Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

CHAPTER 34

Antidiarrheal Agents

Robert J. Washabau

Pathogenesis of Diarrhea

When clinical signs are acute and there are no systemic signs of illness, symptomatic therapy often takes precedence over achieving a precise diagnosis. When the duration of clinical signs is chronic (>3 weeks), or if there are systemic signs of illness, a determined effort should be made to achieve a specific diagnosis. Diarrhea in companion animals may develop through one or more pathophysiologic mechanisms,[1] but one mechanism tends to predominate.[1,2]

Luminal Maldigestion

Small intestinal bacterial overgrowth (SIBO) and Exocrine pancreatic insufficiency (EPI) are the best examples of luminal maldigestion in companion animals. SIBO (or antibiotic-responsive diarrhea) and EPI induce maldigestion, steatorrhea, and diarrhea because of bacterial degradation of pancreatic enzymes (SIBO) or insufficiency of enzyme secretion (EPI). Fat maldigestion and steatorrhea may also result from deficiencies in bile salt secretion (e.g., intra- or extrahepatic cholestasis) or abnormalities in the enterohepatic recirculation of bile salts (e.g., portosystemic vascular shunts).

Villous Atrophy

Atrophy of the villous absorptive surface area occurs with many pathologic processes. Atrophy is caused by accelerated loss of enterocytes or decreased production of enterocytes by stem cells in the crypts. Stem cells retain the ability to reconstitute the overlying mucosa, but regeneration may take days to weeks depending upon the pathologic process. Viral infections (e.g., parvovirus, coronavirus, rotavirus) are the most important causes of damage to villus enterocytes in dogs and cats. Viral enteritides are usually acute, self-limiting infections that resolve over a matter of a few days to 1 to 2 weeks. Villous atrophy may result from immune-mediated processes such as gluten-sensitive enteropathy in the Irish Setter dog,[3] or as a consequence of food sensitivity reactions in both dogs and cats.[4] Food sensitivity reactions are increasingly recognized as an important cause of villous atrophy, malassimilation, and diarrhea in companion animals. Immunosuppressive drugs (e.g., glucocorticoids, vincristine, azathioprine, cyclophosphamide) may also cause severe villous atrophy. Glucocorticoids are frequently prescribed in the management of inflammatory bowel disease (IBD). Antiinflammatory doses of glucocorticoids appear to have minimal effect on epithelial cell turnover, but immunosuppressive doses may abolish epithelial cell renewal. These effects are usually reversible with discontinuation of therapy.

Enterocyte Dysfunction

Enterocyte dysfunction is a common finding in many of the primary gastrointestinal disorders of dogs and cats. Enterocyte dysfunction may be seen with inflammation, infection, malnutrition, malignancy, ischemia, and with certain drug therapies (e.g., misoprostol). Gastrointestinal tract pathology induces enterocyte dysfunction by impeding Cl^- transport, the Na^+/glucose cotransporter, the voltage-dependent calcium channel, or any other component of the cell's signal transduction pathways.[2]

Brush-Border Membrane Maldigestion

SIBO is the major cause of brush-border membrane damage in the canine intestine. Hydrolase and other brush-border transport proteins are degraded by bacteria, particularly anaerobes, during proliferation of small intestinal bacteria. Damage to the brush-border is usually reversible following appropriate antimicrobial therapy. Similar brush-border membrane maldigestion has been documented in canine IBD, but these changes are also readily reversible with resolution of IBD.[1,2] A specific brush-border membrane malabsorption has been documented in Giant Schnauzers with cobalamin deficiency and malabsorption.[5]

Mucosal Barrier Disruption

Just as the stomach has evolved with mucosal barrier properties to reduce the deleterious effects of gastric acidity, the intestine has evolved with mucosal barrier properties to exclude bacterial pathogens and to maintain oral tolerance.[6-9] Barrier disruption may be caused by moderate to severe inflammation, ulceration, ischemia, cytotoxic drugs, and certain protein-losing states. Inflammatory mediators such as interferon-γ, tumor necrosis factor-α, and platelet-activating factor mediate some of the effects on mucosal barrier disruption.[10]

Hypersensitivity

The role of dietary hypersensitivity reactions in the pathogenesis of canine and feline chronic diarrhea is incompletely understood, although recent studies suggest that adverse reactions to food antigens are common in dogs and cats with chronic diarrhea.[4] True allergy or immunoglobulin E–mediated reactions appear to be rare

in companion animals.[4] Food hypersensitivity reactions may evoke more generalized inflammatory responses involving histamine, leukotrienes, prostaglandins, substance P, or 5-HT (serotonin) effects on gastrointestinal absorption, secretion, permeability, and motility.

