Diarrhea

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Definition

Diarrhea is an increase in the frequency, fluidity, or volume of feces[1] that is best characterized by duration (acute versus chronic), pathophysiologic mechanism, and anatomic location. Diarrhea is considered acute if it lasts for less than 14 days, and chronic when it persists for more than 14 days. Acute, self-limiting diarrhea is a relatively common problem in dogs and cats and usually requires minimal diagnostic testing and therapy. In contrast to most animals with acute diarrhea, chronic diarrhea can be particularly challenging to diagnose, because most animals will not respond to empirical therapies, necessitating a well-formulated and cost-effective diagnostic and therapeutic plan. Specific therapeutic modalities are based upon a definitive diagnosis or histologic characterization of intestinal biopsies.

Although diarrhea is the primary sign of intestinal dysfunction, there are a number of secondary clinical signs that may become the principal one for which the animal is presented, and it is noteworthy that diarrhea may or may not accompany these secondary clinical signs. These secondary signs include *abdominal distention, abdominal pain, borborygmus, dehydration, flatulence, halitosis, melena, hematochezia, polydipsia, polyphagia, tenesmus, vomiting,* and *weight loss.* Animals may present with alterations in appetite ranging from polyphagia to anorexia, and these same alterations in food intake can be recognized as a consequence of disease progression (e.g., inflammatory bowel disease, intestinal lymphangiectasia, and lymphoma). Weight loss is often associated with nutrient malabsorption of diffuse mucosal disease. Vomiting can be associated with a variety of gastrointestinal disorders and is relatively common in animals with inflammatory bowel disease (IBD). Colorectal disorders are often associated with tenesmus, dyschezia, and large bowel diarrhea characterized by hematochezia, increased mucus on feces, marked increase in defecation frequency, and a reduction in fecal volume.

Pathophysiology and Mechanisms

There are four major pathophysiologic mechanisms that can result in diarrhea, although more than one mechanism can contribute to diarrhea simultaneously.

Osmotic Diarrhea

Osmotic diarrhea is caused by unusually large amounts of poorly absorbable osmotically active solutes in the intestinal lumen. Osmotic diarrhea occurs with malabsorptive disorders where nutrients are maldigested or malabsorbed, remain within the intestinal lumen, and osmotically attract water. Exocrine pancreatic insufficiency is an example of an osmotic diarrheal disorder. Retention of nutrients can lead to alterations in intestinal microflora and fermentation of carbohydrates, further increasing numbers of osmotically active particles. The fecal water output in osmotic diarrhea is directly related to fecal output of the solute or solutes that are exerting an osmotic gradient across intestinal mucosa. Electrolyte absorption is unaffected by these osmotically active substances, and fecal water typically contains very little unabsorbed sodium or potassium.[2] This is the basis for the calculation of the "fecal osmotic gap." In this calculation, the difference between luminal osmolality (equal to body fluid osmolality, approximately 290 mOsm/kg, because the colon cannot maintain an osmotic gradient against plasma) and osmolality of luminal contents contributed by fecal electrolytes is estimated. The contribution of fecal electrolytes is calculated as twice the sum of sodium and potassium ions to account for the anions that accompany these cations. A fecal osmotic gap greater than 50 mOsm/kg suggests osmotic diarrhea.[2] One of the major hallmarks of osmotic diarrhea is that diarrhea resolves when the patient stops ingesting the poorly absorbable solute.

Secretory Diarrhea

Secretory diarrhea is caused by abnormal ion transport in intestinal epithelial cells. The most common cause of secretory diarrhea in dogs and cats are abnormal mediators resulting in changes in intracellular cyclic adenosine monophosphate (cAMP), cyclic guanosine monophosphate (cGMP), calcium, and/or protein kinases, which in turn cause a decrease in neutral sodium chloride absorption or an increase in chloride secretion.[3] Such mediators include endogenous enteric hormones or neuropeptides, inflammatory cell products, bacterial enterotoxins, laxatives, fatty acids, and bile acids (see Chapters 1 and 57 for more detail). Secretory diarrhea has two important distinguishing features; first, fecal osmolality can be accounted for by sodium, potassium, and their accompanying anions, and thus the osmotic gap is small; and second, the diarrhea usually persists despite fasting because the diarrhea is caused by abnormalities in ion transport that have nothing to do with food. Enteropathogenic *Escherichia coli* and IBD are examples of secretory diarrheas.

Increased Mucosal Permeability

Increased mucosal permeability causes loss of fluids, electrolytes, proteins, and red blood cells into the intestinal lumen. Erosive or ulcerative enteropathies, inflammatory (IBD), or neoplastic disorders (intestinal lymphoma) are common causes of alterations in mucosal permeability.

Deranged Motility

Experimental studies in dogs show that abnormal ileal and colonic motility patterns may contribute to clinical symptomatology of IBD.[4,5] The two major motor abnormalities in intestinal inflammation are suppression of phasic contractions, including migrating motor complexes, and stimulation of giant migrating contractions (GMCs), the powerful ultrapropulsive contractions that usually propagate uninterruptedly form the point of their origin in the small intestine to the terminal ileum and often into the colon.[4] Stimulation of GMCs in fasting and fed states produces ultrarapid transit of intestinal and pancreaticobiliary secretions and undigested food into the colon to increase its osmotic load with resultant diarrhea.[4] Platelet-activating factor (PAF) may be one of the inflammatory response mediators that stimulates GMCs,[5] and it is synthesized and released from several immunocytes, including polymorphonuclear (PMN) leukocytes, monocytes, macrophages, mast cells, and eosinophils.[5]

Differential Diagnosis

Box 11-1 lists differential diagnoses for acute and chronic diarrhea in dogs and cats, as well as those disorders that are potentially life-threatening. Many cases of chronic diarrhea can manifest initially as acute diarrhea. Localization of the disease process into "small bowel" versus "large bowel" has some limitations, as many diarrheal diseases with primary manifestations of one compartment (large bowel or small bowel) may have diffuse gastrointestinal (GI) involvement (large and small bowel). This point is underscored by a study in 40 dogs suggesting that routine collection of ileal biopsies is warranted in dogs with colonopathy, and that routinely sampling of duodenum and ileum increases the diagnostic yield compared to biopsy of one anatomic site.[6] Regardless, the initial differentiation into small and large bowel components helps to further clarify the medical investigation (see Figs. 11-1 and 11-2).

Evaluation of the Patient

Signalment

Awareness of the importance of the animal's signalment and breed predilections for GI disease can facilitate development of a differential diagnosis for the particular animal. A 3-year-old Yorkshire Terrier dog with a 2-month history of small intestinal diarrhea, weight loss, and progressive abdominal distention has a signalment and history suggestive of intestinal lymphangiectasia. Likewise, a young Boxer dog with a 3-month history of tenesmus, hematochezia, increased stool frequency, and mucoid stools could be consistent with histiocytic colitis. Tunnel vision should be avoided, however, as it is plausible that a Boxer dog could have diarrhea from any number of underlying causes.

History

History and physical examination often indicates the anatomic localization and severity of the disease process, and it helps prioritize differential diagnoses. History should ensure that systemic causes of diarrhea are not overlooked. A comprehensive history should also identify important predisposing factors (e.g., exposure to parasites, infectious agents, drugs, toxins). It is equally important to fully characterize the nature of diarrhea and appearance of feces (Table 11-1). For dogs with a history of tenesmus, it is pivotal to determine whether signs are secondary to colitis or to a discrete mass or polyp in the colorectal region. The latter is often associated with a change in the appearance of the stool ("ribbon-like," "pencil-thin") in the

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Box 11-1	**Differential Diagnoses for Acute and Chronic Diarrhea**

Differential diagnoses for acute and chronic diarrhea in dogs and cats, with annotation of potentially life-threatening causes of disease.

