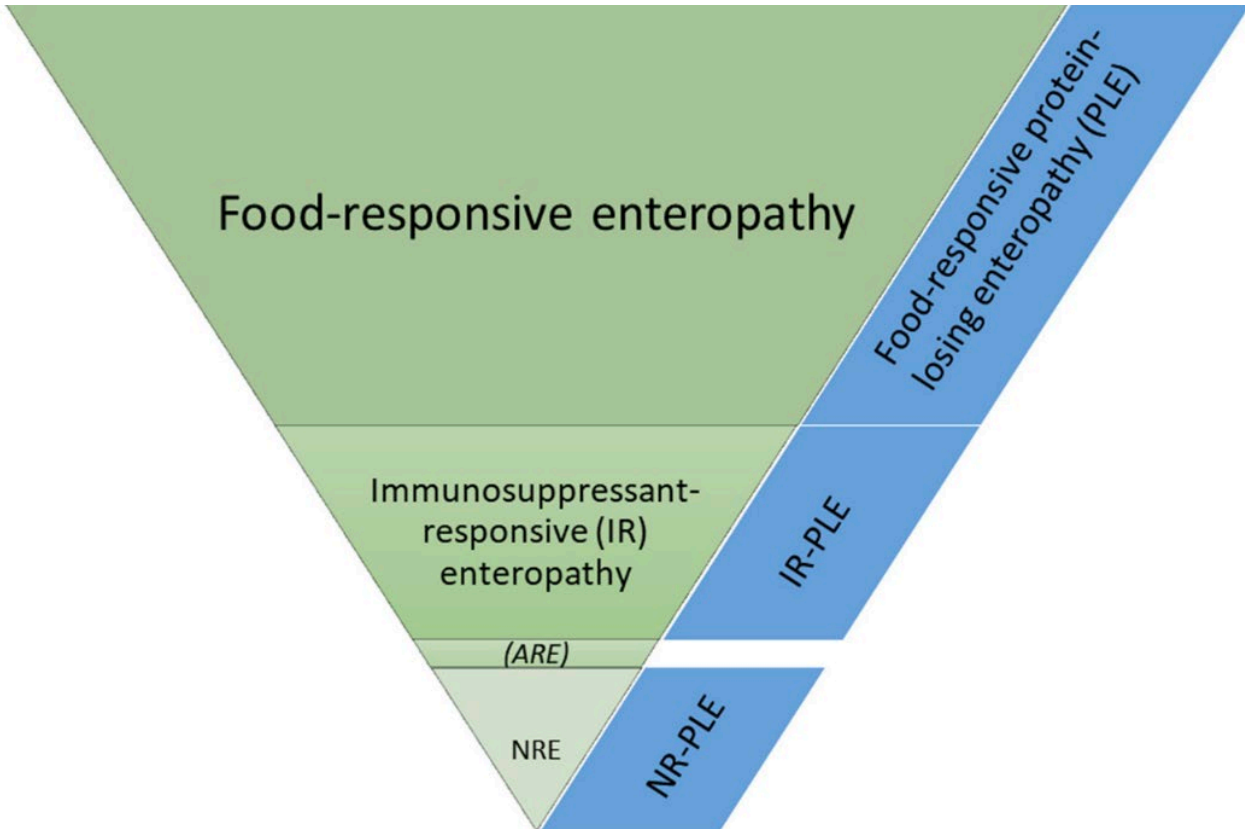
RATIONAL APPROACH TO CHRONIC DIARRHEA IN DOGS

Stanley L. Marks, BVSc, PhD, DACVIM (Internal Medicine, Oncology, Nutrition)
University of California, Davis, School of Veterinary Medicine
Professor of Small Animal Medicine

Chronic diarrhea refers to intermittent or continuous diarrhea of ≥ 3 weeks duration. The diagnosis of dogs and cats with chronic diarrhea is typically more challenging than that of animals with acute diarrhea and requires a comprehensive workup in many of these animals; however, the clinician must apply diagnostic testing and procedures in a rational and judicious fashion. Failure to follow a standardized workup in these animals can result in frustration for the owner and veterinarian and continued diarrhea for the patient.