Mucosal Inflammation

Inflammation is a major cause of chronic diarrhea in both dogs and cats. Although gut inflammation may be induced by many different inciting causes (e.g., dietary antigens, bacterial pathogens, toxins, neoplasia), experimental studies suggest that the immune response is initiated and sustained as a result of exposure to dietary antigens and/or indigenous gut bacteria. Cellular components (T and B lymphocytes, plasma cells, macrophages) and molecular elements (prostaglandins, leukotrienes, complement, platelet-activating factor, nitric oxide, and oxygen-derived free radicals) contribute to the mucosal inflammatory response. The clinical signs of IBD (diarrhea, vomiting, anorexia) are somewhat related to the severity of the mucosal cellular infiltrates and inflammatory mediators.[11,12] (Functional abnormalities, e.g., changes in the permeability or motility of the gut, may contribute to the clinical signs in many animals.)

Neoplasia

Intestinal neoplasia may induce diarrhea by several pathophysiologic mechanisms, including obstruction-induced fluid secretion, release of bioactive substances (e.g., histamine with diffuse mast cell disease, 5-HT with intestinal carcinoid, and gastrin with gastrinoma), bacterial proliferation and overgrowth, protein and lipid exudation, and reduction of the normal villous absorptive surface area.

Lymphatic Transport Disorders

Lymphangitis and intestinal lymphangiectasia are the most common lymphatic transport disorders in the dog. Lymphangiectasia is fairly common in the dog, but rare in the cat. Lymphangiectasia may occur as a primary congenital disorder, or more frequently, it may develop secondarily to IBD,[13] neoplastic infiltration, or right-sided heart failure.

Multiple Pathophysiologic Mechanisms of Diarrhea

Some diarrheal disorders result from one pathogenic mechanism, but others may have several concurrent pathogenic mechanisms, for example, maldigestion, malabsorption, excessive secretion, changes in permeability, protein and lipid exudation, and disordered motility.[2] EPI is often regarded as a classic maldigestive disorder. In the absence of pancreatic enzyme secretion, undigested protein, lipid, or carbohydrate cannot be further absorbed. Affected animals develop diarrhea, steatorrhea, and severe protein-calorie malnutrition. These same animals develop SIBO, gastric acid–induced injury to the intestinal mucosa, cobalamin malabsorption, and hypersecretion of fluid and electrolytes. It is for these reasons that pancreatic insufficient animals may have incomplete response with pancreatic enzyme replacement therapy. Bacterial infection is another example of a diarrheal disorder with multiple pathophysiologic mechanisms. The heat-stable enterotoxin of enteropathogenic *Escherichia coli* stimulates guanylate cyclase production of cyclic guanosine monophosphate (cGMP) and activation of cGMP-dependent protein kinases, culminating in secretory-type diarrhea. At the same time, platelet-activating factor, prostaglandins, and leukotrienes produced during bacterial infection may contribute to the malabsorption and disordered motility of *E. coli* infections.

Specific Therapy of Diarrhea

The best clinical outcomes will be obtained with definitive diagnosis and specific therapy (see Section VI). A cat with intestinal lymphoma, for example, will have a better outcome if it is correctly diagnosed and treated with chemotherapy. Similarly, a German Shepherd dog with diarrhea, steatorrhea, weight loss, and ravenous appetite will have a much better outcome if it is correctly diagnosed with EPI and appropriately medicated with pancreatic replacement enzymes. Table 34-1 outlines other examples of definitive diagnoses and specific therapies.

