminemia, hypocobalaminemia, severe duodenal lesions, and a high clinical disease score.[28,52] Therefore, they do not appear to apply to colonic IBD.

Histiocytic Ulcerative Colitis

Definition

HUC is a form of IBD that occurs most frequently in young Boxer dogs, also known as granulomatous colitis of Boxer dogs. It was first described 30 years ago[53] and has since been reported to occur in many countries, including the United States,[54-56] Australia,[57,58] Japan, and continental Europe and the United Kingdom.[59,60] HUC also occurs infrequently in other breeds, such as Mastiffs, Alaskan Malamutes,[61] French Bulldogs,[62] and English Bulldogs,[56] and has also been described in one cat.[63]

Pathophysiology and Mechanism

The mechanisms involved in the pathogenesis of HUC in dogs have been debated for decades. The recent success of antibiotic treatment raises the question of an infectious origin; however, this hypothesis has been investigated previously. The role played by macrophages containing cytoplasmic material stained by periodic acid-Schiff (PAS) is intriguing, and early electron microscopic studies have demonstrated so-called residual bodies, which resemble bacteria-like organisms in granules of PAS-positive macrophages.[64] These particles contained parallel pairs of membranes and electron-dense particles ranging in size from 100 to 500 nm, and may have represented bacterial cell membranes. Therefore, specific infectious agents, such as *Mycobacteria*, *Mycoplasma*, *Chlamydia*, and *Rickettsiales* ssp. have all been proposed to play a role in the pathogenesis of the disease.[55] However, attempts to reproduce the disease by infecting dogs with *Mycoplasma* spp. have failed.

Some reports have compared human Whipple disease with canine HUC. Whipple disease is caused by *Tropheryma whipplei* and mainly affects the small intestine. There is a striking histologic resemblance between both diseases involving severe granulomatous inflammation and distortion of the intestinal lamina propria. The causative organism in Whipple disease is susceptible to a variety of antibiotics, such as penicillin, chloramphenicol, and tetracycline, but seems to be resistant to fluoroquinolones. *T. whipplei* has not yet been identified in dogs with HUC, but the recent treatment success with enrofloxacin seems to make this organism less likely to be causally involved.

In a recent publication investigating the possibility of an infectious cause for canine HUC, large numbers of coccobacilli were found in the colonic mucosa by fluorescence in-situ hybridization (FISH) in Boxers affected with HUC but not in histologically normal tissues or in the mucosa of dogs with other types of colitis.[65] Further studies using culture, cloning, and sequencing of the colonic flora from Boxers with HUC identified the bacteria to be *E. coli*. Electron microscopy of HUC lesions allowed identification and localization of the bacteria to the intracellular compartment of PAS positive macrophages.[65] Additionally, the intracellular material found in PAS-positive macrophages from dogs with HUC was positively labeled with polyclonal antibodies against *E. coli*.[66] Further classification of the virulence genes and biologic behavior of these bacteria in coculture with epithelial cells and macrophages revealed specific adhesive and invasive properties.[65] The *E. coli* strains associated with HUC have a similar phenotype with adhesive and invasive behavior resembling *E. coli* isolates that were recently associated with Crohn's disease in people.[65] In several studies, a particular strain of *E. coli* (LF82) could be detected in biopsies of 20% to 35% of ileal lesions in Crohn's disease, but only in 6% of ileal samples from healthy controls or other colonic inflammatory diseases.[67] Crohn's disease affects primarily the mucosa and submucosa of the ileum and colon. It resembles canine HUC in its histologic appearance, as granulomas are the main feature of the disease. As in canine HUC, some cases of Crohn's disease are responsive to treatment with antibiotics. The *E. coli* strain LF82 that has increasingly been associated with Crohn's disease is unusual because it adheres to and invades intestinal epithelial cells in culture[68] and has been shown to replicate within the phagolysosomes of macrophages in the granulomatous lesions[69] instead of being cleared by the adaptive immune system. There is evidence that the adhesive and invasive *E. coli* associated with HUC are taken up by endosomes and persist in the macrophages instead of being cleared.[65] These findings support the hypothesis that genetics play a major role in the pathogenesis of Crohn's disease, and has led to recent genome-wide association studies in canine HUC. Certain defects in pattern-recognition receptors (PRRs) of the innate immune system have long been known to be associated with the development of Crohn's disease.[70] These receptors are important for the interaction of the mucosal innate immune system with the microflora of the intestinal lumen. The default response of the gut-associated lymphoid tissue is to clear offending pathogens, but to tolerate commensal organisms from the intestinal lumen.[71] Recent evidence confirms that polymorphisms in certain PRRs, such as NOD2, result in a disturbed response of human monocytes to *E. coli* LF82, linking genetics with functional disease for the first time.[72] Preliminary results from genetic studies in Boxers with HUC and healthy controls point to a defect in a protein in neutrophils that leads to defective clearance in *E. coli* in macrophages.

The inflammatory response normally only occurs as a reaction toward pathogenic bacteria breaching the intestinal barrier, and resembles the lesions observed in the mucosa of people affected with Crohn's disease and dogs with HUC. It is therefore possible that similar defects in PRRs occur in people with IBD and in dogs with HUC. A genetic predisposition for HUC is suspected due to the

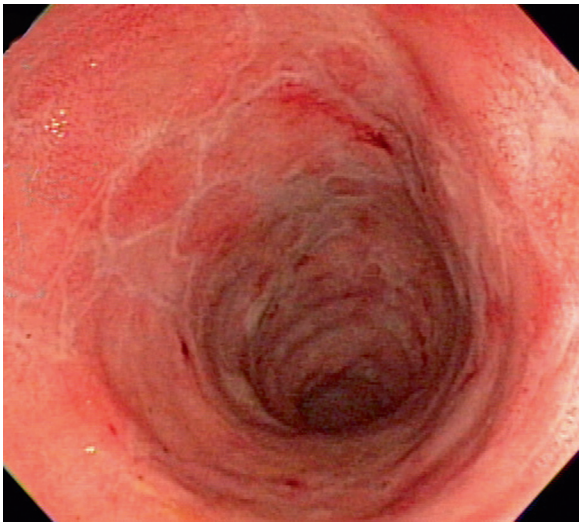

Figure 58-8 Endoscopic view of the descending colon from a dog with severe lymphoplasmacytic colitis. Note the honeycomb pattern that reflects mucosal edema and inflammation.

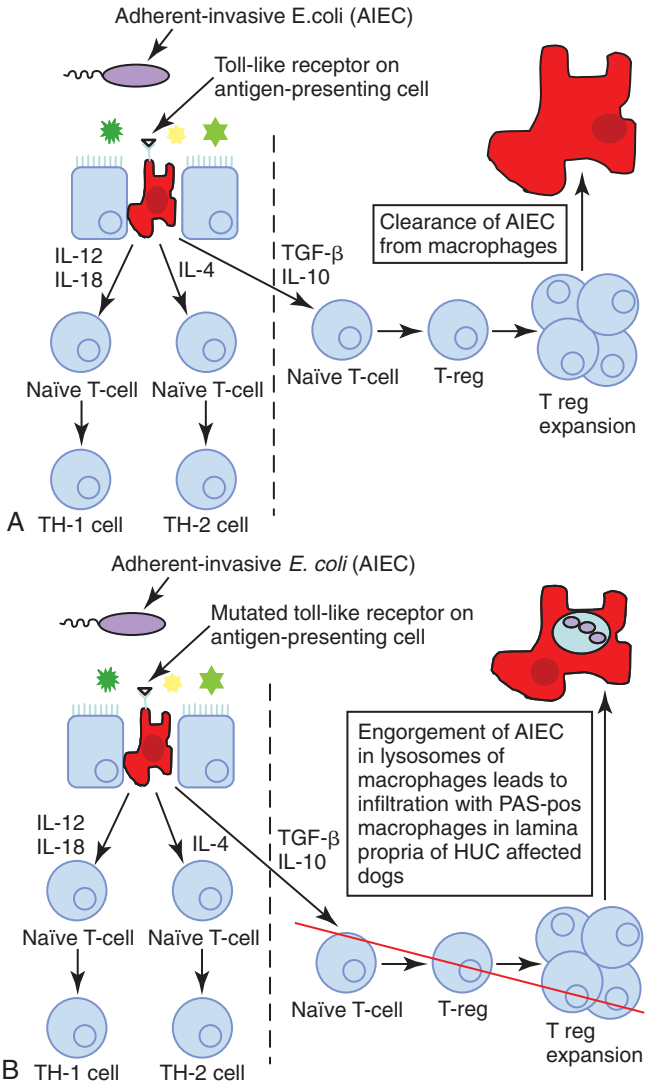

Figure 58-9 **A,** In the normal case scenario, various pathogens in the intestinal lumen, such as bacteria, viruses, and fungi, bind to PRRs on the surface of antigen-presenting cells, such as TLRs. To prevent infection, the innate immune system activates adaptive immune processes by promoting proinflammatory cytokine expression of T cells, such as tumor necrosis factor (TNF), interferon (IFN)-γ, and interleukin (IL)-17. This results in appropriate expansion of the relevant T cells to clear the infection, such as T-helper (Th) 1 cells for viruses and Th2 cells for parasites. In the case of normal commensals and adhesive–invasive *E. coli* (AIEC) in an animal not affected by HUC, T-regulatory cells will produce antiinflammatory cytokines such as IL-10 and transforming growth factor (TGF)-β, which leads to suppression of an inflammatory adaptive immune response and tolerance toward these bacteria. **B,** Hypothetical explanation for the pathogenesis of HUC. Mutations in pathogen recognition receptors, such as TLRs, lead to inappropriate activation of the adaptive immune system. In the case of AIEC, there is no expansion of T-regulatory cells, which results in engorgement of macrophages with AIEC within their lysosomes. The colonic lamina propria in dogs with HUC is filled with macrophages which stain positive for intracellular AIEC.

preponderance of cases in young boxer dogs. In the first report of the disease in 1965, most of the affected dogs could be traced to a single ancestor.[53] Confirmation and identification of mutations in PRRs such as TLRs or NODs in boxers with HUC is still lacking. However, it seems likely that a defect in innate immunity renders dogs with HUC more susceptible to infections with specific bacteria, such as the adhesive and invasive *E. coli* strains described previously (Figure 58-8).

Differential Diagnoses

Typically, HUC is characterized by chronic large intestinal diarrhea in relatively young dogs. Differential diagnoses include parasitic diseases such as infestation with *Trichuris vulpis* or *Giardia* spp., bacterial infections with *Campylobacter* or *Clostridia*, infections with oomycetes (*Pythium* spp.) and fungal microorganisms (*H. capsulatum*), as well as diet-responsive diseases such as food intolerance or food allergy. Further differentials include IBD other than HUC, such as lymphoplasmacytic and eosinophilic colitis. Rectal and colonic polyps as well as neoplastic disorders, such as lymphoma or adenocarcinoma, are less likely to occur in younger animals.

Evaluation of the Patient

History

The onset of disease occurs predominantly before 2 years of age. The clinical signs are those of severe chronic large intestinal inflammation and comprise diarrhea, hematochezia, increased frequency of defecation, tenesmus, and presence of excessive mucus in the feces.

Physical Examination

Physical examination findings are normal in many cases of HUC. However, weight loss and inappetence can be seen in severe cases, and should prompt further more invasive investigations. Fresh blood and mucus can be seen upon rectal examination.

Diagnostic Investigation

The diagnostic approach to cases with HUC is as described for chronic colitis. Typically, colonoscopy reveals sites of severe colonic hemorrhage and ulceration interspersed with stretches of normal appearing mucosa (Figure 58-9). Ten to 15 biopsies should be taken for histopathological analysis. Early lesions can consist of a mixed inflammatory infiltrate in the lamina propria, subjacent to degenerative epithelium.[53,55,73,74] With more extensive lesions and chronic disease, the ulcers become more visible on histology with severe infiltration of the lamina propria and the submucosal regions with

neutrophils, macrophages, lymphocytes, plasma cells and mast cells. There is also usually marked loss of the epithelial surface in biopsies from lesions and loss of goblet cells in the entire colon. Accumulation of large PAS-positive macrophages is pathognomonic for HUC[54,73,75] and remains the best way to confirm the diagnosis (Figure 58-10). In immunohistochemical studies HUC lesions are characterized by an increased number of L1-positive cells (Figure 58-11), as well as major histocompatibility complex (MHC) class II-positive cells, CD3-positive cells, and IgG-positive plasma cells.[60] L1 is a cytosolic calcium-binding protein, the function of which has not been described in detail in the dog. In humans, it is expressed by macrophages and neutrophils at an early stage in their differentiation and is lost when macrophages migrate into tissues and mature. It is possible that in canine HUC recently emigrated blood monocytes progressively differentiate into tissue macrophages, and become eventually filled with PAS-positive material, while L1 expression is downregulated.[55] MHC class II molecules are normally present on macrophages. Therefore it is not surprising to find an increased MHC class II expression associated with PAS-positive macrophages in HUC. Increased T-cell numbers were observed in HUC and are reminiscent of increased numbers of CD3-positive cells seen in other forms of canine IBD, particularly lymphoplasmacytic IBD.[60] Confirmation of the presence of *E. coli* using FISH analysis on formalin-fixed biopsies is now recommended as part of the detailed diagnostic work-up for dogs with suspected HUC.[75a] Up to 43% of dogs with HUC develop enrofloxacin resistance early in the disease process and may be refractory to treatment if they are treated without taking bacterial culture results into account.[75b]

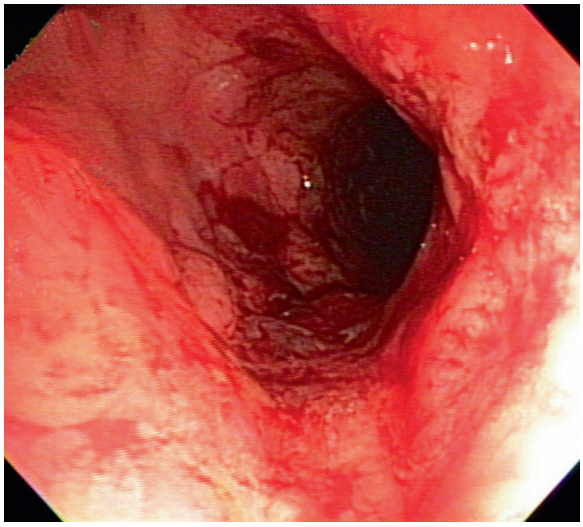

Figure 58-10 Endoscopic view of the descending colon in a young Boxer dog with histiocytic ulcerative colitis (HUC). The mucosa is very irregular, with discolored swollen areas interspersed with fistulae and spontaneous bleeding is observed. The final diagnosis was made after histopathologic evaluation of colonic mucosal biopsies.

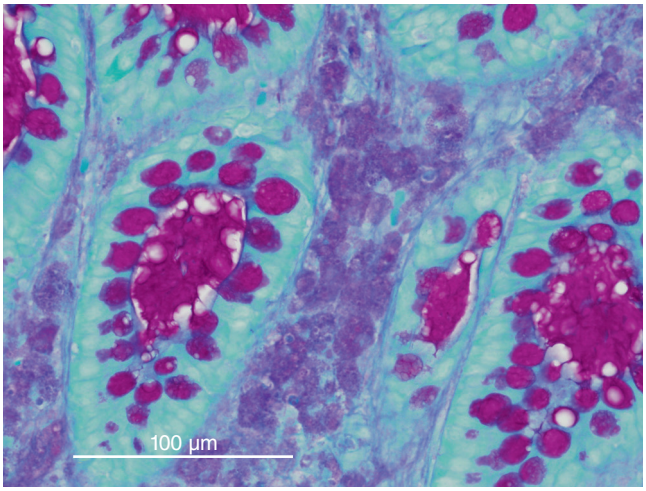

Figure 58-11 Photomicrograph of the colonic mucosa from a Boxer dog with HUC (PAS). The transversely cut colonic crypts have dark magenta-colored mucus in their goblet cells and lumen. There is an inflammatory infiltrate in between the crypts with large mononuclear cells with purple, heterogeneous material in their cytoplasm. This material represents in part phagocytosed *E. coli*. The granulomatous infiltrate and the PAS staining of infiltrating macrophages are diagnostic of HUC.

Treatment and Management

The prognosis for HUC was considered to be guarded to poor until recently. Management of HUC used to consist of various combinations of dietary modification (e.g., increasing fiber content and specific elimination diets), and antiinflammatory or immunosuppressive treatment with sulfasalazine, prednisone, and azathioprine, as described previously for the treatment of chronic colitis. Typically these strategies were not successful, and most cases had to be euthanized because of refractoriness to treatment. In recent years two reports have sparked hope for treatment of HUC: a total of 35 cases have been described and have shown a dramatic response to treatment with enrofloxacin (5 mg/kg PO once daily), or a combination protocol with enrofloxacin, amoxicillin (20 mg/kg PO twice daily), and metronidazole (10 to 15 mg/kg PO twice daily).[56] Reports of the disease almost 30 years ago also occasionally described a good response to treatment with antibiotics, namely chloramphenicol and tetracycline.[76] The response to treatment with enrofloxacin in the more recent reports was dramatic, with all dogs responding within 3 to 12 days of initiating therapy. It is particularly encouraging that several dogs were reportedly disease-free after the drug had been discontinued following a 4- to 6-week course of treatment.[56]

This implies that HUC can be cured in some cases. Five dogs were rebiopsied when they were in clinical remission after completion of the antibiotic treatment. A dramatic improvement in the histologic lesions was evident in all cases, with disappearance of PAS-positive macrophages in three dogs and marked reduction in the number of macrophages in the other two cases.[56]

However, care must be taken to treat dogs with HUC long enough to avoid relapse after discontinuation of treatment. In addition, it may be prudent to send intestinal biopsies for culture and sensitivity before starting treatment, so that the use of antibiotics can be tailored to the specific sensitivity profile of the cultured *E. coli*.[75a,77]

Colitis Associated with Anal Furunculosis

Anal furunculosis (AF) is a chronic and painful disease of the anorectum in dogs that preferentially affects German Shepherd dogs and is characterized by inflammation, ulceration, and sinus tract formation. Clinical signs include a painful ulcerated perineal region that may cause tenesmus, hematochezia, and even anorexia and weight loss. Histologic evidence of colitis has been documented in several cases of AF.[78,79] This association is interesting because

chronic fistulation is frequently observed in people with Crohn disease. Moreover, PRRs are thought to play an important role in the pathogenesis of IBD in people and dogs, and have been the object of recent research in dogs with AF. One study found dysfunctional NOD2 responses in German Shepherd dogs with AF.[80] Moreover, a restricted allelic variation in TLR1, TLR5, and TLR6 was found in German Shepherd dogs. However, there were no significant associations between these PRR polymorphisms and AF. Nevertheless, these polymorphisms may influence innate immune responses in German Shepherd dogs and may be an important predisposing factor for the development of AF in that breed.[81] In other studies, increased prevalence of a specific haplotype of alleles of genes encoding class II molecules of the canine MHC was shown in German Shepherd dogs with AF, suggesting a possible defect in antigen presentation associated with the disease.[82] Finally, it is noteworthy that feeding a restricted antigen diet maintained more than 80% of dogs with AF in complete remission after en bloc surgical excision and anal sacculectomy,[83] and that both AF and IBD respond to treatment of immunosuppressive drugs such as prednisone and cyclosporine.[84] These similarities underline the possibility of a comparable pathomechanism for both diseases.