Dietary
Abrupt dietary change*
Overeating*
Dietary indiscretion*
Dietary intolerance/allergy‡

Inflammatory
Inflammatory bowel disease†
Antibiotic-responsive diarrhea†
Lymphangiectasia†
Hemorrhagic gastroenteritis # *

Infectious
Parasitic helminths,‡ protozoa‡
Bacterial *Salmonella*,#,* *Campylobacter*,* *Clostridium perfringens*,#,* *Clostridium difficile*,#,* *E. coli*,#*
Viral parvovirus,#* coronavirus,* feline leukemia virus (FeLV),† feline immunodeficiency virus (FIV)†
Fungal histoplasmosis,#,† *Pythium*,#,† cryptococcosis#,†
Rickettsial salmon poisoning#*

Extraintestinal Disorders
Pancreatitis#*
Exocrine pancreatic insufficiency†
Liver disease#,‡
Kidney disease#,‡
Hypoadrenocorticism#,‡
Hyperthyroidism†

Functional Ileus/Mechanical Obstruction
Miscellaneous
Toxemia (pyometra, peritonitis)#*
Septicemia (leptospirosis)#,‡
Apudomas (gastrinomas, VIPomas, carcinoid syndrome)#,‡

Neoplastic
Carcinoma#,‡
Mast cell tumors#,‡
Leiomyosarcomas (gastrointestinal stromal tumors)#,‡
Lymphoma#,‡

Drugs and Toxins
Nonsteroidal antiinflammatory drugs‡
Antibiotics‡
Digoxin‡
Cancer chemotherapeutics‡
Copper chelators‡

Key: #, potentially life-threatening; *, typically associated with acute diarrhea; †, typically associated with chronic diarrhea; ‡, associated with acute or chronic diarrhea.

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absence of a marked increase in frequency of bowel movements or increased fecal mucus as seen with colitis. Likewise, absence of clinical signs of diarrhea does not rule out severe underlying intestinal disease; dogs with protein-losing enteropathy (PLE) may have anorexia and weight loss without associated vomiting and diarrhea. Failure to consider the role of diet or dietary supplements in precipitating or alleviating the diarrhea can cause delayed diagnosis or improper dietary recommendations. Box 11-2 outlines specific questions that should be addressed.
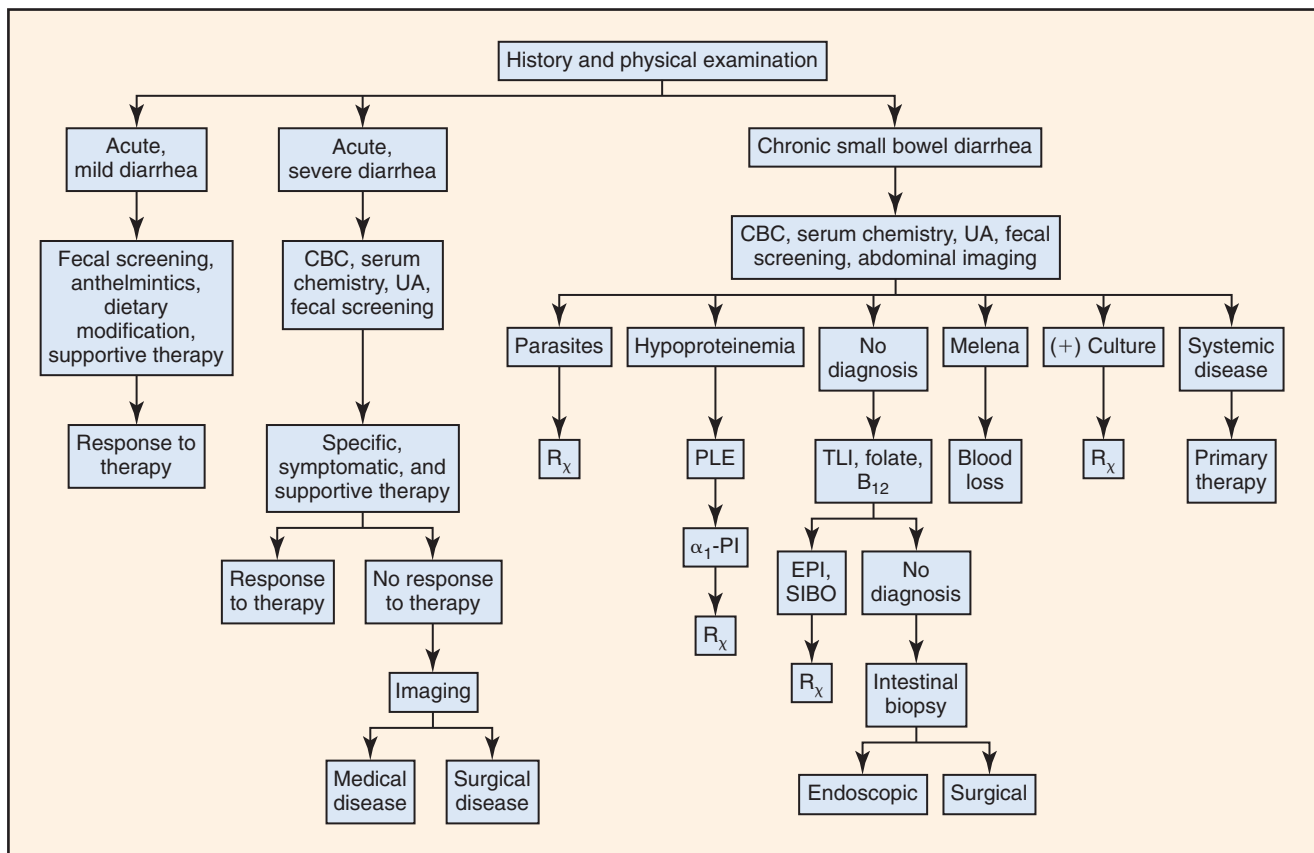
Figure 11-1 Medical workup for dogs and cats with diarrhea primarily of small bowel origin.
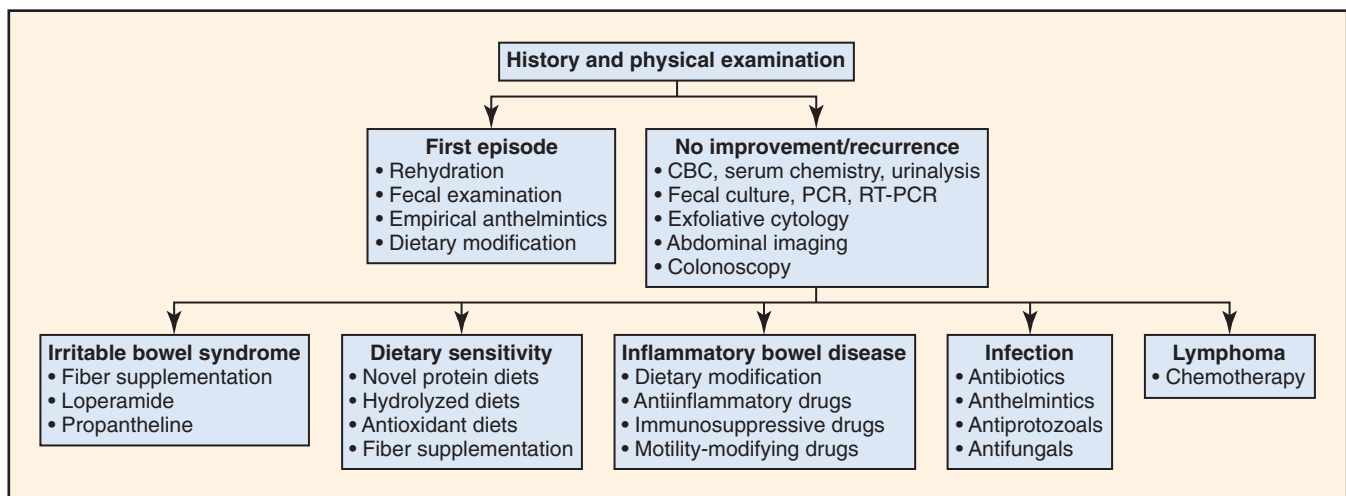
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History and physical examination
    ├── Acute, mild diarrhea
    │       └── Fecal screening, anthelmintics, dietary modification, supportive therapy
    │               └── Response to therapy
    ├── Acute, severe diarrhea
    │       └── CBC, serum chemistry, UA, fecal screening
    │               └── Specific, symptomatic, and supportive therapy
    │                       ├── Response to therapy
    │                       └── No response to therapy
    │                               └── Imaging
    │                                       ├── Medical disease
    │                                       └── Surgical disease
    └── Chronic small bowel diarrhea
            └── CBC, serum chemistry, UA, fecal screening, abdominal imaging
                    ├── Parasites → Rχ
                    ├── Hypoproteinemia → PLE → α1-PI → Rχ
                    ├── No diagnosis → TLI, folate, B12
                    │       ├── EPI, SIBO → Rχ
                    │       └── No diagnosis → Intestinal biopsy
                    │                               ├── Endoscopic
                    │                               └── Surgical
                    ├── Melena → Blood loss
                    ├── (+) Culture → Rχ
                    └── Systemic disease → Primary therapy
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Figure 11-1 Medical workup for dogs and cats with diarrhea primarily of small bowel origin.