Nonspecific Therapy of Diarrhea

Definitive diagnosis and specific therapy may not be possible in all cases. This is especially true of cases of IBD in which sequential, nonspecific therapy may be needed to control mild to severe clinical signs (Box 34-1).[2,11,12,14] The pet owner may not permit a detailed medical investigation, or a definitive diagnosis may not be reached despite a detailed and appropriate medical investigation. In these cases, it would be entirely appropriate to consider nonspecific forms of therapy. The criteria for commencing nonspecific therapy should include: (a) the diarrhea is chronic, frequent, and/or severe; (b) definitive diagnosis is not forthcoming; and (c) the client does not desire definitive diagnosis.[2,12,14]

Dietary Therapy

The precise immunologic mechanisms of canine and feline IBD have not yet been determined, but a prevailing hypothesis for the development of IBD is the loss of immunologic tolerance to the normal bacterial flora or food antigens. Accordingly, dietary modification may prove useful in the management of canine and feline IBD. Several nutritional strategies have been proposed for the management of gastrointestinal tract disease including novel proteins, hydrolyzed diets, antioxidant diets, prebiotics, medium-chain

Table 34-1 Examples of Definitive Diagnoses and Specific Therapies

Pathogenesis	Specific Therapy
Food sensitivity reaction	Dietary modification
Bacterial infection	Antibiotics
Parasitic infection	Anthelmintic agents
Fungal infection	Antifungal agents
Pancreatic insufficiency	Pancreatic enzymes
Intestinal cancer	Chemotherapy
Lymphangiectasia	Dietary fat modification
Hyperthyroidism	Chemo- or radiotherapy

Box 34-1 Sequential, Nonspecific Therapy in Inflammatory Bowel Disease

1. Dietary modification
2. Physical exercise
3. Antibiotics
4. Probiotics
5. Antidiarrheal agents
6. Restoration of motility
7. Immunosuppressive agents
8. Behavioral modification

triglyceride supplementation, low-fat diets, modifications in the omega-6-to-omega-3 fatty acid ratio, and fiber supplementation. Of these strategies, some evidence-based medicine has emerged for the use of novel protein, hydrolyzed, antioxidant supplemented, and prebiotic diets.[2,11,14]

Novel Proteins

Food sensitivity reactions were suspected or documented in 49% of cats presented because of gastroenterologic problems (with or without concurrent dermatologic problems) in a prospective study of adverse food reactions in cats.[4] Beef, wheat, and corn gluten were the primary ingredients responsible for food sensitivity reactions in that study, and most of the cats responded to the feeding of a chicken- or venison-based selected-protein diet for a minimum of 4 weeks. The authors concluded that adverse reactions to dietary staples are common in cats with chronic gastrointestinal problems and that they can be successfully managed by feeding selected-protein diets. Further support for this concept comes from studies in which gastroenterologic or dermatologic clinical signs were significantly improved by the feeding of novel proteins.

Hydrolyzed Diets

Evidence is accruing that hydrolyzed diets may be useful in the nutritional management of canine IBD. The conceptual basis of the hydrolyzed diet is that oligopeptides are of insufficient size and structure to induce antigen recognition or presentation.[15] In one preliminary study, dogs with IBD showed significant improvement following the feeding of a hydrolyzed diet, although they had failed to respond to the feeding of a novel protein.[16] Clinical improvement could not be solely attributed to the hydrolyzed nature of the protein source because the test diet had other modified features; that is, high digestibility, cornstarch rather than intact grains, medium chain triglycerides, and an altered ratio of omega-6-to-omega-3 polyunsaturated fatty acids. Additional studies will be required to ascertain the efficacy of this nutritional strategy in the management of IBD.

Physical Exercise

Experimental IBD in the dog is accompanied by significant abnormalities in the normal gastrointestinal motility. Physical exercise has been shown to disrupt the jejunal, ileal, and colonic migrating motor complexes and to increase the total duration of contractions that are organized as non-migrating motor complexes during the fed state. Exercise also induces giant migrating contractions, defecation, and mass movement in both the fasted and fed states. The increased motor activity of the intestine and colon and extra giant migrating contractions that result from physical exercise may aid in normal gastrointestinal motor function.[17]

Antibiotics

Some IBD cases are initiated by true enteric pathogens, whereas others are complicated by SIBO. Some IBD cases may show short-term responsiveness to one or more antibiotics, for example, tylosin, metronidazole, or oxytetracycline.