Typhlitis

Definition

Typhlitis refers to inflammation of the cecum and is a rare condition in small animals.

Pathophysiology and Mechanism

There are few case reports that describe typhlitis in association with concurrent inflammation of the ileum and/or colon in dogs. The inflammation has been reported to be predominantly eosinophilic in one dog. Little is known about the pathomechanism of disease, but it is likely that the pathogenesis is similar to lymphoplasmacytic and/or eosinophilic IBD in the small and large intestine.

Differential Diagnoses

Typhlitis usually presents in combination with enteritis or colitis, and the clinical signs are associated with small and/or large intestinal chronic diarrhea. In addition, the anatomical location of the cecum makes it more likely that severe inflammation could result in signs of intestinal obstruction or pseudoobstruction. Consequently, differential diagnoses include infectious and inflammatory causes of enteritis and colitis such as *T. vulpis*, as well as causes for obstruction, such as foreign bodies, abscesses, inversion of the cecum into the colon, fecaliths, or neoplasia.

Evaluation of the Patient

History and physical examination in patients with typhlitis resemble those for chronic small intestinal and/or large intestinal diarrhea.[85] In some cases, ileus or pseudoileus can occur as a consequence of obstruction of the cecum, which results in acute or chronic vomiting.[86,87] Radiography may reveal signs of partial or complete ileus. Abdominal ultrasound may show thickening of the cecal mucosa or evidence of obstruction in the cecal lumen. Endoscopy is recommended in all cases of suspected nonobstructive typhlitis as it allows direct visualization of the mucosa and collection of multiple endoscopic biopsies.

Management

If typhlitis occurs secondary to enteritis or colitis, the management consists of treatment of these diseases. If chronic typhlitis has led to obstruction or abscessation, surgical typhlectomy is the treatment of choice and usually results in a favorable prognosis.[86,87]

INFECTION

Jody L. Gookin

Infectious diseases of the canine and feline gastrointestinal tract are numerous and commonly affect function of the small and large bowel. The infectious agents included in this section are those for which the colon is a primary target of injury or for which signs of large intestinal disease are a dominant clinical feature.

Helminths

Heterobilharzia americana

Etiology

Heterobilharzia americana, a fluke parasite, is the causative agent of canine schistosomiasis in North America.[1-5] Infection is enzootic in the Southeastern and Gulf Coast of the United States. Raccoons are considered the most important reservoir host of the parasite. Domestic and wild canid infections are uncommon, but clinically significant. The major intermediate hosts are the freshwater lymnaeid snails, *Lymnaea cubensis* and *Pseudosuccinea columella*.

Pathophysiology

Infection is acquired when free-swimming cercaria, released from the snail intermediate host, penetrate skin. The cercaria migrate through the lung and liver where they mature into adult flukes and then to the terminal mesenteric veins to reproduce. Ova are deposited in the terminal branches of the mesenteric veins and work their way through the intestinal mucosa to the bowel lumen by secretion of proteolytic enzymes. When ova are excreted in feces and come into contact with water, they give rise to miracidia that penetrate susceptible snails to reinitiate the cycle. The presence of ova in the submucosa of the small intestine and colon elicits an intense granulomatous tissue reaction.[2] Lesions are characterized by epithelioid macrophages, usually surrounding parasitic ova, admixed with varying amounts eosinophils, neutrophils, lymphocytes, and plasma cells.[1,2] Ova that do not make it to the intestinal lumen may be hematogenously disseminated to distant sites, particularly via the portal vein to hepatic venules where ova-induced chronic inflammation can lead to hepatic fibrosis and organ failure. Ova and associated granulomatous inflammation may also be found in the pancreas and lungs.

Clinical Examination

Clinical signs range from profuse acute to chronic mucoid diarrhea and tenesmus. Signs of inappetence, weight loss progressing to cachexia, and bloody diarrhea of small bowel (melena) or large bowel (hematochezia) origin are common. Physical examination findings may include thickened loops of intestine, abdominal effusion, peripheral edema, and mild generalized lymphadenopathy. Dermatitis caused by cercarial penetration of the skin or coughing because of lung migration are uncommonly reported. Clinicopathologic abnormalities include anemia, hyperglobulinemia, hypoalbuminemia, eosinophilia, and proteinuria. Dogs with *Heterobilharzia* infection may present with clinical signs arising from moderate to severe hypercalcemia.[1,6] In 2 dogs with *Heterobilharzia* infection, and lack of evidence for malignancy, hypercalcemia was attributed to elevated parathyroid hormone-related peptide concentrations.[6]

Diagnosis

Diagnosis of *H. americana* is made by performing saline sedimentation of feces to observe ova containing miracidia and by the observation of motile miracidia released from ova when exposed to water.[7] In cases where infection is suspected, but ova are not observed in feces, diagnosis may be attempted by detection of circulating anodic antigen in serum by enzyme-linked immunosorbent assay (ELISA).[2]

Treatment

Treatment with high-dose praziquantel (25 mg/kg per os BID-TID for 2 to 3 days)[2,6] or fenbendazole (40 mg/kg per os once a day for 10 days)[8] is reportedly effective is resolving ova shedding and clinical signs.

Prognosis

The prognosis for acute infection is good. Chronic infections may result in liver fibrosis and organ failure.

Strongyloides tumefaciens

Etiology

Strongyloides tumefaciens is a feline threadworm parasite. Infections are rare and observed primarily in temperate regions of the United States Gulf Coast. Infections are more common in tropical and semitropical climates wherein favorable conditions for the free-living stages of the lifecycle can be obtained.

Pathophysiology

Infective larvae penetrate oral-esophageal mucosa or skin and are carried in the circulation to the lungs. Larvae break into alveoli, migrate up the airways, and are subsequently swallowed. Adult parasites are comprised exclusively of parthenogenetic female worms that burrow into the submucosa of the large intestine. Worms, eggs, and larvae reside in submucosal, epithelial-lined cavities where they elicit adenomatous proliferation and infiltration of macrophages, neutrophils, lymphocytes, plasma cells, and connective tissue resulting in visible nodules on the mucosal surface of the colon.

Clinical Examination

Infection is usually asymptomatic, but in clinical cases the parasite causes intractable diarrhea, particularly in young cats and kittens.[9-12] Adult parasites residing in the submucosa are associated with formation of whitish-colored, raised nodules and mucus on the mucosal surface of the colon. Each nodule has a central depression corresponding to an epithelial-lined pore through which the cavities communicate with the lumen of the colon. Coalescence of nodules may give the appearance of adenomatous tumors.

Diagnosis

Embryonated ova are identified in fresh feces by fecal flotation. Larvae may be identified in feces by the Baermann technique and must not be confused with larvae of *Aelurostrongylus abstrusus*. Adult worms, eggs, and larvae may be observed in biopsy specimens of colonic mucosal nodules.

Treatment

Fenbendazole 50 mg/kg once a day for 5 days.

Prognosis

Good.

Trichuris spp.

Etiology

T. vulpis, the parasite responsible for whipworm infection, is likely one of the most common causes of chronic large bowel diarrhea in dogs. In cats, infections are rare and caused by *Trichuris campanula* and *Trichuris serrata*.

Pathophysiology

Worms of the genus Trichuris are parasites of large intestinal mucosa. Infection is transmitted by the fecal–oral route. Eggs are ingested and develop into larvae that hatch in the small intestine where they burrow into the epithelial crypts. Larvae subsequently migrate to the cecum and colon where they develop into adults. Adult worms tunnel their thread-like anterior body into the mucosa and use a mouth spear to puncture and shred tissue, blood vessels, and epithelial cells upon which they feed.[12,13] Heavy infections may produce severe typhlitis and colitis. Cecal inversion is uncommonly reported. Factors contributing to pathogenicity and clinical severity include the number and location of adult worms, degree of mucosal inflammation, severity of anemia or hypoproteinemia, nutritional status of the host, and presence of other GI parasites and microorganisms.[14]

Clinical Examination

Trichuris spp. can infect dogs of all ages. Many, if not most, infections are asymptomatic. Characteristic clinical signs are those of mucoid large bowel diarrhea with tenesmus and hematochezia. Signs may be acute, chronic, or intermittent. Severe infections may be accompanied by eosinophilia, anemia, and hypoproteinemia. Rarely, infected dogs have serum electrolyte abnormalities consistent with hypoadrenocorticism (hyponatremia and hyperkalemia). When tested, these dogs are normoresponsive to adrenocorticotropic hormone stimulation.[15]

Diagnosis

Characteristic bipolar operculated, thick-walled, unembryonated ova are identified by routine fecal flotation. Immature adults can cause severe disease and adults are sporadic egg producers. Accordingly, repeated fecal examination may be necessary to identify ova and negative fecal examinations do not rule out infection. Empirical treatment for occult *Trichuris* infection should always be performed before moving on to a more detailed, costly, and unnecessary medical investigation. Ova of the feline trichurids, *T. campanula* and *T. serrata*, may be easily confused with pseudoparasites, for example, ova of *Trichuris* or *Capillaria* spp. that parasitize feline prey and pass unaltered into feline feces.

Treatment

Drugs effective for treatment of *Trichuris* spp. infections include fenbendazole and febantel. The latter drug is partially metabolized to fenbendazole and oxibendazole. Regular use of milbemycin oxime for heartworm prevention is also effective for treatment and prevention of *T. vulpis* infection.[16] Immature worms are less susceptible to drug treatment and it takes approximately 3 months for larval stages to mature to egg-laying adults. Therefore, treatment should be repeated in 3 weeks and again in 3 months. Whipworm ova survive for prolonged periods of time in the environment and dogs housed in areas that are difficult to decontaminate (e.g., on dirt) may need to be retreated every 2 to 3 months. When possible, feces should be collected and removed.

Prognosis

Excellent.

Protozoa

Balantidium coli

Balantidium coli is a ciliated protozoan that primarily infects swine and nonhuman primates.[17] The infection is rare in dogs[18-22] and is frequently associated with exposure to swine. Trophozoites reside in the colon and result in ulcerative colitis.[19] Dogs are frequently coinfected with *T. vulpis*.[18,20] Clinical signs consist of chronic hemorrhagic colitis. Diagnosis is based on demonstration of large ciliated protozoa with prominent macronuclei in fresh saline smears of diarrheic feces or cysts in feces following zinc sulfate flotation. The distinctive macronuclei of the trophozoite and cyst can only be seen after staining. Treatment for any concurrent helminth infection may alone be curative in some cases.[20] Because of their effectiveness in people, specific therapy for *B. coli* is likely to be attained with tetracycline or metronidazole.

Entamoeba histolytica

Entamoeba histolytica is the causative agent of human amebic dysentery. Infection in dogs[23,24] and cats is rare and acquired by ingestion of food or water contaminated by human or nonhuman primate feces containing infective cysts. Trophozoites dwell in the lumen of the colon and invade the submucosa by secreting lytic factors that allow them to undermine and ulcerate the mucosa. These pathogenic effects result in ulcerative to necrotic colitis and bloody, mucoid large bowel diarrhea. Rarely, trophozoites disseminate to other organs.[24] Diagnosis is made by finding ameboid trophozoites in wet-mount preparations of fresh diarrheic feces, quadrinucleated cysts in feces following zinc sulfate flotation, or trophozoites in colonic biopsy specimens. Treatment with metronidazole alleviates clinical signs of colitis, but dogs may continue to shed trophozoites.[25]

Tritrichomonas foetus

Etiology

T. foetus is a flagellated protozoan characterized by three anterior flagella and an undulating membrane. Trichomonads are obligate parasites of warm, moist and anaerobic sites within the gastrointestinal or genitourinary tract of their hosts. Trichomonads do not form cysts, reproduce by binary fission, and are transmitted directly from host to host in the form of trophozoites. *T. foetus* was first identified as a cause of chronic large bowel diarrhea in cats in 2003 and the duration of its existence in cats prior to that time is unknown.[26] The prevalence of *T. foetus* infection is high among densely housed cats (31% of 117 cats from 89 catteries sampled at an international cat show).[27]

Pathophysiology

In cats, *T. foetus* colonizes the distal ileum and colon where trophozoites can be found in close proximity to the surface of the mucosa or in the lumen of colonic crypts.[28] Less commonly, subepithelial invasion of trichomonads may also be observed. Inflammatory infiltrates consist of plasma cells, lymphocytes, and neutrophils.[29]

Clinical Examination

Cats with symptomatic *T. foetus* infection are generally young. Asymptomatic infection in older cats may be common. Cats originating from a cattery (e.g., purebred) or shelter appear to be at increased risk for infection because of a history of dense housing. A true breed predisposition has not been shown.[27] Clinical signs are characterized by a waxing and waning large bowel diarrhea with occasional fresh blood and mucus. Diarrhea is semiformed to cow pie in consistency and malodorous. The anus may appear inflamed and painful; involuntary dribbling of feces or rectal prolapse may be present. Despite these clinical signs, most cats maintain good health, and normal appetite and body condition.

Diagnosis

Feline *T. foetus* infection may be diagnosed by identifying the organism in feces by direct saline smear examination, selective protozoal culture, PCR using species-specific primers, or by observation of trichomonads in colonic mucosal biopsy specimens. The sensitivity of direct fecal smear examination for diagnosis of *T. foetus* is low (2% in cats with experimentally induced infection and 14% in cats with spontaneous disease). *T. foetus* trophozoites are often misdiagnosed as *Giardia* and can be difficult to distinguish from nonpathogenic trichomonads such as *Pentatrichomonas hominis*. If repeated direct microscopic examination results are negative for *T. foetus*, feces may be cultured in commercially available pouches marketed for diagnosis of *T. foetus* infection in cattle (In Pouch TF, Biomed Diagnostics, White City, OR). Neither *Giardia* spp. nor *P. hominis* organisms survived in In Pouch TF for longer than 24 hours in one study; consequently, positive cultures are strongly suggestive of *T. foetus* infection.[30] A sensitive and specific single-tube nested PCR based on amplification of a conserved portion of the *T. foetus* ribosomal RNA (rRNA) gene unit from feline feces is commercially available (http://www.JodyGookin.com). Nested PCR assays are believed to be superior to fecal culture for diagnosis of infected cats.[31] Histopathology should not be relied upon to make a diagnosis of *T. foetus* infection, although a diagnosis can be attained if organisms are identified.[29]

Treatment

Ronidazole has been demonstrated to be effective at killing feline isolates of *T. foetus* in vitro and eradicated *T. foetus* from experimentally infected cats (on the basis of PCR).[32] The recommended dose is 30 mg/kg q24h PO for 14 days. Ronidazole is not registered for human or veterinary use in the United States and is currently banned for use in food-producing animals because of human hazards. Neurotoxicosis may be a common and serious side effect. Therefore, treatment with ronidazole should only be considered in cases of confirmed *T. foetus* infection where informed consent has been obtained. Follow-up testing by PCR is recommended if diarrhea persists longer than 2 weeks post treatment. Importantly, negative results should be interpreted with caution as PCR cannot prove the absence of infection and prolonged asymptomatic carriage of the organism after antimicrobial therapy may be common.

Prognosis

For single-cat households where reinfection is improbable, the prognosis for eradication of *T. foetus* infection with ronidazole is generally good. When left untreated, 88% of cats with *T. foetus* infection had spontaneous resolution of diarrhea within 2 years (median: 9 months; range: 5 months to 2 years). Time to resolution of diarrhea was significantly longer for cats from multiple-cat households, and those receiving a variety of different diets and antimicrobial drugs in an attempt to treat the condition. Importantly, spontaneous resolution of diarrhea does not imply recovery from infection, as 57% of these cats remain infected with *T. foetus* as determined by PCR when performed 2 to 5 years after diagnosis.[33]

Fungi

Histoplasma capsulatum

Etiology

H. capsulatum is a dimorphic fungus whose free-living mycelial stage flourishes in warm, moist, and nitrogen-rich (contaminated with bird or bat excrement) soil. Although sporadic cases may occur throughout the United States, most infections are diagnosed in animals living or traveling in the Ohio, Missouri, and Mississippi River valleys.

Pathophysiology

Fungal spores (macro- and microconidia) are inhaled and develop into yeast in the lung parenchyma. The yeast are ingested by macrophages wherein they reproduce by budding and may be disseminated via the blood and lymphatics to organs rich in mononuclear phagocytes including the GI tract, lymph nodes, liver, spleen, and bone marrow. Intestinal involvement in the absence of lung disease in many cases suggests that ingestion may also be a route of infection, however experimental studies have failed to produce GI disease reliably after oral administration of *H. capsulatum* spores.[34] Intestinal infection results in a granulomatous inflammatory response, mucosal ulceration, and blood loss.

Clinical Examination

Dogs with intestinal histoplasmosis are typically young, large breed, and have chronic diarrhea, inappetence, weight loss, pale mucous membranes, and fever that is unresponsive to antibiotics.[35] Although signs of large bowel diarrhea (tenesmus, mucus, and fresh blood in the feces) predominate, the small bowel is invariably involved and may result in a voluminous, watery stool, melena, and accompanying protein-losing enteropathy. Clinical signs of intestinal involvement are identified less commonly in cats.[36] Other historical and physical examination findings will depend on organ and tissue involvement.

Diagnosis

Definitive diagnosis of intestinal histoplasmosis is made by demonstrating *Histoplasma* organisms within mononuclear phagocytes by exfoliative cytology, intestinal biopsy, or tissue aspirates. Rectal mucosal scrapings, imprints of colonic biopsy specimens, and aspirates of liver, lung, spleen, and bone marrow are most productive in the dog.[34] For formalin-fixed, paraffin-embedded biopsy specimens, special staining (PAS, Gomori methenamine silver) is needed to demonstrate the organisms. Fungal culture is not recommended as this fosters growth of the mycelial phase, thereby increasing the risk of human inhalation of infective microconidia. Serologic and intradermal skin tests to diagnose histoplasmosis currently lack suitable sensitivity and specificity for clinical use.