Subtypes of Chronic Enteropathy in Dogs



Clinicians must ask the fundamentally important question, "do the clinical signs fit the diagnosis?" in all these cases. There is a plethora of examples in which a diagnosis has been rendered but does not fit the patient's clinical signs. For example, a 9-month kitten from a large cattery that is evaluated for chronic signs of colitis and a positive fecal flotation for *Giardia* does not have colitis secondary to the *Giardia*, because *Giardia* is typically a small bowel pathogen and the clinical signs do not fit. Fecal culture or PCR for *Tritrichomonas foetus* (renamed *Tritrichomonas blagburni*) would be a logical test to perform in this case considering the

signalment and clinical signs. The kitten might improve transiently with metronidazole but will not have a resolution of diarrhea until the proper therapy is implemented (ronidazole for *T. blagburni*). A 7-year cat with chronic refractory diarrhea and weight loss with a diagnosis of moderate lymphocytic and plasmacytic enteritis (the dreaded "IBD" garbage can diagnosis) could have concurrent low grade intestinal lymphoma that is refractory to corticosteroid and dietary therapy. Likewise, a 2-year Boxer with a chronic history of colitis must be comprehensively worked up (colonic biopsies preferably) to rule out granulomatous colitis (GC), an infectious enteropathy caused by an adherent and invasive strain of *E. coli* that requires antimicrobial therapy (typically fluoroquinolones; however, resistance is rapidly increasing to this class of antimicrobials), and not immunomodulatory therapy.

In the authors experience, the most common reasons for a lack of response to therapy in dogs and cats with chronic enteropathies, include:

1) Incorrect diagnosis (misdiagnosis of intestinal lymphoma or misdiagnosis of suppurative (infectious) enteropathy
2) Lack of client compliance
3) Inappropriate dietary selection
4) Suboptimal drug therapy (type, dose, and/or duration)
5) Lack of supplementation of cobalamin
6) Concurrent disorder (e.g., IBD plus pancreatitis; IBD plus pancreatic insufficiency, etc.)
7) Antimicrobial resistance (when antimicrobials are warranted)

<u>Below are a few important "pearls" for clinicians to help diagnose and manage patients with chronic enteropathies more effectively and successfully:</u>

1) ***Always evaluate serum B12 (cobalamin) concentrations in cats and dogs with chronic enteropathies.*** It is likely that mucosal repair is impeded in the initial management of chronic bowel disease when B_{12} is deficient and its absorption impaired. Consideration should be given to B_{12} assays in the initial evaluation of dogs and cats with chronic intestinal disease and to oral or parenteral administration during the initial management of these patients if low serum cobalamin is identified. B12 deficiency has been associated with ongoing diarrhea despite appropriate dietary and steroid or antimicrobial therapy in animals with chronic enteropathy.