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History and physical examination
    ├── First episode
    │     • Rehydration
    │     • Fecal examination
    │     • Empirical anthelmintics
    │     • Dietary modification
    └── No improvement/recurrence
          • CBC, serum chemistry, urinalysis
          • Fecal culture, PCR, RT-PCR
          • Exfoliative cytology
          • Abdominal imaging
          • Colonoscopy

    Irritable bowel syndrome          Dietary sensitivity          Inflammatory bowel disease          Infection            Lymphoma
    • Fiber supplementation           • Novel protein diets        • Dietary modification              • Antibiotics        • Chemotherapy
    • Loperamide                      • Hydrolyzed diets           • Antiinflammatory drugs            • Anthelmintics
    • Propantheline                   • Antioxidant diets          • Immunosuppressive drugs           • Antiprotozoals
                                      • Fiber supplementation      • Motility-modifying drugs          • Antifungals
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Figure 11-2 Medical workup for dogs and cats with diarrhea primarily of large bowel origin.

Physical Examination

A thorough physical examination helps determine severity and likely origin of the problem. Careful attention should be placed on physical appearance of the animal (emaciation or malnutrition suggestive of malassimilation from IBD, intestinal lymphoma, lymphangiectasia, or pancreatic insufficiency); detection of fever (infectious enteropathy or breakdown of the intestinal mucosal barrier); abdominal effusion and edema (secondary to protein losing enteropathies); and mucous membrane pallor (secondary to intestinal blood loss). Abdominal palpation is performed for detection of mass lesions, thickened bowel loops (neoplasia, intussusception, IBD, fungal enteropathies, mesenteric lymphadenopathy), or pain (bowel inflammation, pancreatitis, peritonitis, ischemia of bowel, and gas-associated bowel distention). In cats the thyroid region should be carefully palpated for thyroid nodules, and the kidneys and liver examined for changes in size and contour. Digital rectal palpation is important for detection of rectal masses or irregular thickening of rectal wall, colorectal strictures, and collection of feces for gross inspection and further evaluation. Digital rectal

Table 11-1	**Differentiation of Small Versus Large Bowel Diarrhea**[*]	

Differentiation of small versus large bowel diarrhea based upon clinical signs and the physical appearance of feces.

Sign	Small Bowel	Large Bowel
Frequency of defecation	Normal to mildly increased	Markedly increased
Fecal volume	Normal to increased	Decreased
Fecal mucus	Usually absent	Often present
Fecal blood	Melena	Hematochezia
Tenesmus	Absent	Often present
Urgency	Absent	Often present
Vomiting	May be present	May be present
Steatorrhea	May be present	Absent
Dyschezia	Absent	Often present
Weight loss	Common	Uncommon

*Caution should be heeded with the oversimplistic attempts at compartmentalizing the diarrhea into a small bowel versus a large bowel compartment, as many diarrheal diseases can have diffuse involvement histologically.

Box 11-2	**Questions that Should be Asked in Patients with Diarrhea**

- What is the clinical course or onset of the diarrhea (congenital or acquired; abrupt or gradual in onset; continuous or intermittent)?
- What is the duration of signs?
- What are the physical characteristics of the diarrhea?
- Are there any alleviating or exacerbating factors for the diarrhea such as dietary changes, antibiotic administration, stress, recent travel, or recent kenneling?
- What is the animal's past medical history, and is this diarrhea episode a new problem or a recurrent one? If recurrent, how was the diarrhea managed previously, and what was the outcome?
- What is the animal's anthelmintic and vaccination history?
- Are any other pets in the household similarly affected?
- Is the diarrhea associated with any other systemic (e.g., polyuria/polydipsia) or gastrointestinal signs such as weight loss, vomiting, and anorexia?

palpation of the rectum in cats is usually performed under general anesthesia or deep sedation. Macroscopic examination of a fresh fecal specimen is essential for assessment of bulk, color, consistency, detection of blood and mucus, and detection of foreign material. Small bowel diarrhea is generally free of grossly visible mucus or red blood, but prominent steatorrhea may cause the feces to appear lighter in color. Acholic or pale feces can also be seen in association with extrahepatic bile duct obstruction causing a lack of the bile pigment stercobilin in the feces. Rapid intestinal transit time can be associated with yellow or green stools caused by incomplete metabolization of bilirubin.

Laboratory Evaluation and Tests

An important part of the workup is determining whether the animal has a self-limiting or potentially life-threatening problem. This distinction is pivotal as it determines the level of diagnostic testing and therapy needed and helps determine the likelihood of an animal having a self-limiting diarrhea that could be managed empirically,

or an animal having a chronic disease that warrants hospitalization and a more comprehensive workup. This distinction is based on a comprehensive history, thorough physical examination, clinical experience and judgment, and awareness of the differential diagnoses for the diarrhea. Animals showing one or more of the following physical examination findings or signs at presentation warrant a more comprehensive workup and possible hospitalization: fever; abdominal pain; abdominal effusion; organomegaly; moderate to severe dehydration; severe lethargy; melena or hematochezia; mucous membrane pallor; jaundice or congestion; palpable abdominal mass or dilated loop of bowel; frequent vomiting; or other signs of systemic disease such as polyuria/polydipsia.

For animals with acute, mild diarrhea that appear relatively healthy on physical exam and are deemed likely to have a self-limiting gastroenteropathy, a minimum database consisting of centrifugation fecal flotation using zinc sulfate (specific gravity of 1.18 to 1.2) complemented with a fecal enzyme-linked immunosorbent assay (ELISA) or immunofluorescence test for *Giardia* is typically adequate for assessment of parasitic disease. In addition, measurement of hematocrit and total protein are helpful to assess hydration status. Fecal cytology in diarrheic dogs is a low-yield diagnostic test because finding of "safety pin"-shaped endospores consistent with *Clostridium perfringens* are of no diagnostic value. Their detection does not correlate with the presence of *C. perfringens* enterotoxin, the putative virulence factor associated with diarrhea.[7,8] Likewise, detecting "spiral-shaped" bacteria assuming the appearance of "seagulls" is insufficient for a diagnosis of *Campylobacter*-associated diarrhea because spiral-shaped bacteria resembling *Campylobacter* spp. are commonly identified in feces from healthy, nondiarrheic dogs and cats. Isolation of the microaerophilic organism utilizing selective culture media is a far more sensitive diagnostic tool compared with stained fecal smears.[9] In contrast to direct fecal cytology, exfoliative rectal cytology is a useful diagnostic test in dogs and cats with signs of colitis, and is best indicated for diagnosis of specific enteropathogens such as *Histoplasma* spp., *Pythium insidiosum*, or *Prototheca*,[10] or for colonic neoplasms such as lymphoma and carcinoma.