Treatment

Itraconazole (10 mg/kg PO q12-24h) is the drug of choice for treatment of systemic histoplasmosis.[34,37] Amphotericin B may be combined with itraconazole in cases of severe or fulminating infection. In general, treatment is continued for 2 to 3 months beyond remission of clinical signs and for a minimum of 4 to 6 months. Symptomatic treatment may alleviate clinical signs of intestinal disease. Recommended therapies have included dietary modification (highly digestible diet for small intestinal disease, increased fiber diet for large intestinal disease), antibiotics for control of intestinal bacterial overgrowth, direct antidiarrheal drugs, and antiinflammatory drugs such as the 5-aminosalicylates.[38,39]

Prognosis

Depending on severity of clinical signs and systemic involvement, prognosis can vary from guarded to good.

Oomycetes

Pythium insidiosum

Etiology

P. insidiosum is an aquatic oomycete.

Pathophysiology

In an aquatic environment, *P. insidiosum* releases motile biflagellate zoospores that cause infection by penetrating and encysting in damaged skin and gastrointestinal mucosa. Gastrointestinal pythiosis is characterized by eosinophilic and pyogranulomatous inflammation and necrosis that localizes predominantly in the submucosal and muscular layers of the intestine[40] resulting in severe, segmental thickening that most frequently involves the gastroduodenal and ileocolic sections of the GI tract. However, multisegmental lesions and diffuse involvement of the GI tract have been described.[40-43] Infection may extend directly to adjacent tissues including the mesenteric lymph nodes, blood vessels, pancreas, uterus, and prostate.[40,41,44]

Clinical Examination

Pythium is identified most often in young, male, large breed dogs with recurrent exposure to warm freshwater habitats.[40,45] Gastrointestinal or cutaneous disease may be present, but are rarely found together in the same patient.[45] Gastrointestinal pythiosis in cats appears to be rare.[45] In dogs, GI pythiosis typically results in clinical signs of weight loss, vomiting, diarrhea, and hematochezia in association with a palpable abdominal mass on physical examination.[45] Hematologic and serum biochemistry abnormalities may include anemia, eosinophilia, hyperglobulinemia, and hypoalbuminemia. Cutaneous lesions consist of nonhealing wounds and invasive masses that contain ulcerated nodules and draining tracts.[45]

Diagnosis

A tentative diagnosis of gastrointestinal pythiosis is made by deep wedge biopsy of affected segments of intestine wherein broad, sparsely septate, and occasionally branching hyphae are demonstrated after staining with Gomori methenamine silver or anti–*P. insidiosum* antibodies.[45] Definitive diagnosis of *P. insidiosum* can be made using a species-specific nested PCR assay applied to DNA extracted from cultured isolates, appropriately preserved tissue samples (frozen at −70°C (−94°F) and stored in 95% ethanol at room temperature), or paraffin-embedded specimens.[45-47] Alternatively, a soluble mycelial antigen-based ELISA or Western analysis may be used to detect anti–*P. insidiosum* antibodies in the serum.[48]

Treatment

The treatment of choice for *P. insidiosum* infection is aggressive surgical resection. In the GI tract, 3- to 4-cm surgical margins (beyond tissue pathology) are recommended.[45] Because of frequent postoperative recurrence, postsurgical medical therapy with itraconazole (10 mg/kg PO q24h) and terbinafine (5 to 10 mg/kg PO q24h) is recommended.[45] Medication should be continued for 2 to 3 months at which time ELISA serology should be performed and compared with presurgical values. Medical therapy should be continued until serologic results (checked at 2- to 3-month intervals) are negative for *P. insidiosum* antibodies.[45] Medical therapy alone for treatment of pythiosis is unrewarding; this may be attributed to the

absence of cell membrane ergosterol (the target of most available antifungal drugs) in oomycetes.

Prognosis

Most dogs with GI pythiosis are presented late in the course of infection when complete excision is not possible. The anatomic site of the lesion may also preclude complete resection. Accordingly, the prognosis in most patients is guarded to grave.

Algae

Prototheca zopfii

Etiology

P. zopfii and *P. wickerhamii* are achlorophyllous algae that are ubiquitous to raw and treated sewage, slime flux of trees, and animal wastes with secondary contamination of the environment. *P. zopfii* is responsible for disseminated infections in dogs, whereas *P. wickerhamii* is responsible for cutaneous infections. Only the cutaneous form of infection has been described in cats.

Pathophysiology

It is presumed that *P. zopfii* is ingested by susceptible hosts, passes through the GI tract, replicates by endosporulation in the colon, and is subsequently disseminated to other organ systems via the blood and lymph. The kidney, liver, heart, brain, and eye are the most common sites of systemic dissemination. Inflammatory infiltrates are minimal in active lesions. Less commonly, however, pronounced granulomatous or pyogranulomatous inflammation may be observed.

Clinical Examination

Prototheca infection is predominantly identified in immunocompromised hosts. The most frequently reported clinical sign is intermittent and protracted bloody large bowel diarrhea. Other clinical signs depend on the organ systems involved and include acute renal failure, central vestibular disease, and posterior granulomatous uveitis.

Diagnosis

Diagnosis of protothecosis requires identification of the organisms by cytology, histopathology, or culture for *Prototheca* spp. High-yield, minimally invasive samples for diagnosis of disseminated disease include rectal scrapings, and urine for sediment examination and standard aerobic culture.[49] More invasive samples obtained by vitreocentesis, cerebrospinal fluid tap, or biopsy may be required as indicated by the existence of disseminated disease.

Treatment

Based on previous reports, and in the absence of susceptibility data, *P. zopfii* infection in dogs should be treated with amphotericin B alone or in combination with itraconazole. Aminoglycosides or tetracyclines should also be considered.[50]

Prognosis

The prognosis for disseminated *P. zopfii* infection is guarded to grave. Treatment may prolong the course of infection, but the outcome is uniformly fatal.

Bacteria

Bacterial causes of large intestinal disease in dogs are numerous and increasingly recognized with the advent of molecular diagnostics. Problematic to diagnosis of disease causation is the high prevalence of many of these "pathogens" in healthy animals. Table 58-6 summarizes the bacterial agents to which large intestinal disease have been attributed, their prevalence in normal dogs, clinical signs in symptomatic dogs, diagnostic approaches to their recognition, and efficacy of available tests for determining disease causation.

Anaerobiospirillum

Anaerobiospirillum spp. are small, Gram-negative, spiral bacteria that can be isolated from the throat and feces of normal dogs and cats. In a small number of cats, infection is associated with subacute to acute ulcerative or necrotizing ileocolitis with secondary sepsis. In histologic sections of intestine, *Anaerobiospirillum* were observed in intestinal crypts after staining with Giemsa or Steiner stains, and identified by 16S rRNA gene PCR.[51] Treatment in cats has not been described.

Brachyspira pilosicoli

Etiology

Infection of the mammalian large intestine by diverse populations of spirochetes has been recognized for many decades. Their role in causation of disease is still poorly understood. In dogs, three major groups of spirochetes have been identified in feces on the basis of selective culture, multilocus enzyme electrophoresis, and 16S rRNA gene sequence data: *B. pilosicoli*, *Brachyspira canis*, and *Brachyspira alvinipulli*.[52,53]

Pathophysiology

Pathogenic spirochetes intimately attach to the apical membrane of cecal and colonic epithelial cells. The mechanism(s) by which their cellular interaction results in diarrhea remains unclear. Spirochetes can be found in large numbers in the colonic crypts of normal dogs. In dogs with diarrhea, spirochetes can appear in the feces in large numbers. Whether the spirochetes are causal to the diarrhea or alternatively, mechanically dislodged from the crypts by diarrhea induced by other etiologic factors, remains an area of active debate. In a small number of cases, it has been observed that *B. pilosicoli* can be isolated from dogs with diarrhea and intestinal spirochetosis, whereas *B. canis* were commonly isolated from healthy dogs.[53,54] Furthermore, *B. pilosicoli* will attach to cecal epithelial cells from chicks, whereas *B. canis* will not.[55] Accordingly, the current presumption is that *B. pilosicoli* may be pathogenic and *B. canis* commensal. A characteristic, but not invariable feature of *B. pilosicoli* infection is the attachment of one pole of the spirochete to the intestinal epithelium, resulting in a dense "false brush-border."[53,56] Other pathologic changes include colonic inflammation, thickening of the colonic mucosa, and enlarged Peyer patches and lymphoid follicles.

Clinical Examination

Limited descriptions of diarrhea attributed to *B. pilosicoli* have been reported in dogs housed in pet shops and research colonies.[54,57] Diarrhea has been variably characterized as mucohemorrhagic, watery, or mucoid.[58] Diarrhea appears to be more common in puppies or when intestinal function is compromised by concurrent disease.

Diagnosis

A diagnosis of *B. pilosicoli* infection can be based on anaerobic culture of feces in selective media for isolation of spirochetes and multilocus enzyme electrophoresis, or demonstration of *B. pilosicoli* 16S rRNA genes in fecal samples or cultures by means of PCR.

Table 58-6 Bacterial Causes of Large Intestinal Disease in Dogs, Prevalence of Isolation From Feces of Normal Animals, Clinical Signs of Symptomatic Infection, and Diagnostic Approaches to Infection and Their Efficacy for Determining Disease Causation

Bacterial Agent	Prevalence in Normal Dogs	Clinical Signs	Diagnostic Tests	Utility for Diagnosis of Disease Causation
Brachyspira pilosicoli	6% to 66%	Watery, mucoid, or mucohemorrhagic large bowel diarrhea	Fecal culture in selective media and multilocus enzyme electrophoresis for identification of *B. pilosicoli*	Disease causation of *B. pilosicoli* unclear
			Polymerase chain reaction (PCR) identification of *B. pilosicoli* 16S rRNA in feces	
Campylobacter jejuni	≤90%	Watery, mucoid to bloody diarrhea	Characteristic darting motility observed in fecal wet mounts	None
			Fecal culture in selective media for *Campylobacter*	
			PCR-restriction fragment length polymorphism demonstration of *Campylobacter* genes in feces	
Clostridium perfringens	≥80%	Acute, nosocomial large bowel diarrhea	Fecal culture for *C. perfringens*	None
			Fecal cytology ≥3 endospores per high-power field	Poor
			PCR identification of *cpe* gene	Fair to good (in combination)
			Immunodetection of *C. perfringens* enterotoxin (CPE) in feces	
Clostridium difficile	≤40%	Mixed small and large bowel diarrhea ± acute hemorrhagic gastroenteritis	Fecal culture for *C. difficile*	None
			PCR identification of toxin A or B genes	None
			Immunodetection of toxin A ± toxin B in feces	Fair
			Immunodetection of toxin A ± toxin B in culture isolate of *C. difficile*	Good
Enteropathogenic *Escherichia coli* (EPEC)	≤7%	Acute-to-chronic, watery, sometimes hemorrhagic, diarrhea	Demonstration of attaching and effacing intestinal lesions by electron microscopy or immunofluorescence and absence of *Shiga*-like toxins	Good
			Demonstration of locus of enterocyte effacement (LEE)-associated genes (e.g., *eae*) in fecal extracts or bacterial cultures by PCR or DNA hybridization	Fair
Enterotoxigenic *Escherichia coli* (ETEC)	<3%	Nonbloody, watery, small bowel diarrhea	Demonstration of enterotoxin in fecal extracts or bacterial cultures by (a) Y-1 cell cytotoxicity assay or (b) enzyme-linked immunosorbent assay (ELISA)	Good (in combination)
			Demonstration of enterotoxin genes in fecal cultures by PCR and Southern blot hybridization	
Enterohemorrhagic *Escherichia coli* (EHEC)	≤5% (25% Greyhounds)	Watery or mucoid to hemorrhagic diarrhea	Demonstration of *Shiga*-like toxin in fecal extracts or bacterial cultures by (a) Vero cell cytotoxicity assay or (b) ELISA	Good (in combination)
			Demonstration of *Shiga*-like toxin encoding genes in fecal extracts or bacterial cultures by (a) PCR or (b) in-situ hybridization	
Salmonella	1% to 36%	Watery or mucoid to hemorrhagic diarrhea	Culture or PCR identification of *Salmonella* in feces	Poor
			Culture or PCR identification of *Salmonella* in sterile body fluids	Good

Treatment
The best treatment for *Brachyspira* spp. infection has not been identified.

Prognosis
Likely good, although specific treatment outcomes in dogs with confirmed infection have not been reported.

Campylobacter

Etiology
Campylobacter spp. (*C. jejuni*, *Campylobacter coli*, *Campylobacter helveticus*, and *Campylobacter upsaliensis*) are Gram-negative, microaerophilic, gullwing-shaped and motile, bacterial rods. *Campylobacter* can be cultured from the feces of up to 90% of normal dogs and cats, especially in young animals housed in dense populations such as breeding facilities and shelters.

Pathophysiology
Campylobacter is acquired from contaminated food and water sources and transmitted in contaminated facilities by a fecal–oral route. *Campylobacter* replicate in the lumen of the GI tract, penetrate the mucus lining of the intestine, adhere to the intestinal epithelium, and are variably internalized into the host epithelial cells. Virulence factors are expressed by different *Campylobacter* isolates and include enterotoxins, cytotoxins (e.g., cytolethal distending toxin), and adherence/invasion proteins. Lesions induced by *Campylobacter* infection include typhlitis and colitis characterized by epithelial cell death and attenuation, loss of the microvillus brush-border, depletion of goblet cells, and infiltration of colonic crypts by neutrophils culminating in the formation of microabscesses. The factors responsible for inciting resident *Campylobacter* to become invasive have yet to be determined, although changes in intestinal microflora, the presence of concurrent enteric pathogens, immunoincompetence, and poor environmental hygiene likely play contributory roles.

Clinical Examination
Dogs and cats with *Campylobacter*-associated diarrhea are typically young puppies or kittens, stressed by hospitalization, travel, concurrent disease, or dense housing conditions. Diarrhea ranges from mild loose feces, to watery diarrhea, to bloody mucoid diarrhea. Inappetence, vomiting, fever, and leukocytosis may also be present. Concurrent infections with other enteric pathogens, such as parvovirus, *Giardia*, and *Salmonella*, may play a synergistic role and worsen clinical signs.

Diagnosis
As a result of the high prevalence of *Campylobacter* in normal and diarrheic dogs and cats, demonstration of the organisms in feces is not indicative of disease causation. Methods used to demonstrate *Campylobacter* include (a) phase-contrast or darkfield examination of fresh wet mount preparations of feces for characteristic darting motility; (b) bacterial culture of feces in selective media; or (c) molecular identification of *Campylobacter* in feces on the basis of PCR and restriction fragment length polymorphism of specific genes. The morphologic appearance of *Campylobacter* cannot be adequately differentiated from *Helicobacter* spp. on the basis of Gram staining.

Treatment
Erythromycin is the drug of choice for treatment of *C. jejuni* infections in people and has been shown to decrease fecal shedding within 24 to 48 hours when administered to dogs.[59] Dogs and cats are an important reservoir for *Campylobacter* infection in people, where the infectious dose can be as low as a few hundred organisms. Veterinarians should alert owners of the zoonotic risk of *Campylobacter* infection and stress the importance of appropriate hygienic measures, particularly when pets have diarrhea.

Prognosis
Generally good.

Clostridium difficile

Etiology
Clostridium difficile is a Gram-positive, anaerobic, spore-forming bacillus. These bacteria are the most common cause of nosocomial and antibiotic-associated diarrhea in people. *C. difficile* can be cultured from the feces of up to 40% of normal dogs and cats, with most of these isolates being toxigenic (containing toxin genes).[60-64]

Pathophysiology
Diarrhea is mediated by toxigenic strains of *C. difficile*; that is, those that produce cytotoxic proteins of which toxin A (an enterotoxin) and toxin B (a cytotoxin) are best characterized. Both toxins mediate glycosylation and inactivation of Rho-GTPases (guanosine triphosphatases), resulting in depolymerization of F-actin, loss of epithelial integrity, and cell death. In the lamina propria, toxin A stimulates the synthesis of prostaglandins by macrophages, release of substance P, and degranulation of mast cells. Collectively these effects promote intestinal fluid loss and inflammation. There have been no studies to date evaluating the sensitivity of canine intestinal epithelia to either toxin A or B.

Clinical Examination
Reports clearly attributing diarrhea to *C. difficile* infection are uncommon and experimental infections have not produced diarrhea to date. Although antibiotic administration is a predisposing factor for *C. difficile*–associated disease in humans and horses, this does not appear to be a predisposing factor for dogs, although carriage of *C. difficile* may be more common in a hospital setting.[62,65,66] Dogs with suspected *C. difficile*–associated diarrhea commonly have signs consistent with concurrent involvement of the small and large intestine and occasionally, hemorrhagic gastroenteritis.[65]

Diagnosis
In dogs, there has been no significant association between isolation of *C. difficile* (toxigenic or nontoxigenic) and the presence of diarrhea.[62,64,66,67] Toxigenic *C. difficile* can be isolated from up to 94% of neonatal dogs in the absence of clinical signs of disease.[68] An association has been documented between immunodetection of toxin A in feces and clinical signs of diarrhea in the dog,[66,67] although toxin A was also detected in some dogs without diarrhea. In general, a diagnosis of *C. difficile*–associated diarrhea is supported by laboratory detection of toxin A or B by ELISA. Commercially available assays for detection of toxin A and B have unacceptably low sensitivity when applied to feces, but have reasonably good sensitivity and specificity when applied to culture isolates.[64]

Treatment
Metronidazole is the drug of choice for treatment of dogs and cats with *C. difficile*–associated diarrhea.[69,70] Metronidazole resistance among canine isolates appears to be absent or low.[71]

Clostridium perfringens

Etiology

C. *perfringens* is a Gram-positive, anaerobic, spore-forming bacillus. These bacteria also are members of the normal intestinal flora and can be cultured from 80% or greater normal and diarrheic dogs.[66,67] Most isolates obtained from dogs are biotype A, approximately 15% of which carry the gene encoding C. *perfringens* enterotoxin (CPE).[72]

Pathophysiology

The pathophysiology of C. *perfringens* infection remains poorly understood. It is speculated that in response to changes in diet, antibiotic administration, or coinfection with other intestinal pathogens, commensal enterotoxigenic strains are somehow triggered to undergo massive sporulation and synthesis of CPE. CPE binds to intestinal epithelial cells, forming pores in the plasma membrane that initiate cell death signaling pathways. Subsequent access of CPE to the basolateral epithelium induces structural damage to intercellular tight junctions resulting in increased epithelial permeability.[73] When administered orally or directly into the intestinal lumen of dogs, CPE induces fluid secretion and diarrhea.[74] CPE is one of numerous polypeptide enterotoxins that may be produced by C. *perfringens*. CPE-negative strains of C. *perfringens* may mediate diarrhea by virtue of other virulence factors (e.g., β_2 toxin).