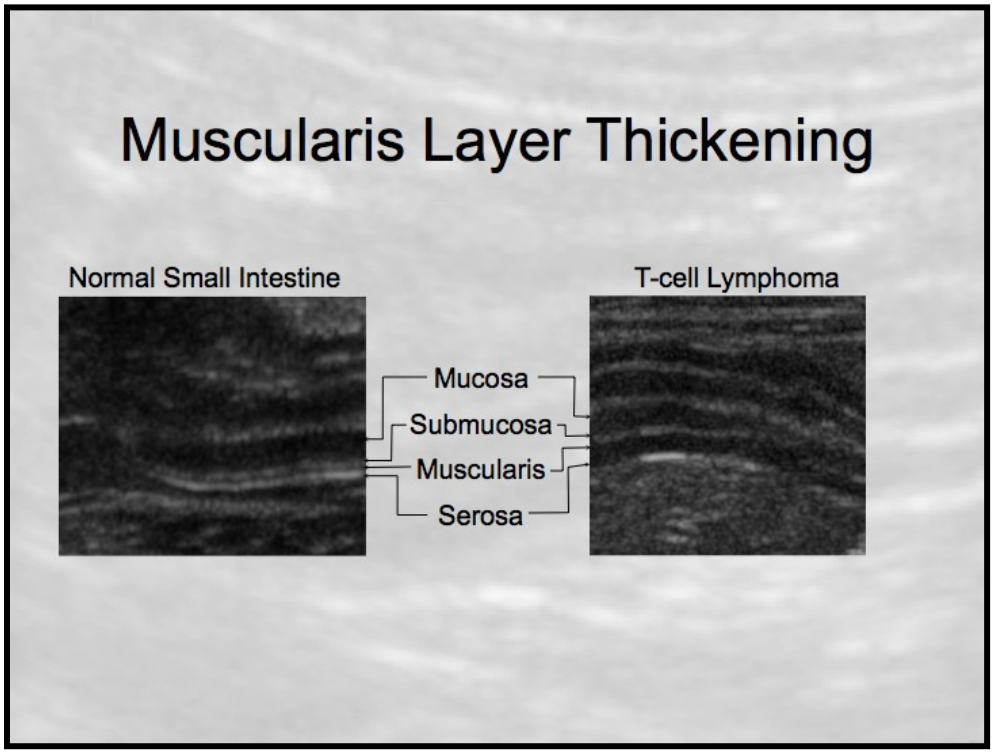
2) ***Protein-losing enteropathies (PLE's) are commonly associated with panhypoproteinemia; however, the absence of hypoglobulinemia does not preclude a diagnosis of PLE***
The serum biochemistry panel can provide additional information pertaining to the likely cause of diarrhea and helps rule out extra-GI causes of diarrhea. Both the serum *albumin* and *globulin* concentrations should always be carefully interpreted, because abnormally decreased values in both parameters are supportive of a *protein-losing enteropathy* (PLE). Protein-losing enteropathies represent a syndrome of intestinal disorders that typically manifest with abnormal loss of serum proteins across an inflamed or abnormally leaky intestinal mucosal barrier. The cholesterol concentration should always be interpreted in animals with gastrointestinal disease, because *hypocholesterolemia* can be seen in association with abnormal loss across the intestinal wall (as with PLE), secondary to decreased production by the liver

(liver failure), or with Addison's disease (dogs). The latter association is particularly important, because Addisonian dogs with only a glucocorticoid deficiency will have normal electrolytes on the serum chemistry panel, and can have clinical signs of lethargy, diarrhea, and vomiting.

3) ***Evaluate BUN and creatinine ratios in all patients with chronic enteropathies***. Most common causes for a discordant BUN:Cr ratio include dehydration, intestinal bleeding, muscle wasting (will decrease Cr and not affect BUN), or high protein meals (will increase BUN).

4) ***The most common ultrasonographic features of IBD and low grade GI lymphoma in dogs and cats include a diffuse thickening of the muscularis propria layer with/without concurrent thickening of the submucosal layer.*** Mesenteric lymph nodes are commonly slightly enlarged due to reactivity. Large, hypoechoic (black) mesenteric lymph nodes are more suggestive of lymphoma.

The mean thickness of the muscularis propria in cats with low grade GI lymphoma or IBD was twice the thickness of that of healthy cats and was the major contributor to significant overall bowel wall thickening in the duodenum and jejunum. A muscularis to submucosa ratio >1 is indicative of an abnormal bowel segment. Colic lymph nodes in cats with lymphoma were increased in size compared with healthy cats. In cats with gastrointestinal lymphoma and histologic transmural infiltration of the small intestines, colic or jejunal lymph nodes were rounded, increased in size and hypoechoic.



5) ***A normal ultrasound study does <u>not</u> rule out IBD or intestinal lymphoma.*** Abdominal ultrasound is complimentary to survey abdominal radiographs and is more sensitive for the

detection of abdominal masses, intestinal mural thickening, intussusceptions, and mesenteric lymphadenopathy. In addition, ultrasound-guided percutaneous biopsy or aspiration of masses is an effective diagnostic procedure. Abdominal ultrasound has also proven useful for the assessment of the bowel layers in cats with intestinal lymphoma and IBD but is an insensitive tool for differentiating the two disorders in cats, in particular cats with low grade GI lymphoma (see above). Despite the inherent benefits of abdominal ultrasound, a normal abdominal study does NOT rule out IBD or intestinal lymphoma.