Animals with potentially life-threatening diarrhea or diarrhea that has not responded to conventional therapeutic approaches within 2 to 4 weeks warrant the time and effort required to make a specific diagnosis. The decision of whether to embark on an attempt to make a specific diagnosis usually depends on the nature of the problem, the availability of specific diagnostic facilities, and any client constraints (e.g., financial). For undiagnosed chronic or life-threatening diarrhea, the minimum database should include a complete blood count (CBC), a serum biochemistry profile, a urinalysis, a centrifugation fecal flotation using zinc sulfate, and a direct smear of saline admixed fresh feces for protozoa. A fecal ELISA for parvovirus in puppies should be considered based on signalment, vaccination history, clinical signs, and hematologic findings. The minimum database is performed to determine whether primary GI or metabolic/systemic disorders are associated with diarrhea. Baseline testing should also include specific tests for common disorders known to be likely in a particular animal (e.g., serum thyroxin testing in a 14-year-old cat with a history of chronic weight loss, diarrhea, and polyphagia).

Baseline Laboratory Tests

Complete Blood Count. The complete blood count may reveal an *eosinophilia* secondary to endoparasitism, eosinophilic enteritis, hypoadrenocorticism, or mast cell neoplasia. *Anemia* may result from enteric blood loss or from depressed erythropoiesis caused by systemic disease, chronic inflammation, or malnutrition. A

peripheral *neutrophilia* could reflect stress, inflammation, or infection. Finding a left shift with toxic neutrophils should warrant an aggressive workup for underlying causes (infection, immune disease, etc.). *Lymphopenia* is a relatively common finding in dogs with intestinal lymphangiectasia.

Serum Chemistry. The serum biochemistry panel should be scrutinized for elevations in *urea* and *creatinine* concentration from dehydration or renal disease. The *blood urea nitrogen (BUN)-to-creatinine* ratio can be discordantly elevated from dehydration (prerenal azotemia) or gastrointestinal bleeding. In addition, *panhypoproteinemia* and *hypocholesterolemia* can be recognized in animals with a protein-losing enteropathy from intestinal lymphangiectasia or other infiltrative bowel disorders. Electrolyte changes as a consequence of diarrhea should be carefully scrutinized, and corrected whenever warranted. *Hyperkalemia* and *hyponatremia* are typical electrolyte alterations commonly found in Addisonian dogs; however, these electrolyte changes have been documented in dogs with whipworm infestations and other enteropathies in the absence of Addison disease (pseudo-Addison disease). In addition, dogs with atypical Addison disease can manifest diarrhea in the absence of electrolyte changes. Elevated hepatic enzyme values should be interpreted cautiously in patients with gastrointestinal disease because drainage of bacteria or endotoxin via the portal circulation can precipitate a reactive hepatopathy with elevations of hepatocellular leakage enzymes. Serum thyroxine concentrations are typically included on serum biochemistry panels performed at reference laboratories, and routine measurement of serum T_4 is warranted in any diarrheic cat older than 8 years, independent of concurrent signs such as polyphagia and weight loss.

Feline Leukemia Virus and Feline Immunodeficiency Virus Serologic Screening. Serologic screening for feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) is warranted in diarrheic cats based upon habitat and housing environment. The enteritis sometimes caused by FeLV and FIV is incompletely understood, although it has long been recognized that FeLV can directly infect intestinal epithelial cells as well as gut-associated lymphoid tissue.[11]

Fecal Enteric Panel. The fecal enteric panel is a low-yield and expensive diagnostic test with misleading results if not performed judiciously in diarrheic dogs and cats. The clinical documentation of enteropathogenic bacteria causing diarrhea in dogs and cats is clouded by the presence of these organisms in apparently healthy animals. A fecal enteric panel consisting of a Gram-stained fecal smear, culture for *Salmonella* and *Campylobacter*, and ELISAs for immunodetection of *Clostridium difficile* toxins A and B and C. *perfringens* enterotoxin is an expensive test (approximately $120 in the author's laboratory) that should be reserved for diarrheic dogs and cats that are systemically ill (fever, severe lethargy, leukocytosis with or without a left shift and toxicity), have an acute onset of hemorrhagic diarrhea, or a recent onset of diarrhea following kenneling or attendance at a show. Lastly, fecal enteric panels should be proactively done when the zoonotic enteropathogens, *Campylobacter* or *Salmonella*, are considerations in diarrheic pets owned by people who are immunocompromised.

Diagnostic Imaging

Survey Abdominal Radiography. Survey abdominal radiographs are a relatively low-yield diagnostic procedure in most dogs and cats with chronic diarrhea, but are indicated in animals for detection of fluid–gas patterns suggestive of mechanical obstruction from foreign bodies, intussusceptions, or masses (see Chapter 26). Although many medical causes of GI disease result in mild to moderate intestinal wall thickening, measurements of wall thickness should not be attempted on survey radiography.

Upper Gastrointestinal Tract Contrast Radiography. Partial or complete mechanical gastrointestinal obstructions are the main indications for upper GI contrast radiography. The modality has been used for determination of gastrointestinal transit; however, disturbances in motility can be difficult to document using liquid barium, and the stress associated with hospitalization can alter gastric and intestinal transit times. Upper GI contrast radiography has also been used to evaluate mucosal abnormalities such as ulcers and filling defects; however, the procedure has limitations and subtle lesions are easily missed (see Chapter 26). The diagnostic yield of upper GI contrast radiography is frequently compromised as a consequence of improper patient preparation (inadequately fasted), too low a volume of barium administered, and insufficient radiographs at suitable time points.

Abdominal Ultrasonography. Abdominal ultrasonography is complementary to survey abdominal radiographs, and has largely replaced contrast radiography for the diagnosis of GI neoplasia, intussusception, and diffuse mural infiltrative disease (see Chapter 26). In addition, ultrasound-guided percutaneous biopsy or aspiration of masses or enlarged mesenteric lymph nodes is an effective diagnostic procedure. Both IBD and small-cell lymphoma of the bowel can have manifestations ranging from normal ultrasonographic appearance to generalized thickening of the intestinal wall with enlarged mesenteric lymph nodes. A loss of intestinal wall layering is more consistent with a diagnosis of lymphoma than IBD. A recent study revealed that cats showing a pattern of thickening of the muscularis propria on ultrasound exam were more likely to have lymphoma compared to cats with IBD and healthy controls.[12] In addition, cats with ultrasonographic evidence of moderate to marked mesenteric lymphadenopathy are more likely to have a diagnosis of intestinal lymphoma.[12]

Specialized Gastrointestinal Function Tests

Serum Trypsin-like Immunoreactivity. Steatorrhea and weight loss in the face of a normal to increased appetite is consistent with a malassimilation disorder such as exocrine pancreatic insufficiency (EPI). A genetic predisposition to development of pancreatic acinar atrophy has been reported in German Shepherd dogs and rough-coated Collies, although many other breeds, including mixed breeds, are affected. Pancreatic acinar atrophy predominantly affects dogs between 1 and 5 years of age, although it also may occur in older dogs. Pancreatic insufficiency is rare in cats, and occurs as a consequence of chronic, intermittent bouts of pancreatitis in this species. In contrast to most dogs with the disease, cats often have loss of both exocrine and endocrine pancreatic function, and are thus typically diabetic as well. The optimal test for the diagnosis of EPI in dogs and cats is a species-specific assay of trypsin-like immunoreactivity (TLI). Assay of fecal proteolytic activity (PA) using an azoprotein- or casein-based method can also be used, but it is not as sensitive as the TLI assay and is more impractical to perform. Microscopic examination of Sudan- and iodine-stained fecal smears for excessive fat droplets and undigested starch muscle is subjective, imprecise, and notoriously unreliable.