Clinical Examination

The clinical spectrum of GI disease attributed to C. *perfringens* varies considerably and ranges from mild self-limiting diarrhea to fatal acute hemorrhagic gastroenteritis. C. *perfringens* is believed to be a major cause of acute, nosocomial large bowel diarrhea that begins with 1 to 5 days of boarding or kenneling. Clinical signs of large intestinal diarrhea including mucus, increased frequency, tenesmus and hematochezia are most often attributed to C. *perfringens*. However, acute and chronic diarrhea of both large and small bowel origin have been described.

Diagnosis

Diagnosis of C. *perfringens* as a causative agent of diarrhea remains highly problematic. At present, the optimum diagnostic approach is demonstration of CPE (protein) in feces by ELISA (C. *perfringens* Enterotoxin Test, TECHLAB, Blacksburg, VA) in conjunction with PCR, performed on culture isolates, for the presence of the *cpe* gene. Although immunodetection of CPE has been significantly associated with diarrhea in dogs, CPE is also detected in dogs without diarrhea,[66,67] and available methods for immunodetection of CPE have poor sensitivity and specificity. Fecal culture or endospore enumeration are unreliable tests for establishing C. *perfringens* infection in the dog because the bacteria are commensal and there appears to be no association between fecal endospore numbers and presence of diarrhea or between spore counts and detection of CPE.[66,67,75]

Treatment

Drugs commonly used for treatment of C. *perfringens* diarrhea include ampicillin, erythromycin, metronidazole, and tylosin. Because of a high incidence of resistance, the use of tetracyclines is discouraged.[71]

Prognosis

The prognosis for recovery is excellent.

Enterohemorrhagic *Escherichia coli*

Etiology

Enterohemorrhagic *E. coli* (EHEC) mediate disease by production of *Shiga*-like toxins (Stx). These toxins are uniquely characterized by cytotoxic effects on cultured Vero (African green monkey kidney) cells and are therefore also referred to as *Verotoxins*. *E. coli* of a broad range of O:H serotypes are capable of producing Stx, of which *E. coli* O157:H7 is but one member. Verotoxigenic *E. coli* may be isolated from 2% to 13.8% and 0% to 4.8% of healthy cats and dogs, respectively.[76-80] Carriage of EHEC may be greater in Greyhound dogs, where 25% of normal animals in one study were found to be infected. A higher prevalence of EHEC in Greyhounds may be attributed to the common practice of feeding raw meat.[81] Most EHEC recovered from dogs and cats are *not* serotype O157:H7.

Pathophysiology

EHEC colonize the colon and produce Stx, which is translocated from the lumen of the intestine, across the intestinal epithelial cells, and into the bloodstream. The bacteria do not invade the intestinal epithelium, nor are they suspected to directly mediate toxic effects on the intestine. Rather, Stx is disseminated in the bloodstream and binds to glycolipid receptors that are expressed in abundance by the kidney and intestine. At these sites, Stx interacts with endothelial cells to disable 28S rRNA, inhibit protein translation, and thereby mediate cell death. When experimentally injected into the bloodstream of Greyhound dogs, *Shiga* toxins mediate severe bloody diarrhea and hemolytic uremic syndrome within 48 to 52 hours.[82]

Clinical Examination

Intestinal manifestations of EHEC infection range from asymptomatic disease, to watery or mucoid diarrhea with slight blood,[83] to anorexia, vomiting, and hemorrhagic diarrhea.[84-86] Extraintestinal sequelae of EHEC infection in dogs are reported rarely[84-86] and have not been reported in the cat. In these cases, hemorrhagic diarrhea is followed by a hemolytic uremic syndrome characterized by a triad of acute renal failure, microangiopathic hemolytic anemia, and thrombocytopenia.

Diagnosis

A diagnosis of EHEC infection is based on demonstration of Stx (ELISA) and/or Stx genes (PCR or in-situ hybridization) in extracts of feces or in culture isolates of *E. coli* obtained from the feces. Sensitivity is improved by demonstrating both the toxin and gene and by performing such assays on culture isolates, rather than feces. There is little information on potential sequence heterogeneity of Stx in the dog and cat, and accordingly, the sensitivity and specificity of commercially available tests used for demonstration of Stx genes or antigen. In Greyhound dogs, a significant association was found between the presence of diarrhea and demonstration of the *stx1* gene or *Shiga* toxin in fecal cultures.[81] Although *Shiga* toxin was demonstrated in 43% of Greyhound dogs with diarrhea in the study, 25% of dogs without diarrhea also had *Shiga* toxin-producing *E. coli* present. In cats, *E. coli* strains isolated from feces of diarrheic animals produced verotoxin more frequently than did *E. coli* strains isolated from those without diarrhea.[80]

Treatment

Too few cases in dogs and cats have been described to make solid recommendations on the appropriateness or choice of antibiotic

treatment for EHEC infection. In people, treatment with antibiotics is contraindicated because of increased risk of developing hemolytic uremic syndrome as a consequence of lysis of bacteria with release of additional toxin into the lumen of the intestine. Accordingly, treatment of infection may be limited largely to supportive care.

Prognosis

The prognosis is likely good for hemorrhagic diarrhea alone. The prognosis is guarded for cases characterized by hemolytic uremic syndrome.

Enteropathogenic *Escherichia coli*

Etiology

Enteropathogenic *E. coli* (EPEC), also termed *attaching and effacing E. coli* (AEEC), possess key attributes that enable them to intimately attach to intestinal epithelial cells, into which they inject bacterial proteins, and initiate intracellular signaling pathways leading to diarrhea.

Pathophysiology

EPEC adhere, in part, to intestinal epithelial cells by virtue of an adherence factor plasmid that contains genes encoding bundle-forming pili. The EPEC genome also contains a "pathogenicity island," called the *locus of enterocyte effacement* (LEE), which contains genes encoding a type III secretory system, multiple EPEC-secreted proteins, a bacterial adhesin called *intimin* (*eae*), and a translocated intimin receptor called *Tir*. EPEC use the type III secretory system as a "molecular syringe" to inject Tir into the host cell whereupon it is translocated to the host cell membrane and serves as a receptor for the bacterial-expressed adhesin intimin. Bacterial attachment results in considerable cytoskeletal reorganization leading to the effacement of microvilli, the formation of pedestals beneath the attached bacteria and disruption of epithelial barrier function. Diarrhea is attributed to a combination of malabsorption, water and electrolyte secretion, increased permeability of tight junctions, and epithelial synthesis of cytokines and chemokines that promote mucosal inflammation.

Clinical Examination

Dogs in which EPEC infection has been described are typically younger than 1 year of age, have acute to chronic, sometimes hemorrhagic, diarrhea, and are often concurrently infected with other diarrheal agents such as distemper virus, parvovirus, coccidia, *Giardia*, or *Cryptosporidium*.[78,87] Fatal EPEC infection has been documented in a 2-month-old kitten and an adult cat in which attaching and effacing lesions and acute mucosal inflammation were present in the ileum and colon.[88]

Diagnosis

Diagnosis of EPEC infection is based on documentation of attaching and effacing histologic lesions, and absence of Stx. The latter is important as some strains of enterohemorrhagic *E. coli* can also cause attaching and effacing lesions. Attaching and effacing lesions are characterized by accumulation of F-actin beneath the adherent bacteria and can be demonstrated by transmission electron microscopy or by staining of F-actin with fluorescent-labeled phalloidin. In dogs, attaching and effacing lesions have been reported in both the small and large intestine. Studies seeking to diagnose EPEC by demonstration of LEE-associated genes in feces have found such genes to be commonly present in the flora of both healthy and diseased individuals.[89]

Treatment

Treatment consists of supportive care, parenteral fluid therapy, and administration of antimicrobial drugs with Gram-negative activity including amoxicillin-clavulanate, first- or second-generation cephalosporins, or enrofloxacin.

Prognosis

Prognosis depends on the cause and severity of concurrent intestinal infectious disease. Death in puppies with EPEC and concurrent enteric infection is common.

Table 58-7 discusses the section of intestine most commonly affected, type of intestinal lesion(s), invasiveness, virulence characteristics, and mechanism of diarrhea of enteric *E. coli* infecting dogs.

Salmonella

Etiology

Salmonella are motile, non–spore-forming, Gram-negative bacterial rods. The species most commonly isolated from diseased animals and people is *Salmonella typhimurium*. *S. typhimurium* is ubiquitous in the environment because of direct or indirect fecal contamination of food, water, or fomites. In dogs, infection is most commonly acquired through the practice of feeding raw,[90,91] dehydrated (e.g., dog chews made from animal hide[92]), or improperly cooked meat products. *Salmonella* spp. were isolated from 80% of samples taken from a bones-and-raw-food diet and from 30% of fecal samples from dogs fed the diet.[91] A conservative prevalence of *Salmonella* infection in clinically healthy or hospitalized dogs is 1% to 36% and from healthy cats is 1% to 18%.[93]

Pathophysiology

Following ingestion, *Salmonella* adhere via fimbriae to intestinal epithelial cells and M cells. *Salmonella* translocates bacterial proteins into these host cells by virtue of a type III secretion system. The translocated proteins interact with Rho-family guanosine triphosphate–binding proteins to facilitate internalization of the bacteria into host cell vesicles and stimulate host cell secretion of cytokines such as interleukin-8. A resulting influx of neutrophils transmigrate across the epithelium resulting in loss of barrier integrity. A fraction of *Salmonella*-containing vesicles are transported to the basolateral membrane where released *Salmonella* enters macrophages in which they multiply and disseminate systemically. Factors contributing to susceptibility to *Salmonella* infection include young age, nutritional deficiency, impaired immune defense, concurrent GI infection, and disruption of the normal intestinal flora (e.g., antibiotics) leading to loss of colonization resistance. Intestinal lesions are usually confined to the distal small bowel, cecum, and colon, and consist of mucosal inflammation and epithelial sloughing.

Clinical Examination

Clinical signs of salmonellosis are most severe in puppies and kittens younger than 1 year of age and geriatric animals. Diarrhea varies from watery to mucoid, with fresh blood present in severe cases. In addition to diarrhea, other clinical signs, such as fever, anorexia, vomiting, and abdominal pain, may be present. Patients developing bacteremia or endotoxemia may be obtunded, weak, have pale mucous membranes, tachycardia, hypothermia, and vascular collapse. The clinical and pathologic features of salmonellosis may be indistinguishable from those of canine parvovirus and feline panleukopenia infection.

Table 58-7 Section of Intestine Most Commonly Affected, Type of Intestinal Lesion(s), Invasiveness, Virulence Characteristics, and Mechanism of Diarrhea of Enteric *Escherichia coli* Infecting Dogs

	Disease Localization	Intestinal Lesions	Invasion of Intestinal Epithelial Cells	Virulence Characteristics	
Enteropathogenic *E. coli* (EPEC)	Small and large intestine	Effacement of microvilli and pedestal formation Mucosal inflammation	Variable	Adherence factor plasmid contains genes encoding bundle-forming pili Locus for enterocyte effacement contains bacterial genes encoding intimin (*eae*), a type III secretory apparatus, translocated intimin receptor, and EPEC-secreted proteins	Malabsorption, water and electrolyte secretion, increased permeability of tight junctions, and mucosal inflammation
Enterotoxigenic *E. coli* (ETEC)	Small intestine	Minimal histologic changes or inflammation	Noninvasive	Heat-labile toxins stimulate adenylyl cyclase activity by activational adenosine diphosphate-ribosylation of $G_{s\alpha}$, thereby increasing the synthesis of cyclic adenosine monophosphate Heat-stabile toxins bind to and activate membrane-bound guanylyl cyclase, thereby increasing the synthesis of cyclic guanosine monophosphate	Secretory diarrhea ("traveler's diarrhea" in people): stimulate Cl^- secretion by crypt epithelium and inhibit NaCl absorption by villous epithelium
Enterohemorrhagic *E. coli* (EHEC) and *E. coli* 0127:H7	Large intestine	Edema and submucosal hemorrhage, arteritis, and microvascular thrombosis of intestinal arterioles	Noninvasive	*Shiga*-like verotoxins inhibit protein synthesis resulting in cell death	Hemorrhagic colitis Hemolytic uremic syndrome

Diagnosis

Isolation of *Salmonella* organisms is the most definitive means of confirming infection. Because of the high prevalence of asymptomatic carriage of *Salmonella*, isolation from normally sterile samples (e.g., urine, blood) may allow a definitive diagnosis and indicate disseminated disease. In addition, failure to isolate *Salmonella* does not rule out infection because of the fastidious nature of *Salmonella* in culture. Use of PCR for identification of *Salmonella* in dogs has been described[94] but is not yet widely applied.

Treatment

Treatment varies according to the severity of the clinical signs. Acute gastroenteritis, without clinical signs of systemic disease may be treated with fluid therapy and supportive care. Antibiotic therapy may prolong fecal shedding and induce drug resistance and is therefore reserved for patients with severe hemorrhagic diarrhea, history of immunosuppression, suspected or documented septicemia, evidence of systemic inflammatory response syndrome, or a combination of these symptoms.

Antibiotics reported to be effective for treatment of *Salmonella* include chloramphenicol, amoxicillin, trimethoprim-sulfa, and enrofloxacin. Posttreatment cultures should be performed to confirm eradication, and pet owners should be advised of the public health importance of the disease.

Prognosis

The prognosis for enteritis alone is generally good. The prognosis for patients with disseminated disease, endotoxemia, or sepsis is more guarded. Some patients may remain chronic carriers with recrudescence during periods of stress or unrelated disease.

Yersinia enterocolitica

Y. enterocolitica and *Yersinia pseudotuberculosis* are motile, Gram-negative, coccobacilli that can be isolated from the feces of clinically normal dogs and cats. *Yersinia* has been cultured on rare occasions from the feces of dogs and cats with abdominal discomfort or bloody diarrhea.[95-97]

Viruses

Feline Enteric Coronavirus

Although uncommon, colonic disease may be a primary manifestation of feline infectious peritonitis (FIP) infection in the cat.[98,99] Clinical signs of diarrhea or constipation may be present. Physical examination reveals a palpable abdominal mass of the colon or ileocecocolic junction. Histopathology is consistent with pyogranulomatous inflammation with intralesional feline coronavirus demonstrable by immunohistochemistry. In the majority of cases reported,

cats were euthanized or died from the effects of multisystemic FIP infection.

OBSTRUCTION

Robert J. Washabau

Intussusception

Etiology

Intussusception is an invagination of one segment of the gastrointestinal tract into the lumen of an adjoining segment. The intussusceptum is the invaginated segment of the alimentary tract, whereas the intussuscipiens is the enveloping segment. Invagination may occur in an antegrade (aborad) or retrograde (orad) direction, but is most commonly in the antegrade direction. Any portion of the alimentary tract may be involved, but enterocolic intussusceptions account for almost two-thirds of the published cases in dogs and cats. Enterocolic intussusceptions can be further divided into three types: cecocolic (or cecal inversion), with the inverted cecum forming the apex[1]; ileocolic, with the ileum forming the apex; and ileocecal, with the ileocecal junction forming the apex.[2] Of these three forms of enterocolic intussusception, the ileocolic intussusception is the one most frequently encountered in clinical practice. A number of conditions are reported to predispose to intussusception, including intestinal parasitism, viral enteritis, foreign bodies, and masses, but in dogs and cats most intussusceptions are idiopathic.[3-5]

Pathophysiology

The initiating events in an intussusception are often difficult to identify retrospectively, but all intussusceptions appear to share three important features: (a) inhomogeneity in a bowel segment, a region in which the gastrointestinal tract undergoes a sudden anatomic change in diameter (e.g., ileocolic junction) or a bowel segment that is either flaccid or indurated; (b) mechanical linkage of nonadjacent segments, which can be intraluminal (e.g., linear foreign bodies or parasites) or extramural (e.g., fibrous adhesions or bands); and (c) peristaltic activity of the gut.[2] Invagination begins as a result of peristaltic contraction. Once the invagination has begun, its progress may be rapid, involving as much as several centimeters of intestinal tract within just a few hours. Invagination and intussusception result in luminal obstruction, which may be partial or complete. Obstruction usually results in distention of the bowel segment proximal to the intussusception. The degree of distention is dependent upon the completeness and duration of the obstruction, volume of fluid secretion, degree of vascular compromise, and volume of gas production from bacterial fermentation. Because the mesentery and blood supply are included in the invaginating segment, vascular compromise can occur, which initially leads to intramural hemorrhage and edema and eventually to ischemia and necrosis of the bowel. Full-thickness necrosis may ensue but perforations are rare.

Clinical Examination

The most important clinical signs with ileocolic intussusceptions are intermittent vomiting, progressive loss of appetite, mucoid bloody diarrhea, and a palpable cylinder-shaped mass in the cranial abdomen. Abdominal pain is not a consistent finding in affected animals. Clinical signs may persist for several weeks and affected animals eventually succumb to the effects of starvation rather than dehydration, electrolyte imbalances, or acid–base disturbances.

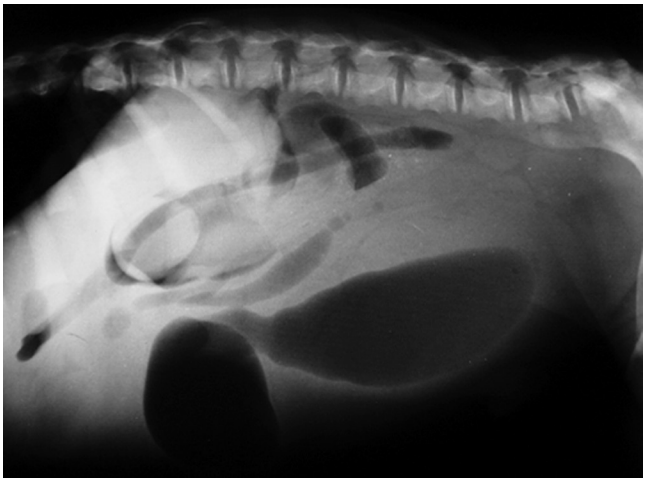

Figure 58-12 Abdominal survey radiographic evidence of intussusception.

Diagnosis

With some ileocolic intussusceptions, the intussuscepted bowel may protrude through the anus and must be differentiated from a rectal prolapse. This is accomplished by passing a blunt probe between the protruding segment and the anal sphincter. If the probe can be passed cranial to the pubis without reaching a fornix, then the protruding bowel is the apex of an intussusception rather than rectal prolapse.