6) ***Dogs and cats with chronic enteropathies that are relatively stable (not anorectic, febrile, or showing evidence of severe weight loss) should be initially managed with an elimination diet containing a novel, single protein source or a hydrolyzed-protein diet. An alternative option for dogs with signs of colitis is a fiber-enhanced diet that contains a blend of fermentable and non-fermentable fiber sources.*** The diet should be fed exclusively for 2-3 weeks because almost all animals should show a marked improvement or resolution in their clinical signs within the first 10-14 days.

7) ***The biggest indications for hydrolyzed protein diets in dogs and cats*** include those with a complicated dietary history (owner has chopped and changed from one diet to another over the past few months) or in animals with severe IBD.

8) ***Antimicrobials should be used judiciously in all animals with chronic enteropathies.*** Antibiotic administration is associated with the development of intestinal dysbiosis, antimicrobial resistance, and potential exacerbation of diarrhea. Metronidazole and tylosin have a very limited role in the management of dogs with chronic enteropathies and there is increasing evidence documenting the benefits of modified fiber diets, probiotics, or fecal microbiota transplantation in lieu of antimicrobial therapy. Antimicrobials are warranted for the treatment of granulomatous colitis in Boxers and French bulldogs (see table 1).

9) ***Prednisone or prednisolone (cats) must be administered at the correct dose and for the appropriate duration when warranted***. Most cats (average size) are started off at 5 mg prednisolone BID with a gradual taper over 10-12 weeks. Dogs are typically dosed with prednisone at 1-2 mg/kg BID with a similar taper over 10-12 weeks.

10) ***Never exceed a total dose of prednisone of 25 mg BID (50 mg total) in a dog, regardless of the animal's size or weight.*** I typically manage a Labrador retriever size animal (60-70 lb) with a starting dose of prednisone of 20 mg BID.

11) ***Animals needing more aggressive immunotherapy (severe IBD, etc) should be given a second immunomodulator such as cyclosporine (dogs) or chlorambucil (cats)***. Never give more than 2 immunomodulators concurrently to a dog or cat.

12) ***Always evaluate for the underlying cause(s) of hypocholesterolemia in affected dogs*** and be sure to rule out Addison's disease in all of these animals. Other causes for

hypocholesterolemia include liver failure, intestinal malabsorption, and hemophagocytic histiocytic lymphoma.

13) **Dogs with glucocorticoid deficient hypoadrenocorticism (GDH) commonly present with non-specific GI signs** and there is no single diagnostic variable, including lymphocyte count, eosinophil count, albumin/globulin ratio, adrenal gland size, serum cobalamin, or abdominal ultrasound that reliably distinguishes dogs with GDH and other causes of GI disease. Resting cortisol testing is thus pivotal in all dogs that present with non-specific signs of GI disease.

14) Always ***obtain multiple gastric and intestinal biopsies*** in animals during the laparotomy procedure, even if the stomach and intestine appear grossly normal. It is preferable to obtain 3 gastric biopsies and 2 biopsies from the duodenum and jejunum, and 1-2 biopsies from the ileum. An excisional biopsy of a regional (mesenteric) lymph node can be very helpful for diagnosing lymphoma or an infectious enteropathy.

15) ***A lack of vomiting or diarrhea in a cat with a history of weight loss does NOT rule out primary gastrointestinal disease.*** Primary GI disorders such as IBD and low grade GI lymphoma can manifest with only weight loss (with/without anorexia) in the absence of vomiting or diarrhea. In contrast to dogs, panhypoproteinemia is relatively uncommon in cats, even when diagnosed with intestinal lymphoma. Gastrointestinal endoscopy and biopsy or exploratory laparotomy with biopsy is a reasonable diagnostic approach in cats with a history of weight loss only, particularly when a minimum data base (CBC, chemistry panel, T4, urinalysis) has ruled out extra-GI causes of weight loss, and an oral examination followed by abdominal imaging has revealed no evidence of a cause for the weight loss. Measurement of serum B12 concentrations is pivotal in all cats with a history of weight loss with/without evidence of diarrhea or vomiting.