Serum Cobalamin and Folate. Measurement of serum vitamin B_{12} (cyanocobalamin) and folate concentrations are used to evaluate the absorptive function of the ileum and jejunum, respectively, and

are abnormally decreased in infiltrative bowel disorders such as IBD or lymphoma affecting these regions of bowel. A deficiency of cyanocobalamin can adversely affect DNA replication in the intestinal crypts, and affect the overall response of the animal to dietary and medical therapy. Cyanocobalamin is easily supplemented via parenteral (subcutaneous) injection on a weekly basis for 6 weeks, with periodic reevaluations of serum cyanocobalamin concentrations recommended thereafter. Measurement of serum cobalamin and folate concentrations are also commonly utilized to diagnose "small intestinal bacterial overgrowth" (SIBO) in dogs, although several studies highlight the relative insensitivity of this assay for this specific purpose.[13,14]

^{51}Cr-EDTA, Polyethylene Glycols, and Differential Sugar Absorption Studies. The integrity of the barrier function of the GI tract has been evaluated by permeability testing in several species, and many different marker molecules, including ^{51}chromium-labeled ethylenediaminetetraacetate[15] (^{51}Cr-EDTA), polyethylene glycols, and mono- and disaccharides have been evaluated.[16] Mannitol and lactulose are nonmetabolizable, hydrophilic, and lipophobic, with negligible affinity for the monosaccharide transport system, and are absorbed passively by nonmediated means. Recovery in urine is almost total and renal clearance is high. The simultaneous use of two allows a differential estimation of transcellular pathways through small-size channels, and paracellular pathways through large-size channels (tight junctions). Furthermore, the simultaneous use of these two sugars and the calculation of the ratio of the sugars makes the test independent of the degree of completion of the urine collection. Finally, it is known that intestinal permeability to mannitol is close to that of rhamnose and permeability to lactulose is similar to that of ^{51}Cr-EDTA.[17] GI permeability and mucosal function testing is used predominantly in the research arena, and not used very often in routine clinical practice.

Fecal α_1-Proteinase Inhibitor. PLE is a syndrome caused by a variety of gastrointestinal diseases causing enteric loss of albumin and globulin. Intestinal inflammation, infiltration, ulceration, blood loss, and primary or secondary lymphangiectasia are well-documented causes of PLE. If left untreated, the final outcome of PLE is panhypoproteinemia with decreased intravascular oncotic pressure and the development of abdominal and pleural effusion, peripheral edema, and death. Protein-losing enteropathy is uncommon in cats, and most cats with PLE are diagnosed with intestinal lymphoma or severe IBD. Serum albumin and total protein should be carefully evaluated in all patients with a history of weight loss, anorexia, vomiting, or diarrhea. Although PLE is typically associated with panhypoproteinemia, the absence of hypoglobulinemia does not preclude a diagnosis of PLE because chronic antigenic stimulation could increase the serum globulin concentration into the "normal" reference range. Additional abnormalities found on the serum biochemistry profile in association with PLE include hypocholesterolemia (secondary to malabsorption) and hypocalcemia. The causes for the hypocalcemia are multifactorial and include hypoalbuminemia (affects total calcium), decreased absorption of vitamin D, and malabsorption of magnesium.

Measurement of fecal α_1-proteinase inhibitor (α_1-PI) can be used to further support a diagnosis of PLE in animals with concurrent liver disease or protein-losing nephropathy (PLN), although this test is limited by logistical constraints in that samples must be shipped frozen, and there is currently only one laboratory that performs the ELISA at Texas A&M University.[18] α_1-PI is the same size as albumin and is lost in the intestinal tract and excreted via the feces where it can be measured as a marker for PLE. Three separate voided fecal specimens are collected into special volume-calibrated cups available from the laboratory. It is important that fecal specimens be naturally voided as digital extraction of the fecal specimen can result in microscopic blood loss and false elevations in fecal α_1-PI. Fecal specimens should be immediately frozen after collection and shipped on ice via overnight mail to the laboratory.

Intestinal Biopsy

Flexible Endoscopy and Biopsy. Endoscopic examination with mucosal biopsy is warranted for definitive diagnosis and to provide prognostic information for patients with chronic diarrhea once dietary, parasitic, systemic or metabolic disorders, and infectious diseases have been excluded (see Chapter 27). There are several inherent disadvantages of flexible endoscopy, including the inability to access the entire length of the gastrointestinal tract (unless enteroscopy is performed), and the inability to acquire deep biopsies involving the muscularis mucosa or submucosa consistently.

Rigid Proctoscopy and Biopsy. Rigid proctoscopy can be performed using a stainless steel or plastic Welch-Allyn sigmoidoscope, which consists of a hollow tube with an eyepiece on the proximal end, an insufflation bulb, and a cold light source with a fiber bundle for the transmission of light to the distal end. Sigmoidoscopy only allows direct examination of the rectum and descending colon; however, the procedure entails less risks, time, and cost than colonoscopy, and is able to diagnose the majority of large bowel disorders because of the diffuse nature of the disease. Flexible colonoscopy is indicated for evaluation of upper colonic disease, including cecal inversion, colonic neoplasia, and occult *Trichuris* infection, and is also warranted for examination and biopsy of the ileum (see Chapter 27).

Exploratory Celiotomy and Biopsy. Exploratory celiotomy allows direct visual inspection, palpation, and collection of multiple full-thickness intestinal mucosal specimens, which can facilitate the differentiation of IBD from intestinal lymphoma. In addition, procurement of biopsy specimens from the liver, mesenteric lymph nodes, and pancreas can be performed.

Treatment and Management of Acute, Self-Limiting Diarrhea

General Principles

Symptomatic therapy of the dog and cat with acute, self-limiting diarrhea typically involves empirical therapy because the causes for many of these diarrheal disorders are often undetermined. Principal goals of symptomatic therapy are restoration and maintenance of fluid and electrolyte balance, dietary modification, administration of broad-spectrum anthelminthics such as fenbendazole, and judicious use of antimicrobials when warranted. The unfounded recommendation of withholding food for 24 to 48 hours to facilitate "bowel rest" is completely unsubstantiated, and there is growing evidence that the benefits of early enteral nutritional support are far superior for promoting intestinal integrity, promoting weight gain, and improving patient outcome.[19]

Medical

Dietary Therapy

Dietary therapy consisting of either a highly digestible, moderately fat-restricted, low-residue intestinal formula or an elimination diet consisting of a novel, select protein source are typically used for animals with acute diarrhea. Fat delays gastric emptying, and

fat-restricted diets appear to be better tolerated in a variety of gastrointestinal diseases. Assimilation of dietary fat is a relatively complex process, and malabsorbed fatty acids are hydroxylated by intestinal and colonic bacteria. Hydroxy–fatty acids stimulate colonic water secretion and exacerbate diarrhea and fluid loss.[20] Fat malassimilation can also be associated with malabsorption of bile acids, resulting in deconjugation of unabsorbed bile acids and increased mucosal permeability and secretion.[21]

Antimicrobials

Use of antimicrobials as empirical therapy in the management of uncomplicated or noninfectious diarrhea is not recommended because of adverse effects of the antibiotics on the normal intestinal microflora (dysbiosis) and their tendency to promote resistant strains of bacteria. Antibiotics are indicated when specific bacterial or protozoan enteropathogens, such as *Campylobacter*, *Clostridium*, or *Giardia* are isolated from the feces. In addition, broad-spectrum bactericidal antibiotics should be considered in conditions associated with severe mucosal damage and a high risk of bacterial translocation with consequent bacteremia or endotoxemia. Lastly, antibiotics such as tylosin or metronidazole can be used to manage dogs with antibiotic-responsive diarrhea, a chronic disorder that is seen more commonly in large-breed dogs, and that is a diagnosis of exclusion.