Survey abdominal radiographs are often nondiagnostic, but may reveal distention and obstruction proximal to the intussusception (Figure 58-12). Barium-contrast studies (barium enema or upper GI series) are often diagnostic, but abdominal ultrasonography is the preferred method of diagnosis. The appearance of a target-like mass consisting of two or more hyperechoic and hypoechoic concentric rings in transverse section or the appearance of multiple hyperechoic and hypoechoic parallel lines in longitudinal section is virtually diagnostic of an intussusception (Figure 58-13).[6] The ultrasound scan might also identify a mass associated with the intussusception. Endoscopy may be performed in suspected cases of suspected neoplasia, otherwise endoscopy does not confer any additional benefits over abdominal ultrasound or CT scanning.

Treatment

The surgical management of ileocolic intussusception involves either reduction or resection, and anastomosis, or both.[7,8] Secretory diarrhea may persist following relief of the obstruction and affected animals may need continuous crystalloid and colloidal therapy. If possible, the ileocecal sphincter should be preserved to reduce reflux and contamination of the distal small bowel. Cecocolic intussusceptions or inversions should also be treated with surgical resection. Surgical resection of the cecocolic intussusceptions is generally curative. Enteroplication procedures have been recommended,[9] but they do not appear to reduce recurrence rates.[7,8]

Prognosis

The most common complications following treatment of intussusception are recurrence, dehiscence of the anastomosis, ileus, intestinal obstruction, peritonitis, and short bowel syndrome. The

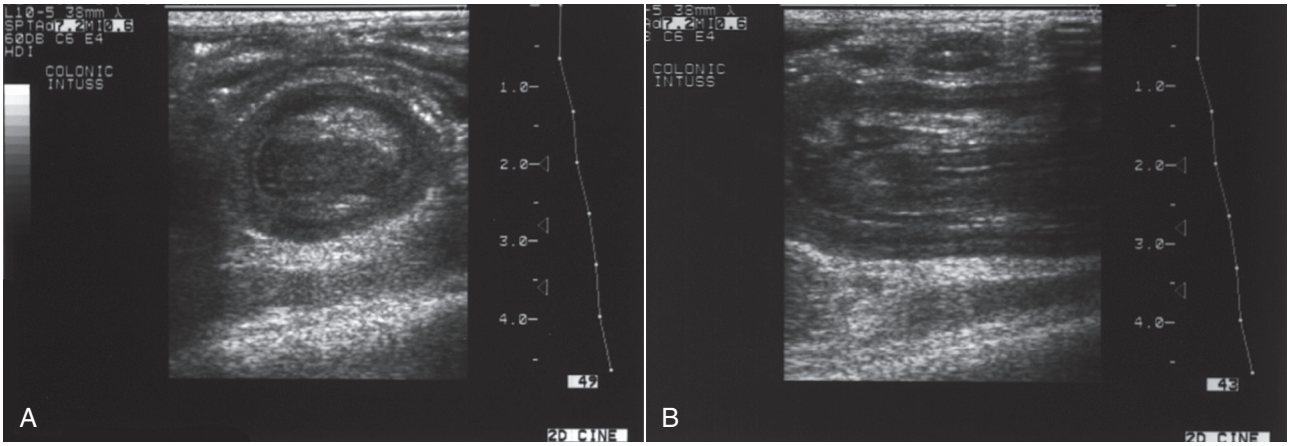

Figure 58-13 Abdominal ultrasonographic appearance of intussusception. Target-like mass consisting of two or more hyperechoic and hypoechoic concentric rings in transverse section (**A**) and the appearance of multiple hyperechoic and hypoechoic parallel lines in longitudinal section (**B**) are virtually diagnostic of an intussusception.

recurrence rate in dogs is reported to be between 11% and 20%. In dogs in which no surgical procedure was performed to prevent recurrence, intussusception recurred in 25% of dogs that underwent manual reduction alone and in 19% of dogs that underwent resection and anastomosis. Enteroplication does not appear to reduce recurrence rates any further.[7,8] Indeed, 19% of dogs undergoing enteroplication in one study experienced severe complications that required a second surgery. Intestinal obstruction was a complication of the enteroplication in those patients.[8]

Pyogranulomatous Inflammation

Histoplasma capsulatum

Etiology

Histoplasmosis is a systemic fungal disease of dogs and cats caused by *H. capsulatum*. In the environment, *H. capsulatum* organisms are mycelial, saprophytic soil fungi. In infected tissue or when cultured at 30°C (86°F) to 37°C (98.6°F), the organism is a yeast. The fungus is endemic throughout most of the temperate and subtropical regions of the world. Most cases of histoplasmosis in the United States occur in the central states, with the geographic distribution following the Mississippi, Ohio, and Missouri Rivers.[10,11]

Pathophysiology

Infection is probably via inhalation or ingestion of infective conidia from the environment. The respiratory system is thought to be the primary route of infection in cats and dogs, although the gastrointestinal tract may also be an important route in the dog. After inhalation or ingestion, conidia transform from the mycelial phase and are phagocytized by macrophages, where they grow as facultative intracellular organisms. Hematogenous and lymphatic dissemination results in multisystemic disease. Organisms can be disseminated to any organ system, but the lungs, gastrointestinal tract, lymph nodes, liver, spleen, bone marrow, eyes, and adrenal glands are the most common organs of dissemination in the dogs; lungs, liver, lymph nodes, eyes, and bone marrow are most commonly affected in cats. Cell-mediated immunity induces a granulomatous inflammatory response in most infection.[12]

Clinical Examination

Dogs with gastrointestinal histoplasmosis are typically presented with mild fever, anorexia, lethargy, weight loss, vomiting, diarrhea, hematochezia, and tenesmus. Cachexia is a common physical examination finding. Other historical and physical examination findings (dyspnea, cough, ascites, lameness, oropharyngeal ulcerations, chorioretinitis, neuropathy) will depend upon organ and tissue involvement. The small intestinal form of histoplasmosis is described in more detail in Chapter 57.

Diagnosis

Organism identification is required for definitive diagnosis. The most common means of organism identification is cytology. Cytology from affected tissue reveals pyogranulomatous inflammation, often with numerous small, round to oval intracellular yeast cells (2 to 4 μm in diameter) characterized by a basophilic center and a light halo. Exfoliative cytology during colonoscopy is particularly useful in diagnosing the disease. Histopathology is helpful if cytology is nondiagnostic or inconclusive. Multiple endoscopic colonic biopsies are usually sufficient to diagnose the disease. The yeast form does not stain well with routine hematoxylin and eosin stains, so special stains such as PAS and Gomori methenamine silver stain are often used to demonstrate organisms. Fungal culture from affected tissue can be used for diagnosis but is rarely needed in clinical cases. Currently available serologies have poor specificity and sensitivity.[12]

Treatment

Itraconazole (5 mg/kg PO BID for 2 to 4 months) is considered the treatment of choice for feline histoplasmosis. In one study, itraconazole therapy cured histoplasmosis infections in all eight study cats.[13] Ketoconazole and amphotericin B have been described as the treatments of choice for canine histoplasmosis. With colonic involvement, additional gastrointestinal therapy may be useful in affected dogs, for example, dietary modification, treatment for small intestinal bacterial overgrowth, and direct antidiarrheal therapy. Corticosteroids may have been used successfully in the treatment of airway obstruction secondary to hilar lymphadenopathy in chronically infected dogs.[14]

Prognosis

There may be important species differences in prognosis although the paucity of reports, especially of prospective clinical trials, makes it difficult to generalize. It would seem that the prognosis is guarded in dogs, but fair to good in cats.

Pythium insidiosum

Etiology

P. insidiosum is an aquatic oomycete that causes severe gastrointestinal pathology in a range of hosts in the tropical and subtropical climates.[15] Based on ribosomal RNA gene sequence data, members of the class *Oomycetes* are phylogenetically distinct from the kingdom *Fungi*, and are more closely related to algae than to fungi.[16] The oomycetes differ from fungi in two important properties: cell wall and cell membrane composition. Chitin is an essential component of the fungal cell wall, but it is generally lacking in the oomycete cell wall. Oomycetes also differ from fungi in that ergosterol is not a principal sterol in the oomycete cell membrane. This difference may explain why ergosterol-targeting drugs like itraconazole are less effective in the medical treatment of pythiosis.[16]

Pathophysiology

The infective state of *P. insidiosum* is thought to be the motile zoospore, which is released into stagnant water in warm environments, and likely causes infection either by encysting in the skin, or by being ingested into the gastrointestinal tract. Ingested zoospores encyst and adhere to the gastric, jejunal, and colonic epithelium with a polarity oriented toward the submucosa for rapid tissue penetration following germ tube eruption. *Pythium* induces a chronic pyogranulomatous response in the gastrointestinal tract and mesenteric lymph nodes. The gastric outflow tract and ileocolonic junction are the most frequently affected portions of the GI tract, and it is not uncommon to find two or more segmental lesions in the same patient.[17] Inflammation in affected regions is typically centered on the submucosa, with variable mucosal ulceration and occasional extension of disease through serosal surfaces, resulting in adhesion formation and peritonitis.

Clinical Examination

Weight loss, vomiting, diarrhea, and hematochezia are the most important clinical signs. Physical examination often reveals emaciated body condition and a palpable abdominal mass. Signs of systemic illness such as lethargy and depression are not typically present unless intestinal obstruction, infarction, or perforation occurs.

Diagnosis

Ileocolonic wall thickening, obliteration of the normal layered appearance, and regional lymphadenopathy are common ultrasonographic features of canine intestinal pythiosis.[18] Of course, these findings cannot be readily differentiated from those associated with intestinal malignancy. Definitive diagnosis requires histologic demonstration or immunohistochemical staining of the organism and/or positive ELISA or PCR assays. The histologic findings associated with pythiosis generally are characterized by eosinophilic granulomatous to pyogranulomatous inflammation with fibrosis. Affected tissue typically contain multiple foci of necrosis surrounded and infiltrated by neutrophils, eosinophils, and macrophages. Discrete granulomas composed of epithelioid macrophages, plasma cells, multinucleate giant cells, and neutrophils and eosinophils may also be observed. *Pythium* zoospores may be cultured directly from affected tissue in antibiotic-containing (e.g., streptomycin and ampicillin) media. More recently, sensitive and specific ELISA and PCR assays have been developed for the accurate diagnosis of pythiosis in dogs.[19-21]

Treatment

Aggressive surgical resection remains the treatment of choice for pythiosis in dogs. Because it provides the best opportunity for long-term cure, complete resection of infected tissue should be pursued whenever possible. Segmental lesions of the GI tract should be resected with 3- to 4-cm margins whenever possible. Medical therapy for the oomycetes has not been very promising. This may relate to the absence of ergosterol (cell membrane target of most currently available antifungal drugs) in the oomycete cell membrane. Clinical and serologic cures have been obtained in a small number of dogs following therapy with amphotericin B lipid complex (2 to 3 mg/kg QOD administered to a cumulative dose of 24 to 27 mg/kg) or itraconazole (10 mg/kg q24h for 6 to 9 months).

Prognosis

Unfortunately, most dogs with GI pythiosis are not presented to the veterinarian until late in the course of the disease, when complete excision is not possible. The anatomic site of the lesion (e.g., pylorus or ileocolic sphincter) may also prevent complete excision. Consequently, the prognosis is usually grave in most animals.[16]

Feline Infectious Peritonitis

FIP is a well-known and widely distributed coronavirus-induced systemic disease in cats, characterized by fibrinous to granulomatous serositis with protein-rich effusions in body cavities and granulomatous inflammatory lesions in multiple organs. One of its morphologic hallmarks is a granulomatous to necrotizing phlebitis and periphlebitis.[22,23] Affected cats develop signs caused by granulomatous lesions in target organs (central nervous system, eyes, and parenchymatous organs) and vasculitis leading to fluid redistribution into third spaces with fluid accumulation in body cavities.[22] In addition to the well-known multisystemic condition, some unusual problems have been described, including focal pyogranulomas of the gastrointestinal tract. In a survey of 156 cats with disseminated FIP, 26 had solitary mural intestinal lesions.[24] Predominant clinical signs included diarrhea and vomiting for 3 months or less before intestinal biopsy. All cats had a mass, believed to be a neoplasm, in the colon or ileocecocolic junction. Affected intestine was markedly thickened, nodular, firm, and white, with multifocal pyogranulomas extending throughout the wall of the intestine, and the regional lymph nodes were uniformly involved. Most cats were euthanized or died within 9 months of histologic findings, many with signs of multisystemic FIP.[24]

Nonneoplastic Stricture

The etiologies for nonneoplastic colonic strictures include foreign bodies, postoperative complications, inflammatory disease (e.g., IBD, diffuse perianal fistula disease), and congenital malformation.[25] Postoperative complications are probably the most important cause of colonic strictures in dogs and cats,[25] which emphasizes the importance of good surgical principles in performing colonic surgery.[26] Nonneoplastic strictures of the colon are fairly rare. Nonneoplastic strictures of the rectum are more common (see Chapter 59).

DYSMOTILITY

Robert J. Washabau

Constipation

Etiology

The etiopathogenesis of idiopathic megacolon is still incompletely understood. Several reviews have emphasized the importance of

Table 58-8 Causes of Constipation

Type	Cause
Mechanical obstruction	
Intraluminal	Bones, hair, neoplasia, rectal diverticulum, stricture, deviation/sacculation associated with perineal hernia
Intramural	Neoplasia
Extramural	Pelvic fractures, neoplasia, prostatic disease
Inflammation	Perianal fistula, anal sac disease, perineal wounds
Neuromuscular dysfunction	Lumbosacral disease, cauda equina syndrome, sacral spinal cord deformities (Manx cat)
	Hypogastric or pelvic nerve disorders–trauma, neoplasia, dysautonomia
	Colonic smooth muscle–idiopathic megacolon
Metabolic, endocrine	Dehydration, hypokalemia, hypocalcemia
	Hypothyroidism, nutritional secondary hyperparathyroidism, obesity
Pharmacologic	Opioids, atropine, anticholinergics, diuretics, barium sulfate, phenothiazines, β-agonist drugs
Environmental	Soiled/absent litterbox, inactivity, hospitalization, multicat households, competition

Adapted from Washabau RJ, Hasler AH: Constipation, obstipation, and megacolon. In: August JR, editor: Consultations in Feline Internal Medicine, ed 3. Philadelphia, 1997, Saunders, p 106.

considering an extensive list of differential diagnoses (e.g., neuromuscular, mechanical, inflammatory, metabolic/endocrine, pharmacologic, environmental, and behavioral causes) for the obstipated cat (Table 58-8). A review of published cases suggests that 96% of cases of obstipation are accounted for by idiopathic megacolon (62%), pelvic canal stenosis (23%), nerve injury (6%), or Manx sacral spinal cord deformity (5%).[1,2] A smaller number of cases are accounted for by complications of colopexy (1%) and colonic neoplasia (1%); colonic hypo- or aganglionosis was suspected, but not proved, in another 2% of cases. A definitive case of colonic hypoganglionosis was reported in an 11-week-old female domestic shorthaired cat.[3] Inflammatory, pharmacologic, and environmental/behavioral causes were not cited as predisposing factors in any of the original case reports. Endocrine factors (e.g., obesity and hypothyroidism) were cited in several cases, but were not necessarily impugned as part of the pathogenesis of megacolon. It is important to consider an extensive list of differential diagnoses in an individual animal, but it should be kept in mind that most cases are idiopathic,[1,2] orthopedic,[1,2] or neurologic[4] in origin. Behavioral (e.g., stress) and/or environmental (e.g., competition for the litterbox) factors very likely play an important role in the development of this lesion, but this has been poorly studied in retrospective or prospective studies.

Pathophysiology

Megacolon develops through two pathologic mechanisms: *dilation* and *hypertrophy*. *Dilated megacolon* is the end stage of colonic dysfunction in idiopathic cases. Cats affected with idiopathic dilated megacolon have permanent loss of colonic structure and function. Medical therapy may be attempted in such cases, but most affected cats eventually require colectomy. *Hypertrophic megacolon*, on the other hand, develops as a consequence of obstructive lesions (e.g., malunion of pelvic fractures, tumors, foreign bodies). Hypertrophic megacolon may be reversible with early pelvic osteotomy or it may progress to irreversible dilated megacolon if appropriate therapy is not instituted.[5]

Constipation and *obstipation* are earlier manifestations of the same problem. Constipation is defined as the infrequent difficult evacuation of feces but does not necessarily imply a permanent loss of function. Many cats suffer from one or two episodes of constipation without further progression. Intractable constipation that has become refractory to cure or control is referred to as *obstipation*. The term *obstipation* implies a permanent loss of function. A cat is assumed to be obstipated only after several consecutive treatment failures. Recurring episodes of constipation or obstipation may culminate in the syndrome of *megacolon*.

The pathogenesis of idiopathic dilated megacolon appears to involve functional disturbances in colonic smooth muscle. In vitro isometric stress measurements have been performed on colonic smooth muscle obtained from cats suffering from idiopathic dilated megacolon.[6,7] Megacolonic smooth muscle develops less isometric stress in response to neurotransmitter (acetylcholine, substance P, cholecystokinin), membrane depolarization (potassium chloride), or electrical field stimulation, when compared with healthy controls.[6,7] Differences have been observed in longitudinal and circular smooth muscle from descending and ascending colon. No significant abnormalities of smooth muscle cells or of myenteric neurons were observed on histologic evaluation. These studies initially suggested that the disorder of feline idiopathic megacolon is a generalized dysfunction of colonic smooth muscle, and that treatments aimed at stimulating colonic smooth muscle contraction might improve colonic motility. The lesion begins in the descending colon and appears to progressively involve the ascending colon over time.[8]

Clinical Examination

History

Constipation, obstipation, and megacolon may be observed in cats of any age, sex, or breed, however, most cases are observed in middle aged (mean: 5.8 years), male cats (70% male, 30% female) of domestic shorthair (46%), domestic longhair (15%), or Siamese (12%) breeding.[1] Affected cats are usually presented for reduced, absent, or painful defecation for a period of time ranging from days to weeks or months. Some cats are observed making multiple, unproductive attempts to defecate in the litterbox, while other cats may sit in the litterbox for prolonged periods of time without assuming a defecation posture. Dry, hardened feces are observed inside and outside of the litterbox. Occasionally, chronically constipated cats have intermittent episodes of hematochezia or diarrhea as a result of the mucosal irritant effect of fecal concretions. This may give the pet owner the erroneous impression that diarrhea is the primary problem. Prolonged inability to defecate may result in other systemic signs, including anorexia, lethargy, weight loss, and vomiting.