16) ***Histologic interpretation of endoscopically obtained GI biopsies should be interpreted cautiously***
The interobserver variation among histopathologic evaluations of intestinal tissues from dogs and cats is unacceptably high. Willard et al. reported lack of uniformity in the assessment of 50% of biopsy samples examined by 5 veterinary pathologists. With the support of the WSAVA, the GI Standardization Group has proposed to develop a standardized histologic evaluation system that will be applied to all companion animal gastroenterologic disorders. Standardization will yield several obvious benefits including uniform diagnosis of disease, staging of disease, and the subsequent development of controlled clinical trials for the treatment of canine and feline gastrointestinal disorders. This should facilitate the diagnosis of IBD in dogs, which will be a tremendous benefit for pathologists and veterinarians alike.

Inflammatory bowel disease is a diagnosis of exclusion, and careful attention should be paid to the quantity, quality, and interpretation of gastrointestinal biopsies. Morphologic and inflammatory changes of IBD in the canine duodenal mucosa include morphological criteria (villus stunting, epithelial injury, crypt distension, lacteal dilation, and mucosal fibrosis) together with inflammatory criteria (intraepithelial lymphocytes, lamina propria lymphocytes/plasma cells, eosinophils, and neutrophils). *The mere presence of mild lymphocytic/plasmacytic enteritis*

in duodenal biopsies lacking changes in architecture is NOT synonymous with a diagnosis of inflammatory bowel disease. In addition, the finding of increased neutrophils and tissue macrophages (granulomatous inflammation) warrants a comprehensive search for an underlying infectious etiology before immunomodulatory therapy is administered. Special stains should be applied to the biopsies and FISH (fluorescent in-situ hybridization) should be considered on biopsies as well.

16) ***Giardia spp. can be associated with small bowel diarrhea in dog or cats; however, infection is more commonly associated with lack of clinical signs.*** *According to the CAPC (Companion Animal Parasite Council), an asymptomatic dog or cat found to be infected with Giardia may be treated with a single course of anti-Giardial therapy. A study at UC Davis evaluating 300 apparently healthy dogs that frequented dog parks in northern California diagnosed Giardia in 50 of the dogs (17%) and most of the infected dogs had normal stools.* ***Repeated courses of treatment are not indicated in dogs or cats without clinical signs even if persistently positive for Giardia.***

17) ***What are the latest recommendations for the management of dogs with Exocrine Pancreatic Insufficiency (EPI)?***

- Dogs with EPI should be maintained on a premium complete and balanced commercial diet that is NOT restricted in dietary fat.
- The diet should be fed twice daily and NOT given in multiple smaller meals.
- Commercial enzyme powder containing animal protein sources such as Pancrezyme (manufactured by Virbac) should be administered with each meal, and one should avoid tablet forms of the enzyme supplement. One can obtain commercial pancreatic extract of animal origin that is far more cost effective from a company called Enzyme Diane (information about purchasing can be found online via Google).
- There is no need to incubate the enzyme powder with each meal. The enzyme powder can be mixed with the meal and given immediately.
- Most dogs with EPI have an abnormal intestinal microflora; however, the routine administration of metronidazole or tylosin should be avoided.
- Administration of cobalamin (Vitamin B12) should be done in dogs with subnormal serum levels. Vitamin B12 is typically administered at 250 μg-1,500 μg per dog (toy breeds receive 250 μg and giant breeds receive 1,500 μg) administered SQ once weekly for 6 consecutive weeks. Oral supplementation of cobalamin is equally effective to parenteral supplementation but takes longer to attain therapeutic plasma concentrations.
- Raw pancreas is equally effective to commercial pancreatic enzyme formulations and can be administered at 100 grams of raw pancreas (bovine, porcine, or ovine sources are equally effective) per 20 kg body weight.
- The raw pancreas should be pre-weighed and stored in appropriate aliquots in a freezer in plastic zip-lock bags. Aliquots should be slowly thawed in warm water prior to mixing with a meal and should not be boiled or microwaved as this will destroy the enzymes.

- Consider concurrent disease (such as IBD) in dogs that fail to respond completely to management of EPI.