Probiotics

Probiotics are living organisms with low or no pathogenicity that exert beneficial effects (e.g., stimulation of innate and acquired immunity) on the health of the host. The Gram-positive commensal lactic acid bacteria (e.g., lactobacilli) have many beneficial health effects, including enhanced lymphocyte proliferation, innate and acquired immunity, and anti-inflammatory cytokine production. *Lactobacillus rhamnosus* GG, a bacterium used in the production of yogurt, is effective in preventing and treating diarrhea, recurrent *Clostridium difficile* infection, primary rotavirus infection, and atopic dermatitis in humans.[18] *L. rhamnosus* GG has been safely colonized in the canine gastrointestinal tract, although probiotic effects in the canine intestine have not been firmly established.[19] The probiotic organism, *Enterococcus faecium* (SF68), has been safely colonized in the canine gastrointestinal tract, and it has been shown to increase fecal immunoglobulin A content and circulating mature B ($CD21^+$/major histocompatibility complex class II^+) cells in young puppies.[20] It has been suggested that this probiotic may be useful in the prevention or treatment of canine gastrointestinal disease. This organism may, however, enhance *Campylobacter jejuni* adhesion and colonization of the dog intestine, perhaps conferring carrier status on colonized dogs.[21] *Lactobacillus acidophilus* has also been shown to safely colonize the canine gastrointestinal tract.

Antidiarrheal Agents

The major physiologic functions of the small intestine are luminal and brush-border digestion, secretion, and absorption (see Chapter 1). Other physiologic properties of the small intestine, for example, motility and blood flow, have evolved to regulate digestion, secretion, and absorption. The anatomic structures in support of these functions include the serosa, longitudinal smooth muscle, myenteric or Auerbach's plexus, circular smooth muscle, submucosal or Meissner's plexus, muscularis mucosa, and mucosa. Epithelial cells in the intestinal mucosa are specialized primarily for membrane brush-border enzymatic (e.g., disaccharidases, peptidases) digestion, fluid and electrolyte secretion, and absorption. The crypt is the germinal center of the intestinal epithelium. Crypt epithelial cells are primarily secretory in function—water, solutes, and bicarbonate are secreted into the intestinal lumen to solubilize the chyme, neutralize gastric acid, and reduce the bacterial microflora. As cells migrate up the intestinal villi, they mature into absorptive cells. Villus epithelial cells are primarily absorptive in function—water, solutes, glucose and other monosaccharides; amino acids and small peptides; free fatty acids and glycerol; minerals and vitamins; and other nutrients are absorbed from the lumen into villus epithelial cells. Submucosal plexus neurons innervate the overlying mucosa and regulate absorption and secretion by the villus and crypt epithelial cells, respectively. Myenteric plexus neurons innervate the longitudinal and circular smooth muscle layers and regulate intestinal motility. Contraction of longitudinal smooth muscle stimulates peristaltic type activity and net fluid transit, while contraction of circular smooth muscle mediates segmentation type activity and delay in fluid transit.

In health, villus epithelial cells actively absorb Na^+ and Cl^-, and passively absorb H_2O (see Fig. 1-17). In malabsorptive disorders, Na^+, Cl^-, and H_2O absorption are often markedly reduced in villus epithelial cells. Absorption may be inhibited through a number of mechanisms, including the effects of prostaglandins (e.g., prostaglandin E_2), leukotrienes, cyclic nucleotides (cyclic adenosine monophosphate, cGMP), serotonergic (serotonin or 5-hydroxytryptamine), and vasoactive intestinal polypeptide receptor activation. Stimulation of absorption by these cells, on the other hand, is mediated by noradrenergic (norepinephrine) and opioid (μ,δ-opioid) receptor activation. The pathophysiology of malabsorptive disorders serves as the basis for medical therapy such as prostaglandin synthetase inhibitors, μ,δ-opioid agonists, serotonergic antagonists, and noradrenergic agonists (see Fig. 1-17).

In health, crypt epithelial cells actively secrete Cl^- or HCO_3^-, and H_2O (see Fig. 1-17). In hypersecretory disorders, Cl^- and H_2O secretion is often markedly increased in crypt epithelial cells. The

pharmacology of the secretory crypt cell is remarkably similar to that of the absorptive villus cell. Thus, crypt epithelial cell secretion may be stimulated by prostaglandins (e.g., prostaglandin E_2), leukotrienes, cyclic nucleotides (cyclic adenosine monophosphate and cGMP), serotonergic (serotonin or 5-hydroxytryptamine), and vasoactive intestinal polypeptide receptor activation (see Fig. 1-17). Inhibition of secretion by these cells, on the other hand, is mediated by noradrenergic (norepinephrine) and opioid (μ,δ-opioid) receptor activation. The pathophysiology of hypersecretory disorders serves as the basis for medical therapy, for example, prostaglandin synthetase inhibition, serotonergic receptor antagonism, noradrenergic receptor agonism, and μ,δ-opioid receptor agonism (see Fig. 1-17).