Physical Examination

Colonic impaction is a consistent physical examination finding in affected cats. Other findings depend upon the severity and pathogenesis of constipation. Dehydration, weight loss, debilitation, abdominal pain, and mild to moderate mesenteric lymphadenopathy may be observed in cats with severe idiopathic megacolon. Colonic impaction may be so severe in such cases as to render it difficult to differentiate impaction from colonic, mesenteric, or other

abdominal neoplasia. Cats with constipation caused by dysautonomia may have other signs of autonomic nervous system failure, such as urinary and fecal incontinence, regurgitation as a consequence of megaesophagus, mydriasis, decreased lacrimation, prolapse of the nictitating membrane, and bradycardia. Digital rectal examination should be carefully performed with sedation or anesthesia in all cats. Pelvic fracture malunion may be detected on rectal examination in cats with pelvic trauma. Rectal examination might also identify other unusual causes of constipation, such as foreign bodies, rectal diverticula, stricture, inflammation, or neoplasia. Chronic tenesmus may be associated with perineal herniation in some cases. A complete neurologic examination with special emphasis on caudal spinal cord function should be performed to identify neurologic causes of constipation, for example, spinal cord injury, pelvic nerve trauma, or Manx sacral spinal cord deformity.

Diagnosis

Although most cases of obstipation and megacolon are unlikely to have significant changes in laboratory data (e.g., complete blood cell count, serum chemistry, urinalysis), these tests should nonetheless be performed in all cats presented for constipation. Metabolic causes of constipation, such as dehydration, hypokalemia, and hypercalcemia may be detected in some cases. Basal serum T_4 (thyroxine) concentration and other thyroid function tests should also be considered in cats with recurrent constipation and other signs consistent with hypothyroidism. Although hypothyroidism was documented in only one case of obstipation and megacolon, obstipation is a frequent clinical sign in kittens affected with congenital or juvenile-onset hypothyroidism.[1] Constipation could also theoretically develop following successful treatment of feline hyperthyroidism.

Abdominal radiography should be performed in all constipated cats to characterize the severity of colonic impaction, and to identify predisposing factors such as intraluminal radiopaque foreign material (e.g., bone chips), intraluminal or extraluminal mass lesions, pelvic fractures, and spinal cord abnormalities (Figure 58-14). The radiographic findings of colonic impaction cannot be used to distinguish between constipation, obstipation, and megacolon in idiopathic cases. First or second episodes of constipation in some cats may be severe and generalized but may still resolve with appropriate treatment.

Ancillary studies may be indicated in some cases. Extraluminal mass lesions may be further evaluated by abdominal ultrasonography and guided biopsy, whereas intraluminal mass lesions are best evaluated by endoscopy. Colonoscopy may also be used to evaluate the colon and anorectum for suspected inflammatory lesions, strictures, sacculations, and diverticula. Barium enema contrast radiography may be used if colonoscopy is not possible. Both colonoscopy and barium-contrast enema radiography require general anesthesia and evacuation of impacted feces. Cerebrospinal fluid analysis, CT or magnetic resonance imaging (MRI), and electrophysiologic studies should be considered in animals with evidence of neurologic impairment. Finally, colonic biopsy or anorectal manometry will be necessary to diagnose suspected cases of aganglionic megacolon.

Treatment

The specific therapeutic plan will depend upon the severity of constipation and the underlying cause.[2] Medical therapy may not be necessary with first episodes of constipation. First episodes are often transient and resolve without therapy. Mild to moderate or recurrent episodes of constipation, on the other hand, usually require some medical intervention. These cases may be managed, often on an outpatient basis, with dietary modification, water enemas, oral or suppository laxatives, and/or colonic prokinetic agents (Table 58-9). Severe cases of constipation usually require brief periods of hospitalization to correct metabolic abnormalities and to evacuate impacted feces using water enemas, manual extraction of retained feces, or both. Followup therapy in such cases is directed at correcting predisposing factors and preventing recurrence. Subtotal colectomy will become necessary in cats suffering from obstipation or idiopathic dilated megacolon. These cats, by definition, are unresponsive to medical therapy. Pelvic osteotomy without colectomy may be sufficient for some cats suffering from pelvic canal stenosis and hypertrophic megacolon.[9] Figure 58-15 provides an algorithm for the therapeutic approach to the constipated, obstipated, and megacolonic cat.

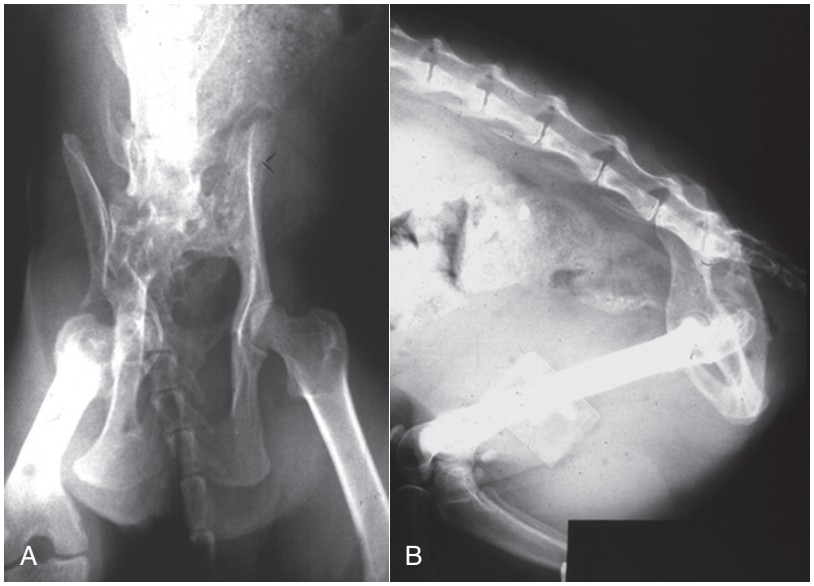

Figure 58-14 Lateral and ventrodorsal radiographs of the pelvis of a cat with megacolon. Note the healed malaligned fracture of the ilium obstructing the pelvic canal.

Table 58-9 Mechanisms, Sites of Activity, Indications, and Doses of Currently Available Gastrointestinal Prokinetic Agents

Drug Classification/ Mechanism	Sites of Activity	Indications	Dose	Other properties
Dopaminergic D_2 Antagonist Drugs				
Metoclopramide	GES, stomach, intestine, CRTZ	Vomiting disorders, gastroesophageal reflux, delayed gastric emptying, ileus/pseudoobstruction	0.2 to 0.5 mg/kg PO, IV TID; 0.01 to 0.02 mg/kg/h infusion	α_2-Adrenergic antagonist β_2-Adrenergic antagonist 5-HT_4 serotonergic agonist 5-HT_3 serotonergic antagonist
Domperidone	GES, CRTZ	Vomiting disorders, gastroesophageal reflux	0.05 to 0.10 mg/kg PO BID	α_2-Adrenergic antagonist β_2-Adrenergic antagonist
Serotonergic 5-HT_4 Agonist Drugs				
Mosapride	Stomach	Delayed gastric emptying	0.25 to 1.0 mg/kg PO BID	None
Prucalopride	Stomach, colon	Delayed gastric emptying, constipation	0.01 to 0.20 mg/kg PO BID	None
Cisapride*	GES, stomach, intestine, colon, CRTZ	Gastroesophageal reflux, delayed gastric emptying, ileus/pseudoobstruction, constipation, chemotherapy-induced vomiting	0.1 to 0.5 mg/kg PO TID (doses as high as 0.5 to 1.0 mg/kg have been used in some dogs)	5-HT_3 serotonergic antagonist 5-HT_1 serotonergic antagonist 5-HT_2 serotonergic agonist
Tegaserod*	Intestine, colon	Constipation, ileus/ pseudoobstruction	0.05 to 0.10 mg/kg PO or IV, BID	5-HT_1 serotonergic antagonist
Motilin-Like Drugs				
Erythromycin	GES, stomach, intestine, colon	Gastroesophageal reflux, delayed gastric emptying, constipation (dogs)	0.5 to 1.0 mg/kg PO IV TID	5-HT_3 serotonergic antagonist
Acetylcholinesterase Inhibitors and Cholinomimetic Agents				
Ranitidine	Stomach, colon	Delayed gastric emptying, constipation	1 to 2 mg/kg PO BID-TID	H_2 histaminergic antagonist
Nizatidine	Stomach, colon	Delayed gastric emptying, constipation	2.5 to 5.0 mg/kg PO SID	H_2 histaminergic antagonist
Bethanechol	Esophagus	Canine idiopathic megaesophagus	Dog: 5 to 15 mg/dog PO TID	
Nitric Oxide Donors				
AMU-301	Stomach	Diabetic gastroparesis	Not yet established	
Prostanoids				
Misoprostol	Colon	Constipation	Dog: 2 to 5 µg/kg PO TID-QID	

*Removed from many international markets.
CRTZ, chemoreceptor trigger zone; GES, gastroesophageal sphincter.

Removal of Impacted Feces

Removal of impacted feces may be accomplished through the use of rectal suppositories, enemas, or manual extraction.

Rectal Suppositories. A number of pediatric rectal suppositories are available for the management of mild constipation. These include dioctyl sodium sulfosuccinate (emollient laxative), glycerin (lubricant laxative), and bisacodyl (stimulant laxative). The use of rectal suppositories requires a compliant pet and pet owner. Suppositories can be used alone or in conjunction with oral laxative therapy.

Enemas. Mild to moderate or recurrent episodes of constipation may require administration of enemas and/or manual extraction of impacted feces. Several types of enema solutions may be administered, such as warm tap water (5 to 10 mL/kg), warm isotonic saline (5 to 10 mL/kg), dioctyl sodium sulfosuccinate (5 to 10 mL/cat), mineral oil (5 to 10 mL/cat), or lactulose (5 to 10 mL/cat). Enema solutions should be administered slowly with a well-lubricated 10 to 12 rubber catheter or feeding tube. Enemas containing sodium phosphate are contraindicated in cats because of their propensity for inducing severe hypernatremia, hyperphosphatemia, and hypocalcemia in this species.[10]

Manual Extraction. Cases unresponsive to enemas may require manual extraction of impacted feces. Cats should be adequately rehydrated and then anesthetized with an endotracheal tube in place to prevent aspiration should colonic manipulation induce vomiting. Water or saline is infused into the colon while the fecal mass is manually reduced by abdominal palpation. Sponge forceps may also be introduced rectally (with caution) to break down the fecal mass. It may be advisable to evacuate the fecal mass over a period of several days to reduce the risks of prolonged anesthesia and perforation of a devitalized colon. If this approach fails,

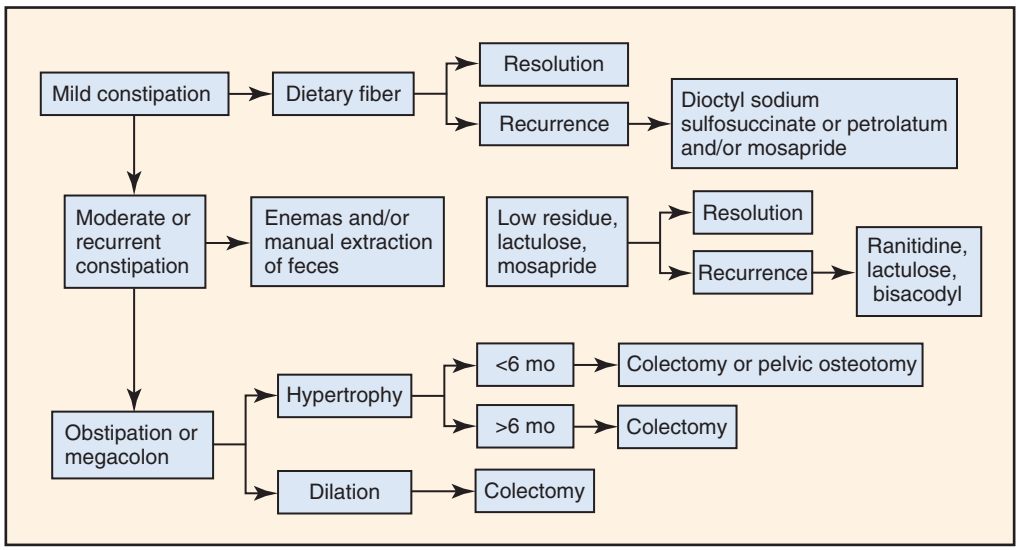

Figure 58-15 Suggested management of mild, moderate, or recurrent constipation and obstipation or megacolon.

colotomy may be necessary to remove the fecal mass. Laxative and/or prokinetic therapy may then be instituted once the fecal mass has been removed.

Established Laxative Agents

Laxatives promote evacuation of the bowel through stimulation of fluid and electrolyte transport or increases in propulsive motility. They are classified as bulk-forming, emollient, lubricant, hyperosmotic, or stimulant laxatives according to their mechanism of action. There are literally hundreds of products available for the treatment of constipation. Chapter 50 provides more detail about laxative agents.

Bulk-Forming Laxatives. Most of the available bulk-forming laxatives are dietary fiber supplements of poorly digestible polysaccharides and celluloses derived principally from cereal grains, wheat bran, and psyllium. Some constipated cats will respond to supplementation of the diet with one of these products, but many require adjunctive therapy (e.g., other types of laxatives or colonic prokinetic agents).[11] Fiber supplemented diets are available commercially, or the pet owner may wish to add psyllium (1 to 4 tsp per meal), wheat bran (1 to 2 tblsp per meal), or pumpkin (1 to 4 tblsp per meal) to canned cat food. Cats should be well hydrated before commencing fiber supplementation to maximize the therapeutic effect. Fiber supplementation is most beneficial in mildly constipated cats, prior to the development of obstipation and megacolon. In obstipated and megacolon cats, fiber may in fact be detrimental. Low-residue diets may be more beneficial in obstipated and megacolonic cats.

Emollient Laxatives. Emollient laxatives are anionic detergents that increase the miscibility of water and lipid in digesta, thereby enhancing lipid absorption and impairing water absorption. Dioctyl sodium sulfosuccinate and dioctyl calcium sulfosuccinate are examples of emollient laxatives available in oral and enema form. Dioctyl sodium sulfosuccinate at a dosage of 30 mg/kg/day had no effect on fecal consistency in Beagle dogs.[12]

Lubricant Laxatives. Mineral oil and white petrolatum are the two major lubricant laxatives available for the treatment of constipation. The lubricating properties of these agents impede colonic water absorption, as well as permit greater ease of fecal passage. These effects are usually moderate, however, and, in general, lubricants are beneficial only in mild cases of constipation.

Hyperosmotic Laxatives. This group of laxatives consists of the poorly absorbed polysaccharides (e.g., lactose, lactulose), the magnesium salts (e.g., magnesium citrate, magnesium hydroxide, magnesium sulfate), and the polyethylene glycols. Lactose is not effective as a laxative agent in all cats.[13] Lactulose is the most effective agent in this group. The organic acids produced from lactulose fermentation stimulate colonic fluid secretion and propulsive motility. Lactulose administered at a dosage of 0.5 mL/kg of body weight every 8 to 12 hours fairly consistently produces soft feces in the cat. Magnesium salts are not currently recommended in the treatment of feline constipation and idiopathic megacolon. Anecdotal reports of therapeutic successes have been reported with the polyethylene glycols.

Stimulant Laxatives. The stimulant laxatives (bisacodyl, phenolphthalein, castor oil, cascara, senna) are a diverse group of agents that have been classified according to their ability to stimulate propulsive motility. Bisacodyl, for example, stimulates nitric oxide–mediated epithelial cell secretion and myenteric neuronal depolarization.[14] Diarrhea results from the combined effect of increased mucosal secretion and colonic propulsion. Bisacodyl, at a dosage of 5 mg every 24 hours PO, is the most effective stimulant laxative in the cat. It may be given individually or in combination with fiber supplementation for long-term management of constipation. Daily administration of bisacodyl should probably be avoided, however, because of injury to myenteric neurons with chronic usage.[14]

Newer Laxative Agents

Chloride Channel Activators. Chloride channels are voltage-gated anion channels that allow the transport of chloride ions across cell membranes and play a critical role in fluid transport, maintenance of cell volume, and intracellular pH.[15,16]

Lubiprostone. Lubiprostone is a member of a group of compounds referred to as *prostones*.[17] Prostones are naturally occurring

bicyclic fatty acids formed by enzymatic oxidation of the 15-hydroxyl group of prostaglandins to the keto form. Lubiprostone is approved by the U.S. Food and Drug Administration for the treatment of chronic idiopathic constipation in humans. Lubiprostone activates type 2 chloride channels in the apical membrane of intestinal epithelial cells. This activity stimulates chloride secretion, followed by passive secretion of sodium and water (see Figure 1-17 in Chapter 1). The fluid-induced bowel distention secondarily induces peristalsis, but lubiprostone has no direct stimulatory effect on gastrointestinal smooth muscle. Insufficient safety and efficacy data are currently available to recommend the routine use of lubiprostone in dogs and cats.

Guanylate Cyclase Activators. Activation of the guanylate cyclase-C receptor increases cyclic guanosine monophosphate, thereby inducing signaling pathways that stimulate chloride and bicarbonate secretion through CFTR chloride channel–dependent mechanisms and, to a lesser extent, CFTR chloride channel–independent mechanisms, and inhibit sodium absorption by a sodium-proton exchanger.[15,16]

Linaclotide is a guanylate cyclase-C receptor agonist and intestinal secretagogue that improves bowel symptoms and accelerates colonic transit in chronic constipation.[18,19] Linaclotide has also been shown to attenuate nociceptive reflexes in response to colonic distention in three rodent models of visceral hypersensitivity.[18] Insufficient safety and efficacy data are currently available to recommend the routine use of linaclotide in dogs and cats.

μ-Opioid Antagonists. Postoperative ileus has multiple pathogenetic mechanisms. A dominant theme is the activation of enteric μ-opioid receptors resulting in inhibition of enteric nerve activity.[15,16]

Methylnaltrexone is a quaternary derivative of the μ-opioid receptor antagonist naltrexone.[20] N-terminal methylation reduces lipid solubility and prevents the drug from crossing the blood–brain barrier. Methylnaltrexone's reversal of opioid-induced inhibition of enteric nerve activity increase propulsion and secretory activity. Methylnaltrexone is clearly beneficial in the treatment of opioid-induced constipation; its efficacy in the treatment of postoperative ileus has not yet been definitively established. Insufficient safety and efficacy data are currently available to recommend the routine use of methylnaltrexone in dogs and cats.

Alvimopan has all of the same properties as methylnaltrexone; additionally, alvimopan accelerates colonic transit in healthy individuals, suggestive of a direct prokinetic effect.[20] Insufficient safety and efficacy data are currently available to recommend the routine use of alvimopan in dogs and cats.