Oral Protectants

Oral protectants such as kaolin-pectin, bismuth, activated charcoal, and barium are purported to act locally within the gut lumen to adsorb bacteria and toxins and to provide a protective coating on inflamed mucosal surfaces. Bismuth subsalicylate is the most useful of these agents because it has antienterotoxin, antibacterial, antisecretory, and antiinflammatory actions. Caution should be heeded with the use of salicylate-containing compounds in cats because of the prolonged elimination of this compound in cats. Bismuth dosed at 0.5 to 1 mL/kg BID for 2 to 3 days is safe in cats.

Fluids

Acute diarrhea may cause severe dehydration for which intravenous fluid therapy may be required (see Chapter 48).

Treatment and Management of Chronic Diarrhea

Medical

Dietary Therapy

Dietary management for dogs and cats with chronic diarrhea is dependent upon the underlying diagnosis. Elimination and hydrolyzed protein diets have proved to be effective for the management of dogs and cats with IBD involving the small and large bowel. Elimination diets contain single, novel protein sources, whereas hypoallergenic diets contain hydrolyzed protein sources that have been enzymatically hydrolyzed into polypeptides. Although more expensive and less palatable, hydrolyzed diets are particularly beneficial as elimination diets for the diagnosis and management of food hypersensitivity, when a patient appears to be allergic to multiple allergens, when a complicated dietary history makes it difficult to identify a "novel" protein, or when a patient has severe IBD.[22] The supplementation of *fermentable fiber* sources such as psyllium or oat bran may be necessary in patients with IBD involving the large intestine that show partial resolution of their clinical signs. The gelling and binding properties of fatty acids and deconjugated bile acids in fermentable fibers may be beneficial in certain gastrointestinal diseases. The use of fermentable fiber in preference to nonfermentable fiber is generally advocated because most soluble fibers

generate butyrate, the principal source of energy for the colonocyte, and other short-chain fatty acids. Short-chain fatty acids may lower the colonic luminal pH, impeding the growth of pathogens.[23] The health benefits derived from dietary supplementation of *prebiotics* have yet to be fully recognized in dogs and cats with chronic diarrhea, although prebiotic administration has been shown to decrease the concentrations of fecal ammonia and amines and increased the numbers of bifidobacteria in dog feces.[24]

Fish oil is reported to be beneficial in ulcerative colitis and Crohn disease patients,[25] but the results are controversial. Only a few studies found significant decreases in rectal leukotriene (LT) B$_4$ concentrations; the others simply reported clinical improvement. There are no published studies in the veterinary literature to date demonstrating the efficacy of n-3 fatty acid supplementation in managing canine or feline patients with IBD. *Water-soluble vitamins* are often depleted by the fluid losses associated with diarrhea and *fat-soluble vitamin* loss can be significant in animals with steatorrhea. *Magnesium* deficiency has been documented in Yorkshire Terriers with severe IBD and lymphangiectasia,[26] and dogs that are severely hypomagnesemic warrant parenteral supplementation of magnesium sulfate administered at 1 mEq/kg/24h as a constant-rate infusion.[26] Magnesium can also be supplemented orally as magnesium hydroxide (milk of magnesia) at a dosage of 5 to 15 mL per dog q24h. Cats and dogs with severe IBD frequently have subnormal serum *cobalamin* concentrations. Cyanocobalamin should be supplemented parenterally (subcutaneously), and is empirically administered at a dose of 250 μg per cat or toy-breed dog up to 1000 μg per large- or giant-breed dog, at a dosing interval of once weekly for 6 consecutive weeks. Cyanocobalamin concentrations should be rechecked every 6 to 8 weeks, particularly in cats, given the shorter half-life of the vitamin in cats.

The goal of therapy for intestinal lymphangiectasia, a common cause of PLE, is to decrease the enteric loss of plasma protein, resolve associated intestinal or lymphatic inflammation, and control effusion or edema. *Marked dietary fat restriction* is one of the most important aspects in the management of dogs with intestinal lymphangiectasia. Diets that are highly digestible and that contain less than 20% fat calories on a metabolic equivalent basis are recommended.[27] The author recommends feeding of a premium commercial-based diet if possible; however, there are a small number of dogs with severe lymphangiectasia that will need further fat restriction than available in commercial diets, and home-cooked diets are warranted. These home-cooked diets should be made up by a veterinary nutritionist to ensure that the diets are complete and balanced. Dogs with concurrent IBD and lymphangiectasia are more challenging to manage from a dietary perspective because these animals need a novel, select protein source diet that is also markedly fat restricted and virtually no commercial diet fits these criteria. An alternative to consider is the use of hypoallergenic diets containing hydrolyzed protein sources and moderate amounts of dietary fat. Failure to respond favorably to these diets warrants a home-cooked diet that is more fat-restricted and contains a novel, select protein source. Administration of medium-chain triglycerides (MCTs) to enhance the caloric density of the diet is controversial because of unpleasant taste and potential for inducing diarrhea. MCTs are not transported entirely via the portal circulation to the liver and can exacerbate lymphangiectasia.

Antimicrobials

Metronidazole (Flagyl), an inhibitor of cell-mediated immunity,[28] has been frequently used as an adjunctive agent for the management of IBD. The dose of metronidazole is 10 to 15 mg/kg q12h.

Metronidazole tablets have a sharp, unpleasant, metallic taste when scored that can cause severe salivation. Side effects are rare, although metronidazole is associated with a peripheral neuropathy in humans and animals. Less-common side effects include inappetence, nausea, vomiting, seizures, and reversible neutropenia. Reversible genotoxicity in feline peripheral blood mononuclear cells has been observed in cats after only a single dose of metronidazole, but resolved within 6 days of discontinuing the metronidazole.[29]

Tylosin (Tylan) is a macrolide antibiotic that has been reported to be effective and safe in managing canine IBD and antibiotic-responsive diarrhea (ARD).[30] Although the drug's mechanism of action is unknown, it appears to be effective in some dogs refractory to other forms of therapy. The dose range is 20 to 30 mg/kg q12h.

Motility Modifiers

Motility modifiers are *only* indicated as a last resort if the diarrhea is intractable, other causes of diarrhea have been ruled out, the diarrhea is *not* due to an infectious cause, and the patient has failed to respond to appropriate conventional therapy (e.g., diet change, deworming, corticosteroids, antibiotics). The opiate and opioid narcotic analgesics such as loperamide (Imodium; 0.1 to 0.2 mg/kg q8-12h [dogs], q12h [cats] PO) are the most effective motility modifiers for managing diarrhea. Anticholinergic agents are contraindicated because they may cause generalized suppression of all motility and potentiate ileus.