Prostaglandin Synthetase Inhibitors

Sulfasalazine is a highly effective prostaglandin synthetase inhibitor that has proven efficacy in the therapy of large bowel IBD in the dog.[2,14] Sulfasalazine is a compound molecule of mesalamine (formerly 5-aminosalicylate) and sulfapyridine linked in an azo chemical bond. Following oral dosing, most of the sulfasalazine is transported to the distal gastrointestinal tract where cecal and colonic bacteria metabolize the drug to its component parts. Sulfapyridine is largely absorbed by the colonic mucosa, but much of the 5-aminosalicylate remains in the colonic lumen where it inhibits mucosal lipoxygenase and the inflammatory cascade. Sulfasalazine has been recommended for the treatment of canine large bowel IBD at doses of 10 to 30 mg/kg PO q8-12h for 4 to 6 weeks. With resolution of clinical signs, sulfasalazine dosages are gradually decreased by 25% at 2-week intervals and eventually discontinued while maintaining dietary management. Salicylates are readily absorbed and induce toxicity in cats, therefore this drug classification should be used with great caution in cats.[22] If used in cats, some authors have recommended using half of the recommended dog dose (i.e., 10 to 30 mg/kg PO q8-24h). Sulfasalazine usage has been associated with the development of keratoconjunctivitis sicca in the dog, so tear production should be assessed subjectively (by the pet owner) and objectively (by the veterinarian) during usage.[23,24]

Other 5-Aminosalicylates

This drug classification was developed to reduce the toxicity of the sulfapyridine portion of the parent molecule (sulfasalazine) and to enhance the efficacy of the 5-aminosalicylate. Mesalamine (Dipentum, Asacol) and dimesalamine (olsalazine) are available for use in the treatment of canine large bowel IBD. Olsalazine has been used at a dosage of 10 to 20 mg/kg PO q8h in the dog. Despite the formulation of sulfa-free 5-aminosalicylate preparations, instances of keratoconjunctivitis sicca have still been reported in the dog.

μ,δ-Opioid Agonists

These drugs stimulate circular smooth muscle contraction and therefore intestinal segmentation. Loperamide concurrently stimulates absorption, and inhibits secretion of, fluid and electrolytes. Loperamide, at a dose of 0.1 mg/kg PO q8-12h, is the preferred drug in this category.

5-HT_3 Serotonin Antagonists

Antagonists of the neuronal 5-HT_3 receptor inhibit Cl^- and H_2O secretion from intestinal epithelial cells. Examples of drugs in this classification include ondansetron (Zofran, Glaxo) at a dose of 0.5 to 1 mg/kg BID PO; granisetron (Kytril, SmithKline Beecham) at a dose of 0.1 to 0.5 mg/kg PO or IV q12h; tropisetron (Navoban, Novartis) at a dose of 0.5 to 3 mg/kg BID PO; and dolasetron (Anzemet, Sanofi-Aventis) at a dose of 0.6 to 1 mg/kg BID PO, IV, SQ.

α_2-Adrenergic Antagonists

These drugs must be used carefully as they can activate α_2-adrenergic receptors in the chemoreceptor trigger zone and cause vomiting. Clonidine, at a dose of 5 to 10 μg/kg BID-TID SQ/PO, is the best example in this classification.

Restoration of Normal Motility

The mixed μ,δ-opioid agonist, loperamide, stimulates fluid and electrolyte absorption while stimulating segmentation-type intestinal motility. Loperamide (0.1 mg/kg PO q8-12h) may be beneficial in the treatment of difficult or refractory cases of IBD.

Immunosuppressive Therapy

Glucocorticoids

Antiinflammatory to immunosuppressive doses of prednisone or prednisolone may be used to treat IBD in dogs that have failed to respond to dietary management, sulfasalazine, or metronidazole, and as adjunctive therapy to dietary modification in feline IBD.[14] Prednisone or prednisolone are used most frequently, as both have short durations of action, are cost-effective, and are widely available. Equipotent doses of dexamethasone are equally effective but may have more deleterious effects on brush-border enzyme activity. Prednisone should be used for 2 to 4 weeks depending upon the severity of the clinical signs. Higher doses of prednisone (e.g., 2 to 4 mg/kg PO daily) may be needed to control severe forms of eosinophilic colitis or hypereosinophilic syndrome in cats. Combination therapy with sulfasalazine, metronidazole, or azathioprine may reduce the overall dosage of prednisone needed to achieve remission of clinical signs. As with sulfasalazine, the dose of glucocorticoid may be reduced by 25% at 1- to 2-week intervals, while hopefully maintaining remission with dietary modification.