TABLE 1: Diagnostic Approach to Dogs and Cats with Chronic Enteropathy

Detailed and accurate history, including comprehensive dietary history

Physical examination

Minimum Data Base

CBC
Chemistry panel
Urinalysis
T4 (cats > 5 years)
Fecal centrifugation flotation and direct wet-prep vs. fecal parasite antigen testing vs. fecal parasite PCR testing (KeyScreen)

Additional fecal tests that may be warranted

Fecal *Giardia* ELISA or IFA test for *Giardia* and *Cryptosporidium*
Fecal InPouch culture or PCR for *Tritrichomonas foetus* (cats with colitis)
Fecal PCR diarrhea panel
Serology (ELISA) for *Pythium insidiosum* (Auburn University)

Fecal PCR diarrhea panels should be reserved for animals developing diarrhea after kenneling or show attendance, animals with an acute onset of hemorrhagic diarrhea in association with evidence of sepsis, diarrhea outbreaks occurring in more than one pet in a household, determination of enterotoxin genes for Clostridium perfringens, and for testing for zoonotic enteropathogens (Campylobacter jejuni; Salmonella spp.)

Empirical deworming with a broad-spectrum anthelminthic such as fenbendazole
Tests of Assimilation

Trypsin-like immunoreactivity (TLI) *for diagnosis of exocrine pancreatic insufficiency*
Serum cobalamin and folate (*assessment of absorption in the ileum and jejunum of dogs and cats, respectively*)

Imaging

Abdominal ultrasound
Abdominal radiographs (*relatively low yield procedure in animals with chronic diarrhea, but is indicated in dogs and cats suspected of having partial obstructions due to foreign bodies, intussusceptions, bloat, or intestinal torsion*

Diet Trial

Elimination diet or hydrolyzed diet for chronic enteropathies is selected based on the animal's dietary history and is recommended before procuring intestinal biopsies in stable animals with chronic enteropathies (no evidence of hypoalbuminemia, fever). Modified fiber diets can be tried in animals with large bowel disease. The trial should last for 2-3 weeks.

Antibiotic Trial

The author does not advocate the routine administration of tylosin or metronidazole in dogs and cats with chronic enteropathies. Colonic biopsies and culture of colonic mucosal pinch biopsies (endoscopy) should be performed in dogs with suspected granulomatous colitis prior to empiric administration of enrofloxacin (or other fluoroquinolones) in light of the high prevalence of antimicrobial resistance.

Miscellaneous Tests or Procedures

Baseline cortisol or ACTH stimulation test (dogs)
FeLV/FIV serology (cats)
Spec fPL or Spec cPL (pancreatitis)
Rectal scraping *(Pythiosis, Histoplasmosis, Prototheco sis, and eosinophilic colitis or proctitis)*

GI Biopsies

Endoscopy (recommended to procure ileal biopsies when feasible, particularly when B12 is low)
Full-thickness biopsies (laparotomy vs. laparoscopy)

MANAGEMENT OF CHRONIC ENTEROPATHY (CE) IN DOGS AND CATS

The inflammatory bowel diseases (IBDs) are the most common causes of *chronic* vomiting and diarrhea in dogs and cats and refer to a group of poorly understood enteropathies characterized by the infiltration of the gastrointestinal (GI) mucosa by inflammatory cells. The cellular infiltrate is composed of variable populations of lymphocytes, plasma cells, eosinophils, macrophages, neutrophils, or combinations of these cells. Changes in the mucosal architecture characterized by villous atrophy, fusion, fibrosis, and lacteal dilation frequently accompany the cellular infiltrates.

The importance of dietary intervention in the management of dogs and cats with CE cannot be overemphasized. The term *diet-responsive* or *food-responsive* chronic enteropathy has been coined that encompasses food intolerance, food allergy, and mild to moderate IBD that benefit from the ingredient(s) of the new diet. Approximately 40% to 60% of dogs and cats with chronic enteropathies will benefit from an elimination or hydrolyzed protein diet or fiber-enhanced diet, underscoring the importance of dietary elimination trials in stable animals with chronic GI disease before undertaking more invasive diagnostic procedures.