Probiotics

Administration of probiotics to dogs and cats with IBD represents a novel alternative therapeutic modality that warrants further investigation. It has been demonstrated that colitis in both humans and mice is associated with increased levels of cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-12p70, and IL-23.[31,32] Thus a proper selection of probiotic strains for the treatment of IBD is crucial and should be based on the estimation of their capacity to induce antiinflammatory pattern of cytokines (IL-10^{high}, TGF-β^{high}, IL-12p70^{low}, IL-23^{low}, TNF-α^{low}). Apart from immunomodulatory effects, probiotics have a protective effect on the normal microflora of the human gut by their antimicrobial activities directed toward intestinal pathogens.[33]

Probiotics also have been used to facilitate eradication of intestinal parasites. A recent study documented the ability of the probiotic organism *Enterococcus faecium* SF68 (Forta-Flora, Nestle-Purina, St. Louis, MO) to antagonize *Giardia intestinalis* infection in mice.[34] Oral feeding of *E. faecium* strain SF68 starting 7 days before inoculation with *Giardia* trophozoites significantly increased production of specific anti-*Giardia* intestinal immunoglobulin (Ig) A and blood IgG. This humoral response was mirrored at the cellular level by an increased percentage of CD4(+) T cells in Peyer patches and spleens of SF68-fed mice. Improvement of specific immune responses in probiotic-fed mice was associated with a diminution in the number of active trophozoites in small intestine as well as decreased shedding of fecal *Giardia* antigens (GSA65 protein). A recent study evaluating efficacy of *E. faecium* SF68 in 20 adult dogs with chronic naturally acquired giardiasis failed to affect cyst shedding or antigen content and did not alter innate or adaptive immune responses.[35] Additional studies are warranted in dogs and cats to further assess the immunomodulatory effects of probiotics and to evaluate their safety. The latter issue is particularly important given the recent finding of increased intestinal adhesion of *Campylobacter jejuni* in an in vitro model of canine intestinal mucus following incubation with *E. faecium*.[36] It should be noted that this *E. faecium* strain is different from the *E. faecium* SF68

strain available commercially; moreover, there has been no clinical or anecdotal evidence of *Campylobacter*-associated diarrhea in dogs administered probiotics to date.

Despite the paucity of prospective, randomized, placebo-controlled clinical trials in dogs and cats, tremendous interest has been shown among commercial pet food companies who are marketing probiotics for use in these species. Unfortunately, most of the evidence surrounding the use of probiotics in puppies or adult dogs with stress colitis or ARD is anecdotal, with no prospective, randomized, placebo-controlled studies in these disorders published to date.

Immunomodulatory Therapy

Most dogs and cats with moderate to severe IBD (canine IBD disease activity index >6 to 8) will require adjuvant immunotherapy in combination with dietary management and antimicrobial therapy. It is important to understand that the therapy of IBD must be tailored according to each patient's response.

Oral Corticosteroids

Corticosteroids remain the cornerstone of medical therapy for IBD, despite the lack of published controlled clinical trials documenting their benefit in dogs and cats with IBD. The value of corticosteroids relates to their antiinflammatory and immunosuppressive properties, although they also increase intestinal sodium and water absorption in the small and large bowel, and regulate basal colonic electrolyte transport. The dosage and duration of therapy is based on severity and duration of clinical signs, severity and type of inflammation, clinical response, and tolerance to the drug. The initial dosage of prednisone for therapy of IBD in dogs is 1 to 2 mg/kg q12h, not to exceed a total dose of 50 mg q12h. Cats are typically administered prednisolone, and the drug is started at a dose of 5 mg per cat q12h. The drug is gradually tapered over a 6- to 10-week period once clinical remission is attained. Combination therapy with dietary therapy, azathioprine, or metronidazole is undertaken with the goal of attempting to reduce the dose of prednisone. Parenteral corticosteroid therapy is reserved for the initial management of cats and dogs with intractable vomiting or those with severe malassimilation.

Budesonide

Budesonide, an orally administered corticosteroid structurally related to 16-hydroxyprednisolone, has high topical antiinflammatory activity and low systemic activity because of its high affinity to the steroid receptor and rapid hepatic conversion to metabolites with minimal or no steroid activity. Despite the drug's theoretical benefits, budesonide is associated with significant suppression of the hypothalamic–pituitary–adrenal axis.[37] The drug is dosed at 1 mg once daily for cats and toy-breed dogs, up to 2 mg q12h for large- or giant-breed dogs.

Azathioprine

Azathioprine is an antimetabolite that is converted to 6-mercaptopurine in the liver and then to thioinosinic acid. The latter compound impairs purine biosynthesis and this biochemical reaction inhibits cellular proliferation and reduces natural killer cell cytotoxicity.[38] Onset of these immunologic effects is slow and can require several months for maximal effectiveness. The drug is most useful in dogs as adjunctive therapy in severe or refractory IBD. Azathioprine can also be used for its steroid-sparing effects when adverse effects of prednisone are unacceptably high. The dose for dogs is 50 mg/m^2 or 1 to 2 mg/kg q24h for 2 weeks, followed by

alternate-day administration, whereas cats should receive 0.3 mg/kg q48h. The most significant side effect of azathioprine is bone marrow suppression, particularly in cats. Other side effects include anorexia, pancreatitis, and hepatic dysfunction.

Chlorambucil

The alkylating agent chlorambucil is beneficial for managing refractory cases of IBD and T-cell (small-cell) lymphoma of the gastrointestinal tract, particularly in cats.[39] Hematologic monitoring is warranted every 3 to 4 weeks to assess for neutropenia. In dogs chlorambucil is administered at 1.5 mg/m^2 on alternate days.

Cyclosporine

Cyclosporine is effective in dogs with IBD that are refractory to prednisone immunotherapy.[40] The recommended dose of cyclosporine is 5 mg/kg q24h. Although extremely expensive, particularly for large-breed dogs, the drug overall is relatively well tolerated.

Sulfasalazine

The drug consists of sulfapyridine linked to mesalamine (previously called 5-aminosalicylic acid) by an azo bond that is cleaved by colonic bacteria with subsequent release of the active moiety of the drug, mesalamine. Sulfapyridine is almost completely absorbed in the colon, metabolized in the liver, and excreted in the urine. The mesalamine moiety is locally absorbed and inhibits the formation and degradation of inflammatory mediators, including leukotrienes, prostaglandins, thromboxane, platelet activating factor, histamine, and a number of cytokines.[41] Sulfasalazine is of no value in managing small bowel inflammation because colonic bacterial metabolism is needed to release the active moiety. The usual initial dose in dogs is 20 to 40 mg/kg q8h for 3 weeks, followed by a progressive tapering every 2 to 3 weeks of the dose frequency (q8h to q12h to q24h to q48h). The drug should be used with caution and at a lower dose (10 to 20 mg/kg q24h) in cats because of the salicylate portion of the drug. The most common side effects of sulfasalazine are anorexia, vomiting, cholestatic jaundice, allergic dermatitis, and keratoconjunctivitis sicca (KCS).

Colloids

Administration of colloids such as Dextran 70 or hetastarch are used to increase the plasma oncotic pressure in dogs with intestinal lymphangiectasia or other PLEs when severely hypoalbuminemic. Colloids are typically administered prior to surgery in an effort to minimize complications associated with low plasma colloidal oncotic pressure. Administration of fresh-frozen plasma is an expensive and less efficient means of increasing colloidal oncotic pressure in dogs that are severely hypoalbuminemic. Loop diuretics such as furosemide (1 to 2 mg/kg subcutaneously or PO) can be used to decrease abdominal or pleural effusions, although caution should be heeded in monitoring the patient's hydration status and serum potassium concentrations. Potassium-sparing diuretics such as spironolactone (2 to 4 mg/kg PO or IV) can be used together with furosemide to decrease the likelihood of hypokalemia arising.