Budesonide

Because of steroid side effects and suppression of the hypothalamic–pituitary–adrenal axis, several alternative glucocorticoids have been developed that have excellent topical (i.e., mucosal) antiinflammatory activity but are significantly metabolized during first pass hepatic metabolism. Budesonide has been used for many years as an inhaled medication for asthma, and an enteric-coated form of the drug is now available for treatment of IBD in humans (and animals). There is little evidence-based medicine in support of the use of this medication in canine or feline IBD, but doses of 3 mg/m^2 Po once daily every other day have been used with some success in anecdotal cases.

Azathioprine

Azathioprine is a purine analogue that, following DNA incorporation, inhibits lymphocyte activation and proliferation. It is rarely effective as a single agent, and it should instead be used as adjunctive therapy with glucocorticoids. Azathioprine may have a significant steroid-sparing effect in IBD. Doses of 2 mg/kg PO q24h in dogs and 0.3 mg/kg PO q48h in cats have been used with some success in IBD. It may take several weeks or months of therapy for azathioprine to become maximally effective. Cats particularly should be monitored for side effects, including myelosuppression, hepatic disease, and acute pancreatic necrosis.

Cyclosporine

Cyclosporine has been used in the renal transplantation patient for its inhibitory effect on T-cell function. In more recent times, cyclosporine has been used in a number of immune-mediated disorders, including keratoconjunctivitis sicca, perianal fistula (anal furunculosis), and immune-mediated hemolytic anemia. Anecdotal reports

suggest that cyclosporine (3 to 7 mg/kg PO daily) may be useful in the treatment of some cases of refractory IBD. Evidence-based medicine studies are needed to establish efficacy, but anecdotal experience suggests that cyclosporine may be useful in some of the more difficult or refractory cases of IBD. Modified formulations of cyclosporine (i.e., cyclosporine-modified) are preferable to the original (unmodified) formulation.

Chlorambucil

Chlorambucil (1.5 mg/m^2 PO every other day) has been used in place of azathioprine in some difficult or refractory cases of feline IBD.

Behavior Modification

IBD and irritable bowel syndrome very likely have underlying behavioral components. Abnormal personality traits and potential environmental stress factors were identified in 38% of dogs in one study. Multiple factors were present in affected households, including travel, relocation, house construction, separation anxiety, submissive urination, noise sensitivity, and aggression.[25] The role of behavior in the pathogenesis and therapy of canine and feline gastrointestinal disorders remains largely unexplored (see Chapter 42).

Prognosis

Most reports indicate that the short-term prognosis for control of IBD is good to excellent.[12,14] Following completion of drug therapy, many animals are able to maintain remission of signs with dietary management alone. Treatment failures are uncommon and are usually a result of (a) incorrect diagnosis (it is especially important to rule out alimentary lymphosarcoma), (b) presence of severe disease such as histiocytic ulcerative colitis and protein-losing enteropathy or irreversible mucosa lesions such as fibrosis, (c) poor client compliance with appropriate drug/dietary recommendations, (d) use of inappropriate drugs or nutritional therapy, and (e) presence of concurrent disease such as SIBO or hepatobiliary disease. The prognosis for cure of IBD is poor, and relapses should be anticipated.