Dogs and cats with suspected IBD or CE that are deemed to be stable based on the history, physical examination findings, and laboratory workup (for example, no evidence of hypoalbuminemia or fever) should be managed with an elimination or hydrolyzed diet alone before other therapeutics are attempted. The elimination diets are typically fed for 2 to 3

weeks before determination of the need for additional diagnostics such as GI biopsy. Owners should be educated about the importance of strict dietary compliance during the trial period, and any treats, supplements, and flavored medications should be avoided. Animals with colitis may benefit from fiber-enhanced formulas in lieu of elimination diets.

Potential Role of Dietary Components in the Modulation of Intestinal Mucosal Integrity

Abnormal Responses to Dietary Antigens

Regardless of the underlying etiology for any given patient, exaggerated responses to dietary antigens are often suspected in patients with IBD. Also unknown in any given patient is whether any abnormal immune response to the diet is the cause or the result of a mucosal infiltrate. If the cause, it is expected that removal of the inciting antigen would lead to improvement. If the effect, removing the largest single source of antigen during an elimination-diet trial still may be sufficient to reduce the inflammatory stimulus, allowing restoration of normal intestinal immunity. Elimination diets have proved to be effective in dogs and cats with small and large intestinal lymphocytic–plasmacytic, eosinophilic, and mixed cellular infiltrates or forms of IBD.

The theoretical basis for the use of protein hydrolysate diets is that a reduction in immunogenic epitopes being presented to the mucosal immune system while dysregulation is present will increase the potential for resolution. Thus, the argument for the use of a hydrolysate diet is independent of whether a dietary-specific immunologic response is suspected to be present or not. The ability to induce an antibody-mediated hypersensitivity response appears to be dependent on the size and structure of the protein. The allergens in soybean protein, for example, are between 20 and 78 kD, suggesting that soybean proteins with a molecular weight below this threshold would be less likely to illicit an immune-mediated response. Hypoallergenic (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.

Pro- and Prebiotics

Probiotics refer to live microorganisms which when administered in adequate amounts confer a health benefit on the host. The term probiotic was derived from the Greek, meaning “for life.” The Food and Agricultural Organization of the United States (FAO) and the World Health Organization (WHO) have stated that there is adequate scientific evidence to indicate that there is potential for probiotic foods to provide health benefits and that specific strains are safe for human use. There has been tremendous interest among veterinary pet food companies and manufacturers of animal health and wellness products to market probiotic formulations that are safe, pure, stable, and confer a beneficial effect in dogs and cats. These products are generally preferred to the multitude of over-the-counter probiotics marketed for veterinary use, given the concerns pertaining to quality control of the over-the-counter products.

A number of criteria are essential for efficacy and safety of probiotics. These include resistance to gastric acid and bile, ability to colonize the gastrointestinal tract, efficacy against pathogenic

microorganisms, and modulation of the immune system. Several potential mechanisms have been proposed for how probiotics reduce the severity or duration of diarrhea: competition with pathogenic bacteria or viruses for nutrients, competition for receptor sites, modification of the metabolic activity of the intestinal microflora, and the direct antagonism through the action of antimicrobial metabolites.

Fermentable fiber has been shown to profoundly affect intestinal flora, in addition to its effect on enterocytes, by promoting the development of beneficial species. This prebiotic effect has been shown to reduce the extent or prevalence of inflammation in experimental models of IBD. Therefore, a fermentable fiber source should probably be included as part of dietary management, although information regarding which (e.g., resistant starch, fructooligosaccharides [FOS], inulin) and how much is lacking. FOS are carbohydrates that resist digestion by the enzymes in the GI tract and can be metabolized by the microbial species that colonize the distal small intestine and colon.

PHARMACOLOGIC MANAGEMENT

Patients with mild to moderate IBD can often be successfully managed with dietary modification (elimination diet containing single, novel protein source vs. hydrolyzed diet vs. fiber-enhanced formula). Dogs and cats with a lack of response to more conservative therapy or patients with severe IBD based on high activity index scores should be managed with immunomodulatory therapy.