References

1. American Gastroenterological Association on Medical Position Statement: Guidelines for the evaluation and management of chronic diarrhea and AGA technical review on the evaluation and management of chronic diarrhea. *Gastroenterology* 16:1461–1486, 1997.
2. Eherer AJ, Fordtran JS: Fecal osmotic gap and pH in experimental diarrhea of various causes. *Gastroenterology* 103:545–551, 1992.
3. Popoff MR: Interactions between bacterial toxins and intestinal cells. *Toxicon* 36:665–685, 1998.
4. Jouët P, Sarna SK, Singaram C, et al: Immunocytes and abnormal gastrointestinal motor activity during ileitis in dogs. *Am J Physiol* 269:G913-G924, 1995.
5. Jouët P, Sarna SK: Platelet-activating factor (PAF) stimulates giant migrating contractions during ileal inflammation. *J Pharmacol Exp Ther* 279:207–213, 1996.
6. Casamian-Sorrosal D, Willard MD, Murray JK, et al: Comparison of histopathologic findings in biopsies from the duodenum and ileum of dogs with enteropathy. *J Vet Intern Med* 24:40–83, 2010.
7. Marks SL, Kather EJ, Kass PH, Melli AC: Genotypic and phenotypic characterization of *Clostridium perfringens* and *Clostridium difficile* in diarrheic and healthy dogs. *J Vet Intern Med* 16:533–540, 2002.
8. Marks SL, Melli AC, Kass PH, et al: Evaluation of methods to diagnose *Clostridium perfringens*-associated diarrhea in dogs. *J Am Vet Med Assoc* 214:357–360, 1999.
9. Byrne B: Personal communication. University of California, Davis, School of Veterinary Medicine, May, 2008.
10. Stenner VJ, Mackay B, King T, et al: Protothecosis in 17 Australian dogs and a review of the canine literature. *Med Mycol* 45:249–266, 2007.
11. Squires RA: An update on aspects of viral gastrointestinal diseases of dogs and cats. *N Z Vet J* 51:252–261, 2003.
12. Zwingenberger AL, Marks SL, Baker TW, Moore PF: Ultrasonographic evaluation of the muscularis propria in cats with diffuse small intestinal lymphoma and inflammatory bowel disease. *J Vet Intern Med* 24:289–292, 2010.
13. German AJ, Day MJ, Ruaux CG, et al: Comparison of direct and indirect tests for small intestinal bacterial overgrowth and antibiotic-responsive diarrhea in dogs. *J Vet Intern Med* 17:33–43, 2003.
14. Walkley HM, Neiger R: Accuracy of three non-invasive tests to diagnose small intestinal bacterial overgrowth in dogs. 43rd Annual BSAVA Congress, 2000, p 276.
15. Marks SL, Williams DA: Time course of gastrointestinal tract permeability to chromium 51-labeled ethylenediaminetetraacetate in healthy dogs. *Am J Vet Res* 59:1113–1115, 1998.
16. Rodríguez H, Berghoff N, Suchodolski JS, Steiner JM: Kinetic analysis of 5 probes in dog serum after orogastric administration. *Can Vet J* 73:217–223, 2009.
17. Maxton DG, Bjarnason I, Reynolds AP, et al: Lactulose, Cr-labeled ethylenediaminetetra-acetate, rhamnose and polyethylene glycol 400 as probe markers for assessment in vivo of human intestinal permeability. *Clin Sci* 71:71–80, 1986.
18. Murphy KF, German AJ, Ruaux CG, et al: Fecal alpha1-proteinase inhibitor concentration in dogs with chronic gastrointestinal disease. *Vet Clin Pathol* 32:67–72, 2003.
19. Mohr AJ, Leisewitz AL, Jacobson LA, et al: Effect of early enteral nutrition on intestinal permeability, intestinal protein loss, and outcome in dogs with severe parvoviral enteritis. *J Vet Intern Med* 17:791–798, 2003.
20. Hofmann AF, Poley JR: Role of bile acid malabsorption in pathogenesis of diarrhea and steatorrhea in patients with ileal resection: I. Response to cholestyramine or replacement of dietary long chain triglyceride by medium chain triglyceride. *Gastroenterology* 62:918–934, 1972.
21. Cummings JH, Wiggins HS, Jenkins DJA, et al: Influence of diets high and low in animal fat on bowel habit, gastrointestinal transit time, fecal microflora, bile acid, and fat excretion. *J Clin Invest* 61:953–963, 1978.
22. Marks SL, et al: Dietary trial using a commercial hypoallergenic diet containing hydrolyzed protein for dogs with inflammatory bowel disease. *Vet Ther* 23:109–118, 2002.

23. Brockett M, Tannock GW: Dietary influence on microbial activities in the cecum of mice. *Can J Microbiol* 28:493–499, 1982.

24. Hussein HS, et al: Pet food applications of inulin and oligofructose. *J Nutr* 129:1454S-1456S, 1999.

25. Seidner DL, et al: An oral supplement enriched with fish oil, soluble fiber, and antioxidants for corticosteroid sparing in ulcerative colitis: a randomized, controlled trial. *Clin Gastroenterol Hepatol* 3:358–369, 2005.

26. Kimmel SE, et al: Hypomagnesemia and hypocalcemia associated with protein-losing enteropathy in Yorkshire terriers: five cases (1992–1998). *J Am Vet Med Assoc* 217:703–706, 2000.

27. Marks SL, Fascetti AJ. Nutritional management of diarrheal disease. In Bonagura JD, editor: Kirk's Current Veterinary Therapy XIII, 2000, pp 653–658.

28. Grove DI: Suppression of cell-mediated immunity by metronidazole. *Int Arch Allergy Appl Immunol* 54:422–427, 1977.

29. Sekis I, Ramstead K, Rishniw M, et al: Single-dose pharmacokinetics and genotoxicity of metronidazole in cats. *J Feline Med Surg* 11:60–68, 2009.

30. Westermarck E, Skrzypczak T, Harmoinen J, et al: Tylosin-responsive chronic diarrhea in dogs. *J Vet Intern Med* 19:177–186, 2005.

31. Becker C, Dornhoff H, Neufert C, et al: Cutting edge: IL-23 cross-regulates IL-12 production in T cell-dependent experimental colitis. *J Immunol* 177:2760–2764, 2006.

32. Fuss IJ, Becker C, Yang Z, et al: Both IL-12p70 and IL-23 are synthesized during active Crohn's disease and are down-regulated by treatment with anti-IL-12 p40 monoclonal antibody. *Inflamm Bowel Dis* 12:9–15, 2006.

33. Rath HC: The role of endogenous bacterial flora: bystander or the necessary prerequisite? *Eur J Gastroenterol Hepatol* 15:615–620, 2003.

34. Benyacoub J, et al: *Enterococcus faecium* SF68 enhances the immune response to *Giardia intestinalis* in mice. *J Nutr* 135:1171–1176, 2005.

35. Simpson KW, Rishniw M, Bellosa M, et al: Influence of *Enterococcus faecium* SF68 probiotic on giardiasis in dogs. *J Vet Intern Med* 23:476–481, 2009.

36. Rinkinen 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* 92:111–119, 2003.

37. Tumulty JW, Broussard JD, Steiner JM, et al: Clinical effects of short-term oral budesonide on the hypothalamic-pituitary-adrenal axis in dogs with inflammatory bowel disease. *J Am Anim Hosp Assoc* 40:120–123, 2004.

38. Brogan M, et al: The effect of 6-mercaptopurine on natural killer-cell activities in Crohn's disease. *J Clin Immunol* 5:204–211, 1985.

39. Lingard AE, Briscoe K, Beatty JA, et al: Low-grade alimentary lymphoma: clinicopathological findings and response to treatment in 17 cases. *J Feline Med Surg* 11:692–700, 2009.

40. Allenspach K et al: Pharmacokinetics and clinical efficacy of cyclosporine treatment of dogs with steroid-refractory inflammatory bowel disease. *J Vet Intern Med* 20:239–244, 2006.

41. Stevens C, Lipman M, Fabry S, et al: 5-aminosalicylic acid abrogates T-cell proliferation by blocking interleukin-2 production in peripheral blood mononuclear cells. *J Pharmacol Exp Ther* 272:399–406, 1995.