References

1. Hall EJ, Simpson KW: Diseases of the small intestine. In Ettinger SJ, Feldman EC, editors: *Textbook of Veterinary Internal Medicine*, Philadelphia, 2000, Saunders, pp 1182–1238.
2. Washabau RJ, Holt DE: Pathophysiology of gastrointestinal disease. In Slatter D editor: *Textbook of Small Animal Surgery*, Philadelphia, 2003, Saunders, pp 530–552.
3. Hall EJ, Batt RM: Development of wheat-sensitive enteropathy in Irish setters. *Am J Vet Res* 51:983–989, 1990.
4. Guilford WG, Jones BR, Markwell PJ, et al: Food sensitivity in cats with chronic idiopathic gastrointestinal problems. *J Vet Intern Med* 15:7–13, 2001.
5. Fyfe JC, Patterson D: Inherited selective cobalamin malabsorption and cobalamin deficiency in dogs. *Pediatr Res* 29:24–33, 1991.
6. Elwood CA, Hamblin A, Batt R: Quantitative and qualitative immunohistochemistry of T cell subsets and MCH class II expression in the canine small intestine. *Vet Immunol Immunopathol* 58:195–203, 1997.
7. German AJ, Bland PW, Hall EJ, et al: Expression of major histocompatibility complex class II antigens in the canine intestine. *Vet Immunol Immunopathol* 61:171–180, 1998.
8. German AJ, Hall EJ, Morre PF, et al: The distribution of lymphocytes expressing alpha/beta and gamma/delta T-cell receptors, and the expression of mucosal addressin cell adhesion molecule-1 in the canine intestine. *J Comp Pathol* 121:249–263, 1999.
9. Waly N, Gruffydd-Jones TJ, Stokes CR, et al: The distribution of leucocyte subsets in the small intestine of healthy cats. *J Comp Pathol* 124:172–182, 2001.
10. Baumgart DC, McVay LD, Carding SR: Mechanisms of immune cell-mediated tissue injury in inflammatory bowel disease. *Int J Mol Med* 1:315, 1998.
11. Day M, Bilzer T, Guilford G, et al: International standards for the histopathological diagnosis of gastrointestinal inflammation. *J Comp Pathol* 138:S1–S43, 2008.
12. Washabau RJ, Day MJ, Willard MD, et al: ACVIM Consensus Statement—Endoscopic, biopsy, and histopathologic guidelines for the evaluation of gastrointestinal inflammation in companion animals. *J Vet Intern Med* 24:10–26, 2010.
13. Kull P, Hess R, Craig L, et al: Clinical, clinicopathologic, radiographic, and ultrasonographic characteristics of intestinal lymphangiectasia in dogs. *J Am Vet Med Assoc* 219:197–202, 2001.
14. Washabau RJ, Holt DE: Diseases of the large intestine. In Ettinger SJ, Feldman EC, editors: *Textbook of Veterinary Internal Medicine*, ed 6, Philadelphia, 2005, Saunders, 1378–1408.
15. Hall EJ: Food allergy. In *Kirk's Current Veterinary Therapy XIII*, Philadelphia, 1999, Saunders, pp 632–637.
16. Marks SL, Laflamme DP, McAloose D: Dietary trial using a commercial hypoallergenic diet containing hydrolyzed protein for dogs with inflammatory bowel disease. *Vet Ther* 3:109, 2002.
17. Dapoigny M, Sarna SK: Effects of physical exercise on colonic motor activity. *Am J Physiol* 260:G646, 1991.
18. Yan F, Pok DB: Probiotic bacterium prevents cytokine-induced apoptosis in intestinal epithelial cells. *J Biol Chem* 277:50959, 2003.
19. Weese JS, Anderson ME: Preliminary evaluation of *Lactobacillus rhamnosus* GG, a potential probiotic in dogs. *Can Vet J* 43:771, 2002.
20. Benyacoub J, Czarnecki-Maulden GL, Cavadinni C, et al: Supplementation of food with Enterococcus faecium (SF68) stimulates immune functions in young dogs. *J Nutr* 133:1158, 2003.
21. Rinkenin M, Jalava K, Westermarck E, et al: Interaction between probiotic lactic acid bacteria and canine enteric pathogens: a risk factor for intestinal *Enterococcus faecium* colonization? *Vet Microbiol* 92:111, 2003.
22. Grisham MB, Granger DN: 5-aminosalicylic acid concentration in mucosal interstitium of cat small and large intestine. *Dig Dis Sci* 34:573, 1989.
23. Barnett KC, Joseph EC: Keratoconjunctivitis sicca in the dog following 5-aminosalicylic acid administration. *Hum Toxicol* 6:377, 1987.
24. Houston DR, Keller CB: Keratoconjunctivitis sicca in the dog following prolonged use of Salazopyrin and other 5-ASA containing drugs for treatment of canine colitis. *Can Vet J* 30:437. 1989.
25. Leib MS: Treatment of chronic idiopathic large-bowel diarrhea in dogs with a highly digestible diet and soluble fiber: a retrospective review of 37 cases. *J Vet Intern Med* 14:27, 2000.