Colonic Prokinetic Agents

Previous studies of feline colonic smooth muscle function have suggested that stimulation of colonic smooth muscle contraction might improve colonic motility in cats affected with idiopathic dilated megacolon.[6,7,21] Unfortunately, many gastrointestinal prokinetic agents have not proved useful in the therapy of feline constipation either because of significant side effects (e.g., bethanechol), effects limited to the proximal gastrointestinal tract (e.g., metoclopramide, domperidone, erythromycin), or market withdrawal because of cardiac 5-HT_4 effects. Some of the 5-HT_4 serotonergic agonists (e.g., cisapride, prucalopride, tegaserod) appear to have the advantage of stimulating motility from the gastroesophageal sphincter to the descending colon with relatively few side effects. Cisapride, for example, increases gastroesophageal sphincter pressure, promotes gastric emptying, and enhances small intestinal and colonic propulsive motility.[12,22] Cisapride enhances colonic propulsive motility through activation of colonic neuronal or smooth muscle 5-HT receptors in a number of animal species.[23,24] In vitro studies show that cisapride stimulates feline colonic smooth muscle contraction,[7,24] although it has not yet been conclusively shown that cisapride stimulates feline colonic propulsive motility in vivo. Anecdotal experiences suggest that cisapride is effective in stimulating colonic propulsive motility in cats affected with mild to moderate idiopathic constipation; cats with long-standing obstipation and megacolon are unlikely to show much improvement with cisapride therapy. Cisapride was widely used in the management of feline colonic motility disorders throughout most of the 1990s,[22,25,26] until it was withdrawn from the American, Canadian, and certain Western European markets in July 2000 following reports of untoward cardiac side effects in human patients. Cisapride causes QT interval prolongation and slowing of cardiac repolarization via blockade of the rapid component of the delayed rectifier potassium channel (I_{Kr}).[27] This effect may result in a fatal ventricular arrhythmia referred to as *torsades de pointes*. Similar effects have been characterized in canine cardiac Purkinje fibers,[28] but in vivo effects have not yet been reported in dogs or cats. The withdrawal of cisapride has created a clear need for new GI prokinetic agents although cisapride continues to be available from compounding pharmacies throughout the United States and other countries. A recent evidence-based data review of cisapride's efficacy in the treatment of human constipation and constipation-predominant irritable bowel syndrome (IBS) was carried out by the Cochrane Collaboration.[29] The authors concluded that "no clear benefit could be demonstrated with cisapride."[29]

Tegaserod is a potent partial nonbenzamide agonist at 5-HT_4 receptors and a weak agonist at 5-HT_{1D} receptors.[30,31] Tegaserod has definite prokinetic effects in the canine colon, but its effects in the feline colon are not known. Intravenous doses of tegaserod (0.03 to 0.3 mg/kg) accelerate colonic transit in dogs during the first hour after intravenous administration.[30] Tegaserod at doses of 3 to 6 mg/kg PO has also been shown to normalize intestinal transit in opioid-induced bowel dysfunction in dogs,[32] suggesting it could prove useful in other disorders of intestinal ileus or pseudoobstruction. Eventually, tegaserod was also shown to prolong the QT interval and delay cardiac repolarization as had been reported with cisapride. Tegaserod was marketed under the trade name of Zelnorm in the United States in September 2002 and subsequently removed from American and other markets in 2006. As with many other drugs in companion animal medicine, tegaserod was not licensed for the treatment of canine or feline gastrointestinal motility disorders.

Prucalopride is a potent 5-HT_4 receptor agonist that stimulates GMCs and defecation in the dog and cat.[33,34] Prucalopride also appears to stimulate gastric emptying in the dog.[35] In lidamidine-induced delayed gastric emptying in dogs, prucalopride (0.01 to 0.16 mg/kg) dose-dependently accelerates gastric emptying of dextrose solutions. Prucalopride is marketed as Resolor by Movetis in Europe.

Mosapride citrate, a substituted benzamide, is a novel 5-HT_4 receptor agonist that increases gastric emptying in rats and dogs, and increases electrically evoked contractions in the isolated guinea pig ileum.[36,37] Mosapride stimulates acetylcholine release from the myenteric plexus via activation of 5-HT_4 receptors, but has no real affinity for D_2 dopamine, 5-HT_1, 5-HT_2 receptors, or α_1-adrenoceptors. Mosapride restores gastric motility in dogs with vincristine-induced gastric hypomotility,[38] and therefore may be clinically useful in other

gastric emptying disorders. Mosapride is apparently without effect on distal gastrointestinal tract motility, and therefore may not prove useful in disorders of constipation. Mosapride is marketed as Pronamid by DS Pharma Animal Health in Japan.

Misoprostol is a prostaglandin E_1 analogue that reduces the incidence of nonsteroidal antiinflammatory drug-induced gastric injury. The main side effects of misoprostol therapy are abdominal discomfort, cramping, and diarrhea. Studies in dogs suggest that prostaglandins may initiate a giant migrating complex pattern and increase colonic propulsive activity.[39] In vitro studies of misoprostol show that it stimulates feline and canine colonic smooth muscle contraction.[40] Given its limited toxicity, misoprostol may be useful in cats (and dogs) with severe refractory constipation.

Ranitidine and nizatidine, classic histamine H_2 receptor antagonists, may also stimulate canine and feline colonic motility. These drugs stimulate contraction apparently through inhibition of tissue acetylcholinesterase and accumulation of acetylcholine at the motor endplate. It is not yet clear how effective these drugs are in vivo, although both drugs stimulate feline colonic smooth muscle contraction in vitro.[41] Cimetidine and famotidine, members of the same classification of drug, are without this effect.

Surgery

Colectomy should be considered in cats that are refractory to medical therapy. Cats have a generally favorable prognosis for recovery following colectomy, although mild to moderate diarrhea may persist for weeks to months postoperatively in some cases.[42,43] Pelvic osteotomy without colectomy has been recommended for cats with pelvic fracture malunion and hypertrophic megacolon of less than 6 months duration.[44] Symphyseal distraction-osteotomy with spirally fashioned orthopedic wire has also been used in the surgical management of this disorder.[45] Pathologic hypertrophy may be reversible with early pelvic or symphyseal distraction osteotomy in such cases. Some surgeons still prefer colectomy in this instance because of the technical difficulty of some pelvic osteotomies.[46]

Subtotal colectomy is an effective treatment for feline idiopathic megacolon or megacolon secondary to the mechanical obstruction created by old, healed pelvic fractures. Recommendations for removal of the ileocolic valve and ileum vary in cats with megacolon. The ileocolic blood vessels tether the distal ileum and proximal ascending colon, preventing anastomosis to the distal colon; thus if a complete colectomy is performed, these vessels must be sacrificed. This necessitates removing the ileum, which has important normal functions in water, vitamin B_{12}, and bile salt resorption, and performing a jejunocolic anastomosis. In spite of this concern, postoperative intestinal function was normal in four cats evaluated after subtotal colectomy and jejunocolic anastomosis.[43,47] The ileocolic valve also minimizes colonic bacterial access to the small intestine,[44] so preservation of the valve would be ideal to minimize small intestinal bacterial overgrowth and deconjugation of bile salts. However, preservation of the ileocolic junction necessitates leaving several centimeters of the ascending colon to ensure a tension-free anastomosis, possibly predisposing these cats to recurrent constipation. To evaluate these concerns, cats with megacolon treated with colectomy were studied retrospectively. Cats with excision of the ileocolic junction had significantly looser stool on long-term followup.[43] However there was no difference in the incidence of constipation between cats with preservation versus excision of the ileocolic junction.[48] This is perhaps explained by in vitro experiments with ascending and descending colonic smooth muscle from cats with clinical megacolon showing that smooth muscle dysfunction is less severe in the ascending colon.[8]

When the ileocolic junction is preserved, the ascending colon is transected approximately 3 cm distal to the ileocolic junction to ensure a tension-free anastomosis. An end-to-end colocolostomy is performed using single interrupted sutures of 4-0 polydioxanone.[47] The successful use of a biofragmentable anastomosis ring has also been reported.[46] The omentum is wrapped around the anastomotic site and the abdomen is thoroughly lavaged with a warm, balanced electrolyte solution. All lavage fluid is aspirated from the peritoneal cavity before the incision is closed.

Cats recovering from colectomy are maintained on intravenous fluids until they commence eating and drinking. Electrolytes are supplemented if necessary. Bowel movements may be soft or loose and more frequent than normal. A highly digestible, low-residue diet is fed. In cats with profuse postoperative diarrhea in which small intestinal bacterial overgrowth is suspected, a short course of antibiotics is administered.

Prognosis

Many cats have one or two episodes of constipation without further recurrence, although others may progress to complete colonic failure. Cats with mild to moderate constipation generally respond to conservative medical management (e.g., dietary modification, emollient or hyperosmotic laxatives, colonic prokinetic agents). Early use of colonic prokinetic agents (in addition to one or more laxative agents) is likely to prevent the progression of constipation to obstipation and dilated megacolon in these cats. Some cats may become refractory to these therapies, however, as they progress through moderate or recurrent constipation to obstipation and dilated megacolon. These cats eventually require colectomy. Cats have a generally favorable prognosis for recovery following colectomy, although mild to moderate diarrhea may persist for 4 to 6 weeks postoperatively in some cases.

Irritable Bowel Syndrome

IBS is a human chronic gastrointestinal tract disorder of unknown origin that is characterized by abdominal pain and altered bowel habits in the absence of detectable biochemical or structural abnormalities.[49] IBS is one of the most common functional GI disorders with an estimated prevalence of 10% to 15% in Western adult populations. Direct and indirect costs of IBS reach up to $30 billion per year in the United States alone.[49] IBS is commonly subdivided into different phenotypes depending upon the most prevalent bowel habit: diarrhea-predominant IBS (IBS-D), constipation-predominant IBS (IBS-C), and mixed features IBS (IBS-M).[50] Because of the inability of animal species to describe clinical symptoms such as abdominal pain and discomfort, IBS is not a very-well-defined syndrome in veterinary medicine. Nonetheless, recurring vomiting and diarrheal disorders are seen in companion animal species that are unaccompanied by mucosal morphologic change, and are presumed therefore to be of functional or physiological origin.[51] The reader is referred to Chapter 41 for a more detailed discussion of IBS and its management.

A fiber-responsive large bowel diarrheal syndrome similar to IBS in humans has been characterized in dogs.[51] Affected animals have a chronic idiopathic large bowel-type diarrhea characterized by excessive fecal mucus, hematochezia, and tenesmus. Abdominal pain and weight loss are occasionally reported by pet owners. Multiple diet changes and empirical medications fail to relieve clinical signs. Medical investigation is negative for bacterial and other pathogen infections, colitis, and colonic neoplasia, and the term chronic large bowel diarrhea is applied to the patient's disorder. Dogs

affected with this syndrome may respond to the feeding of a highly digestible diet that is supplemented with soluble fiber.[51]

The reader is referred to Chapter 41 for more detailed discussion of IBS and its management.

NEOPLASIA

Robert J. Washabau

Etiology

In dogs, tumors of the large intestine are more common than tumors of the stomach and small intestine. The mean age of dogs affected with colonic neoplasia is variably reported between 7 and 11 years of age.[1] Most colonic tumors of dogs are malignant and include the adenocarcinomas, lymphosarcomas, and gastrointestinal stromal tumors (Table 58-10). Other reported tumors include leiomyosarcoma, neurofibrosarcoma, fibrosarcoma, and ganglioneuroma.[2-11] Leiomyosarcomas are the most common (91%) of the gastrointestinal stromal tumors.[12-15] Most colonic neoplasia develop in the descending colon and rectum, although leiomyosarcomas more frequently develop in the cecum.[4,6] Local tumor invasion apparently occurs at a slower rate with canine colonic neoplasia, and metastasis to distant sites is relatively uncommon. Benign colonic neoplasia (e.g., adenomas, adenomatous polyps, and leiomyomas) also occur, although they are less common than malignant tumors. Malignant transformation of adenomatous polyps to carcinoma in situ and invasive adenocarcinoma has been demonstrated in the dog just as it has in humans.[1,16,17] Extramedullary plasmacytomas are uncommon tumors of the gastrointestinal tract, but many of these occur in the large intestine and rectum.[12,13] All of the aforementioned tumors are associated with signs of inflammation and obstruction (e.g., hematochezia, tenesmus, and dyschezia). Carcinoids (rare 5-hydroxytryptamine [5-HT] secreting tumors) are occasionally associated with diarrhea because of the effects of 5-HT on secretion and motility.

In cats, adenocarcinoma (46%) is the most common tumor of the large intestine (see Table 58-10), followed by lymphosarcoma (41%) and mast cell tumors (9%).[14,15,18] The mean age of cats affected with colonic neoplasia is 12.5 years. The descending colon (39%) and the ileocolic sphincter (28%) are the most common sites of colonic neoplasia in the cat. Unlike colonic tumors in the dog, feline colonic tumors have a high rate (63%) of metastasis and, of course, metastasis is associated with decreased survival time. Metastatic sites include colonic lymph nodes, mesenteric lymph nodes, liver, spleen, bladder, urethra, omentum, mesocolon, lungs, duodenum, and peritoneum.

Table 58-10 Distribution of Colonic Neoplasia in Dogs and Cats

Tumor Type	Dog	Cat
Adenocarcinoma	43%	46%
Lymphosarcoma	19%	41%
Mast cell tumors	<1%	9%
Stromal tumors	19%	2%
Adenomas/polyps	17%	1%
Plasmacytomas	2%	<1%

Alimentary lymphoma is less common in dogs than in cats, representing only 7% of all canine lymphomas.[19] Lymphoma is the most common malignancy in cats, and the GI tract is the most common predilection site for this tumor. Feline alimentary lymphoma may affect any component of the digestive system (stomach, intestine, colon, liver, biliary tract, and pancreas), but it most commonly involves the small intestine.[19-25] Lymphoma can be classified histologically into small cell (lymphocytic; low grade; well differentiated) or large cell (lymphoblastic; high grade; undifferentiated) types.[19] Low-grade lymphocytic lymphoma has a higher reported incidence than high-grade lymphoblastic lymphoma in most case series.[20-25] Large granular lymphoma is a subtype that is characterized by the presence of natural killer T lymphocytes with intracytoplasmic granules. Clinically, these types of lymphoma are distinct entities with different clinical presentations, therapies, and outcomes.[19]

Although infection with FeLV and FIV are major risk factors for the development of feline lymphoma, cats with GI lymphoma are usually serologically negative for both infections.[19] Feline gastrointestinal lymphoma has been associated with *Helicobacter* infection[26] and exposure to household cigarette smoke.[27]

Pathophysiology

Mechanical obstruction is the most common pathophysiologic consequence of locally invasive colonic tumor. Other nonneoplastic processes such as intussusception, FIP granuloma, fibrosing stricture, linear and nonlinear foreign bodies, hematoma, and phycomycosis lesions also cause intraluminal obstruction. Prolonged obstruction induces smooth muscle hypertrophy proximal to the site of the obstruction.[28] Other pathophysiologic consequences of intestinal obstruction are pronounced fluid secretion and malabsorption of water and solutes; fluid, electrolyte, and acid–base disturbances; proliferation and translocation of luminal bacteria; and inflammation, devitalization, and perhaps even perforation of the colon. Secretory diarrheas have been reported with carcinoids of the rectum, colon, and intestine.

Clinical Examination

Most affected dogs have signs of hematochezia, mucoid feces, tenesmus, and dyschezia of varying severity. Importantly, the clinical signs observed with colorectal neoplasia are often indistinguishable from other causes of obstruction or chronic colitis. Hematochezia is infrequently reported with leiomyosarcomas or leiomyomas presumably because these tumors do not typically involve the mucosa. Other clinical signs depend on the tumor type and location. Vomiting, malabsorption, and cachexia may be observed, for example, when multifocal or diffuse tumors (e.g., lymphosarcoma) involve the proximal portions of the gastrointestinal tract. Gastrointestinal stromal tumors, particularly the leiomyomas, have been associated with hypoglycemia and the resulting clinical signs of muscular weakness and seizure activity.[29] Functional plasmacytomas secrete a single class of immunoglobulin and affected animals may go on to develop hyperviscosity syndrome, for example, retinal bleeding and epistaxis. If colonic perforation has occurred, animals may be presented moribund with fever, lethargy, anorexia, vomiting, abdominal pain, and collapse.

Vomiting (65%), diarrhea (52%), and weight loss (46%) are common clinical signs in cats with colonic neoplasia.[16] Most cats with colonic (and alimentary) lymphosarcoma are FeLV-negative. These lymphomas are still believed to be caused by FeLV,

Table 58-11 Characteristics of Feline Alimentary Lymphocytic and Lymphoblastic Lymphoma

Feature	Lymphocytic Lymphoma	Lymphoblastic Lymphoma
Clinical signs	Gradual weight loss, vomiting, diarrhea, decreased appetite	Rapid weight loss, anorexia, vomiting, diarrhea
Duration of clinical signs	Typically prolonged (weeks to months)	Typically acute (days to weeks)
Physical examination and ultrasonographic findings	May be normal; thickened bowel loops; palpable masses uncommon	Palpable mass lesions common
Diagnostic workup	Aspiration cytology, endoscopy, full-thickness surgical biopsy	Aspiration cytology, endoscopy, full-thickness surgical biopsy
Pitfalls of diagnostic testing	False negatives on aspiration cytology; differentiation of LSA from IBD	False negatives on aspiration cytology, differentiation of LSA from IBD
Surgical intervention	Useful for definitive biopsy	Therapeutic if obstructing mass lesions are present
Therapy	Chemotherapy–prednisone and chlorambucil; radiation therapy–may prolong survival	Chemotherapy–CHOP, CCNU, MOPP; radiation therapy–may prolong survival
Response to therapy	75% to 90% response rate	50% to 60% response rate
Outcome	Most cats live >2 years and are managed long-term with chemotherapy	Median survival 6 to 7 months; if complete response to therapy 40% chance of living a year or longer

CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone ± L-asparaginase ± methotrexate; CCNU, lomustine; IBD, inflammatory bowel disease; LSA, lymphosarcoma; MOPP, mustargen, vincristine, prednisone, procarbazine.
Adapted from Gieger T: Alimentary lymphoma in cats and dogs. Vet Clin North Am Small Anim Pract 41:419–432, 2011; with permission.

with integrated virus causing neoplastic transformation in the absence of viral replication. Although most lymphomas in cats appear to be comprised of malignant T lymphocytes, most colonic (and alimentary) lymphomas are of B-cell origin. Alimentary and colonic lymphomas originate primarily from submucosal lymphocytes and/or mucosal lymphoid follicles, although two studies reported an epitheliotropic form of T-cell intestinal lymphomas.[30,31] Epitheliotropic T-cell lymphomas have not yet been reported in the feline colon. Feline lymphocytic lymphoma is typically a slowly progressive disease with a protracted history, whereas lymphoblastic lymphoma is more often characterized by an acute onset (Table 58-11).[19]

Diagnosis

Canine rectal adenocarcinomas are palpable in 60% to 80% of clinical cases, but colonic and cecal lesions are not as readily apparent on physical examination.[1,13,28,32,33] More than 50% of cats with colonic masses have a palpable abdominal mass.[16]

Survey and contrast radiographic and ultrasonographic studies have been employed with varying levels of success in the diagnosis of canine and feline colonic neoplasia. Annular stenotic lesions associated with adenocarcinoma of the colon may manifest as proximal colonic dilation on survey radiographs. Radiographic contrast material more precisely outlines the narrowing of the lumen at the site of the tumor. Although still of some clinical utility, contrast studies have been largely superseded by ultrasonography and other imaging modalities. Ultrasonography is presently considered to be the most effective means of diagnosing colonic tumors in dogs and cats and appears to be useful in evaluating mural lesions and associated abdominal changes such as lymphadenopathy (Figure 58-16).[33] Ultrasonography was reported to be useful 84% of the time in localizing feline colonic neoplasia in one study.[16] Ultrasonographic features of colonic tumors include transmural wall thickening with complete loss of the normal wall layering, fluid accumulation proximal to the lesion, and reduced regional motility.[33] Transabdominal fine-needle aspiration, peritoneal fluid cytology, and endoscopic

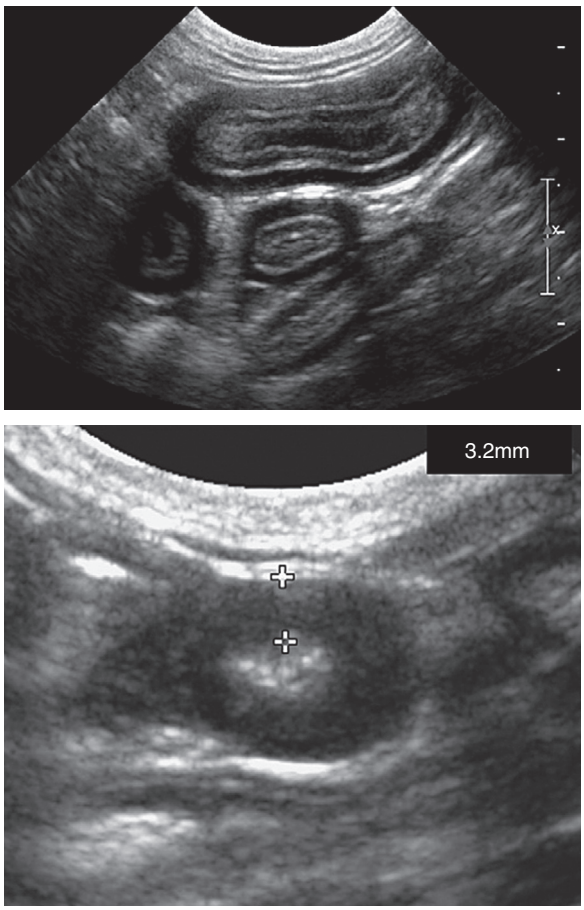

Figure 58-16 Abdominal ultrasonogram of a cat with lymphocytic lymphoma. (Reprinted with permission from Gieger T: Alimentary lymphoma in cats and dogs. Vet Clin North Am Small Anim Pract 41:419–432, 2011.)

exfoliative cytology may be useful in the diagnosis of lymphoma, but histopathology is generally required for a definitive diagnosis of other colonic neoplasia. CT and MRI scanning have not been sufficiently evaluated for reasonable comparisons to be made with ultrasonography.

Flexible colonoscopy with mucosal biopsy is the preferred method of diagnosis for colonic neoplasia. Endoscopic abnormalities may include mass effect, mucosal bleeding, increased mucosal friability, erosions and ulcers, and circumferential luminal narrowing with submucosal infiltrative lesions. Multiple biopsy specimens should always be taken from diseased tissue, adjacent healthy tissue, as well as the transition zone between healthy and diseased tissue. With tumor necrosis, the pathologist has a much better chance of diagnosing and staging the disease by evaluating nonnecrotic tissue.

Treatment

The treatment of colonic neoplasia will depend upon tumor type, anatomic location, and presence and extent of metastases (Box 58-2; see Tables 58-12 and 58-13). Complete surgical excision is the recommended therapy for focal adenocarcinomas, cecal leiomyosarcomas, and obstructive lymphomas. Multiagent chemotherapy (prednisone, vincristine, cyclophosphamide) has been used to treat colonic lymphoma, but it does not appear to alter survival time in affected cats.[16] Cyclooxygenase (COX)-2 upregulation may contribute to the growth characteristics of some canine colonic neoplasia.[34-36] Consequently, selective COX-2 inhibitors (e.g., piroxicam, meloxicam) may be useful in the treatment of some canine colonic neoplasia. Plasmacytomas may be managed with adjuvant chemotherapy (e.g., prednisone and melphalan) following surgical excision. Radiation therapy has been used to palliate recurrent adenocarcinomas with varying results and complications; however, postradiation peritonitis and perforation have been reported in some cases.[37]

Surgery

Preoperative Considerations

In dogs with rectal or colonic tumors, appropriate staging is vital to determine the extent of local and systemic disease. In many cases, a careful digital rectal examination can delineate the extent of local disease in the rectum and provide subjective information on the enlargement of regional lymph nodes. Thoracic radiographs are

Box 58-2 Treatment of Colonic Neoplasia in Dogs and Cats

Colonic tumors	→	Surgical excision
Lymphoma	→	Chemotherapy
Carcinomas	→	Cyclooxygenase-2 inhibitors
Plasmacytomas	→	Prednisone, melphalan
Recurrences	→	Radiation therapy

Table 58-12 Chemotherapy Protocols for Feline Alimentary Lymphocytic Lymphoma

Chlorambucil Dose (PO)	Prednisone Dose (PO)	Response Rate	Median Response Duration (Months)	Median Survival Time (Months)	References
2 mg q48-72h	5 or 10 mg/cat/day	56% CR; 39% PR	30 mo if CR; 14 mo if PR	n/a	25
15 mg/m^2 q24h × 4 days every 3 wk	3 mg/kg q24h then 1 to 2 mg/kg if remission	76% CR	19 mo	19 mo if CR; 4 mo if not CR	24
15 mg/m^2 q24h × 4 days every 3 wk	3 mg/kg q24h then 1 to 2 mg/kg if remission	69% CR	16 mo	17 mo overall; 23 mo if CR	48
20 mg/m^2 every 2 wk	Variable	96% CR	26 mo		23

CR, complete response; n/a, no data available; PR, partial response.
Adapted from Gieger T: Alimentary lymphoma in cats and dogs. Vet Clin North Am Small Anim Pract 41:419–432, 2011, with permission.

Table 58-13 Chemotherapy Protocols for Feline Alimentary Lymphoblastic Lymphoma

Drugs	Response Rate	Median Response Duration (Months)	Median Survival Time (Months)	Reference
CHOP	18% CR	n/a	2.7 mo	48
COP	75% CR	8 mo	9 mo	49
COP	32% CR	7 mo if CR	n/a	18
COP or COP then doxorubicin	n/a	3 mo if COP; 9 mo if COP then doxorubicin	n/a	50
CVM	52%	4 mo	n/a	51
CVM-L	62% CR; 20% PR		7 mo if CR	52
Doxorubicin	42%	Median 2 mo		53
Doxorubicin	22%	n/a	n/a	54
CHOP-L-M	47% CR; 33% PR	22 mo if CR; 4 mo if PR	22 mo if CR; 4 mo if PR	55
CHOP-L-M	n/a	5 mo	10 mo	56
CHOP-L-M	74% CR; 14% PR	9 mo if CR	10 mo if CR	57

C, Cyclophosphamide; CR, complete response; H, hydroxydaunorubicin, doxorubicin; L, L-asparaginase; M, methotrexate; n/a, no data available; O, vincristine; P prednisone or prednisolone; PR, partial response; V, vincristine.
Adapted from Gieger T: Alimentary lymphoma in cats and dogs. Vet Clin North Am Small Anim Pract 41:419–432, 2011, with permission.

made to rule out pulmonary metastatic disease. Abdominal ultrasonography is used to rule out abdominal metastatic disease and to guide aspiration and biopsy of enlarged iliac lymph nodes. Proctoscopy and colonoscopy often reveal the local extent of neoplastic disease. It is vital that colonoscopy be continued oral to rectal tumors as additional neoplasms are reported in the colon in a percentage of these cases.[38,39]

Mechanical cleansing is recommended before surgery of the large intestine in human, although preoperative enemas are contraindicated in cases of suspected large intestinal perforation. Perioperative antibiotics are administered to minimize the chance of surgical infection. Randomized, controlled clinical trials of antimicrobial prophylaxis in canine and feline colonic surgery have not been conducted, but based on human trials,[40] antibiotics effective against aerobes, especially the anaerobes that predominate in the large intestine, are administered intravenously once at the beginning of surgery. Antibiotics are not administered again unless either there is contamination at surgery or the procedure takes longer than 2 hours. In the latter case a second intravenous dose of antibiotics is administered. Antibiotics are continued postoperatively in cases with preoperative or surgical contamination based on the results of operative culture and sensitivity testing.

Operative Considerations

In animals requiring surgery for cecal or colonic disease, a ventral midline laparotomy is performed. After conducting a thorough abdominal exploration for concurrent or metastatic disease, the affected area of the large intestine is packed off with moistened laparotomy sponges. Resection of the cecum can be performed with or without preservation of the ileocolic junction, depending on the extent of the local disease. In most cases of cecal neoplasia a complete resection and jejuno- or ileocolonic anastomosis is performed to ensure adequate tumor resection.

Various techniques and surgical approaches have been described for removal of rectal tumors.[39] The approach and technique vary with the extent and location of the mass(es). Tumors in the proximal rectum may be accessed by a ventral midline laparotomy combined with a pelvic osteotomy. Healing of the distal colon and/or proximal rectum is complicated by the poor blood supply to this area of the large intestine.[41] A dorsal approach has been described for tumors involving the middle third of the rectum[39,42]; however, many tumors in this area are also amenable to resection via a rectal pull-through.[39,43] The plexus of pelvic nerves at the peritoneal reflection is vital to postoperative fecal continence. In an experimental study on healthy dogs, both transection alone and resection of 4 cm of rectum via a dorsal approach resulted in fecally continent dogs. Resection of 6 cm of the rectum, including the peritoneal reflection, caused fecal incontinence.[42] This limitation on resection is problematic in animals with larger rectal tumors, as a 2-cm gross margin is recommended on both sides of the tumor.[39,44,45]

Postoperative Considerations

Postoperative treatment depends largely on the underlying reason for cecal, colonic, or rectal surgery. Pre- or postoperative epidural anesthesia using a combination of local anesthetic and narcotic provides effective pain relief. Animals receiving epidural anesthesia may not be able to urinate normally for 12 to 24 hours, hence bladder size must be evaluated frequently and the bladder gently expressed or catheterized if needed. Narcotics, narcotic agonists/antagonists, partial μ-agonists, and COX-2 inhibitory class nonsteroidal antiinflammatory drugs are alternatives for pain management in dogs. Narcotic agonists/antagonists are effective in cats.

Adequate nutrition is vital for dogs and cats recovering from large intestinal surgery. Early feeding increases anastomosis strength and promotes enteric epithelial proliferation and function.[46,47] Ideally, the diet should provide a source of soluble fiber which, when hydrolyzed to short-chain fatty acids, stimulates colonic mucosal proliferation.[46] In animals with fecal continence difficulties after extensive rectal resection, a low-residue diet is fed twice daily. The animal is then walked for 20 to 30 minutes after eating. In many cases, the gastrocolic reflex will result in defecation and near complete emptying of the colon during this time, minimizing subsequent fecal soiling in the house.

Prognosis

The prognosis for adenomatous polyps, leiomyomas, and fibromas is generally favorable. Adenocarcinomas, lymphosarcomas, and plasmacytomas tend to recur and/or metastasize to distant sites. Dogs with annular colorectal adenocarcinomas have a particularly poor prognosis with a mean survival time of only 1.6 months.[1,32] The prognosis for most malignant tumors is generally guarded. Surgical resection alone results in 22 month (dogs) and 15 month (cats) average survival times in dogs and cats.[1,16] It should be noted that cats undergoing subtotal colectomy for colonic adenocarcinoma had a longer survival time than those receiving mass resection only (median survival time of 138 days versus 68 days).[16] Not surprisingly, cats with metastatic lesions had much shorter survival times, 49 days versus 259 days.[16]

ULCER

David E. Holt and Robert J. Washabau

Ulcer Associated with Intervertebral Disk Disease and Steroid Treatment

Etiology

Colonic ulcers may develop following glucocorticoid therapy and neurosurgery in dogs with spinal cord injury. Gastric ulcers are of greater prevalence in this circumstance, but colonic ulcers may be equally devastating.[1-4] Affected dogs were most often Dachshunds with thoracolumbar disk disease treated with decompressive surgery and dexamethasone at doses of 0.25 to 4.4 mg/kg/day. Colonic ulcer is not a frequent complication of either intervertebral disk disease or corticosteroid therapy. In the initial report of the condition, colonic perforation was described in two dogs out of "several thousand."[1] Ten additional cases were subsequently reported until 1986,[2-4] and since then no additional reports have been published. This may represent increased awareness of the condition, reluctance to publish on a previously described condition, or perhaps a shift away from the use of dexamethasone in dogs with intervertebral disk disease. Colonic perforation is infrequent in humans treated with corticosteroids for neurologic disease[5] but may occur more commonly when dexamethasone is used.[6] In nonneurologic conditions, the frequency of perforation is influenced by the underlying disease and the presence of a diverticulum in the sigmoid colon.[7] Why this lesion develops in some dogs but not others is not readily explained.

Pathophysiology

There are many factors that probably interact to cause colonic perforation in this cohort of dogs. Spinal cord injury and sympathetic nerve stimulation associated with pain likely slow colonic transit and increase fecal retention. It is also likely that immobility and pain associated with abdominal muscle contraction inhibit voluntary defecation in dogs with intervertebral disk disease. This leads to fecal retention and colonic distention. In humans, it is postulated that prolonged increases in colonic intraluminal pressure lead to mucosal ischemia resulting in progressive necrosis, ulceration, and perforation.[6]

The effects of corticosteroids have not been extensively studied in the colon and are largely extrapolated from information gained in gastric studies.[8] Corticosteroids are presumed to decrease colonic mucus production, alter the composition of colonic mucus, and decrease mucosal repair in the colon, leading to perturbations in the colonic mucosal barrier.[3] These effects are thought to be secondary to depletion of local prostaglandin production. In addition, glucocorticoids inhibit the expression of inducible nitric oxide synthase in vascular endothelial cells,[9] perhaps further affecting colonic blood supply.[10] Together, these factors coalesce to induce erosion of the colonic mucosa, colonic perforation, and peritonitis.[3] The relationship between intervertebral disk disease, corticosteroid treatment, and colonic perforation is highlighted by a report describing 29 dogs with gastrointestinal perforation associated with administration of a COX-2 inhibitor. None of the latter dogs were treated for intervertebral disk disease, and none of the perforations were in the colon.[11]

The left colic flexure or proximal portion of the descending colon appears to be at greatest risk for colonic ulceration and perforation; two-thirds of the published cases were reported at this site.[3,4] Nonambulatory neurosurgical patients treated with dexamethasone are at greatest risk for development of colonic perforation. Colonic perforation is often preceded by variable nonspecific signs, most frequently depression, anorexia, and emesis. Perforation appears to be associated with 100% mortality, emphasizing the importance of prevention and early clinical recognition.

Clinical Examination

Middle aged, male dogs are most often affected, usually within 5 to 7 days of surgery. Depression, anorexia, emesis, abdominal pain, constipation, melena, and fever are the most important clinical signs. Many of these signs are subtle and easily missed by some pet owners. The immunosuppressive properties of glucocorticoids may mask the initial signs of peritonitis associated with colonic perforation.

Diagnosis

If suspected, patients at risk should be carefully evaluated for perforation and peritonitis. Imaging studies (radiography and ultrasonography), abdominocentesis, peritoneal lavage, and exploratory surgery, if indicated, should be considered in patients at risk. A diagnosis of peritonitis is made from cytologic evaluation of peritoneal fluid or measurements comparing glucose, pH, and lactate concentrations in peripheral blood and peritoneal fluid.[12] The perforations most often occur on the antimesenteric surface of the proximal descending colon.[3]

Treatment

Treatment involves rapid circulatory resuscitation with crystalloids and colloids, administering broad-spectrum bactericidal antibiotics, and emergency laparotomy. The perforation of the colon is identified, the affected area of bowel is resected, and the remaining colon is anastomosed. The abdominal cavity is thoroughly lavaged with warm balanced electrolyte solution. All of the lavage fluid and associated peritoneal contaminants are aspirated. Depending on the degree of residual peritoneal contamination, the abdomen is either closed, closed after placement of closed suction drains, or left open to facilitate drainage and covered with a sterile bandage.

Prognosis

Colonic ulcer and perforation is generally associated with a poor prognosis. A preventive approach to this complication appears to be warranted in high-risk patients: (a) use of less-potent glucocorticoids (e.g., prednisone or prednisolone) instead of dexamethasone, and (b) limited or no use of glucocorticoids.

Histiocytic Ulcerative Colitis (Granulomatous Colitis of Boxer Dogs)

Etiology

HUC was first reported by Van Kruiningen in a kennel of Boxer dogs in 1965.[13] A number of other cases have been reported since then, and a similar disease process has been reported in the French Bulldog. The pathognomonic lesion of this disease is a mucosal infiltration with large numbers of macrophages staining positively with PAS, and accompanied by mucosal ulceration and loss of goblet cells.[14] Although the term *histiocytic ulcerative colitis* describes many features of the disease, it understates the mixed lymphocytic plasmacytic component of the inflammation, and the term *granulomatous colitis* has been adopted to more completely characterize the histopathology. For the most part, the disease is localized to the large intestine and regional lymph nodes; however, in some instances PAS-positive macrophages may be found in lymph nodes remote from the intestine, suggesting that there is limited systemic distribution of the disease. Historically, an infectious etiology had been speculated but never proved. At least two independent lines of investigation now point to an adherent and invasive *E. coli* as the underlying etiology of granulomatous colitis.[14,15] The pathophysiology, clinical examination, diagnosis, and therapy of granulomatous colitis of Boxer dogs and other breeds are discussed in the "Inflammation" section.

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