Antimicrobial Therapy

The term *antibiotic-responsive therapy* is commonly used for animals that respond to antimicrobials but relapse with diarrhea soon after the antimicrobial is discontinued. The condition is more common in dogs than cats and is not synonymous with *small intestinal bacterial overgrowth* (SIBO). Most dogs with ARD are younger to middle-aged (1 to 6 years), medium-to large-breed dogs with chronic persistent or intermittent diarrhea of small bowel or diffuse bowel origin. German Shepherd dogs appear to be overrepresented. The proposed mechanisms by which the antimicrobials exert their beneficial effect are currently uncertain, although qualitative changes in the intestinal microflora (intestinal dysbiosis) appear to play an important role. The author does not advocate the routine use of metronidazole or tylosin for the management of ARD and recommends the use of fiber-enhanced diets, probiotics, or fecal microbiota transplantation instead of antimicrobials.

Immunomodulatory and Anti-Inflammatory Therapy

Immunomodulatory therapy is reserved for those cases that fail to respond to nutritional and antimicrobial therapy or for cases with documented evidence of severe IBD based on a high canine IBD activity index (CIBDAI).

1. **Prednisone or Prednisolone**

Corticosteroids remain the cornerstone of immunomodulatory therapy for dogs and cats with IBD. The value of corticosteroids relates to their anti-inflammatory 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 the severity and duration of clinical signs, the severity and type of inflammation, the clinical response, and tolerance to the drug. The initial dosage of prednisone for therapy of IBD in dogs is 1-2 mg/kg q12hr, *not to exceed a total dose of 50 mg per dog per day (or 25mg BID)*. The drug is gradually tapered over a 10-12-week period once clinical remission is attained. Most cats are started on prednisolone at 5 mg q12hr (for an average-sized cat), with a gradual taper over the ensuing 10-12 weeks. Combination therapy with dietary therapy, metronidazole, and cyclosporine or azathioprine (dogs only) is undertaken with the goal of reducing the dose of prednisone. Parenteral corticosteroid therapy is reserved for vomiting patients, fractious animals that are difficult to medicate orally, or animals with evidence of severe malassimilation.

2. Budesonide

Budesonide is an orally administered corticosteroid structurally related to 16 hydroxyprednisolone; it has high topical anti-inflammatory 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. The drug is dosed at 1 mg once daily for toy-breed dogs and cats and up to 3 mg once daily for large- or giant-breed dogs.

3. 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. The onset of these immunologic effects is slow and can require several months to reach 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 the adverse effects of prednisone are unacceptably high. The dose for dogs is 50 mg/m^2 or 1 to 2 mg/kg once daily for 2 weeks, followed by alternate-day administration. Side effects of the drug in dogs include anorexia, pancreatitis, and hepatic dysfunction. The drug should be avoided in cats due to it potent myelotoxicity.

4. Chlorambucil

The alkylating agent chlorambucil is beneficial for managing refractory cases of IBD, particularly in cats. Hematologic monitoring is warranted every 3 to 4 weeks to assess for neutropenia. Chlorambucil can be administered at 15 mg PO/m^2 once per day for 4 consecutive days and repeated q3wk (in combination with prednisolone) or administered at 2 mg per cat q3-4d indefinitely. In dogs, chlorambucil is administered at 1.5 mg/m^2 every alternate day.

5. Cyclosporine

Cyclosporine has been demonstrated to be effective in dogs with IBD that were refractory to immunosuppressive doses of prednisone. The dose of cyclosporine used was 5 mg/kg q24hr, and the drug was well-tolerated.

6. 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. 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 q8hr for 3 weeks, followed by 20 to 40 mg/kg q12hr for 3 weeks, then 10 to 20 mg/kg q12hr for 3 weeks. The most common side effects of sulfasalazine include anorexia, vomiting, cholestatic jaundice, allergic dermatitis, and keratoconjunctivitis sicca (KCS). The author's use of sulfasalazine has decreased substantially over the past decade with the advent of successful dietary modification for the vast majority of affected patients.

It is important to emphasize that IBD is a disease of control, and relapses are possible depending on the severity of the disease. Client education is therefore pivotal to avoid frustration and to maximize dietary and medical compliance. Patients that fail to respond to appropriate dietary and medical therapy should be reevaluated for another diagnosis before implementing more aggressive therapy.

RECOMMENDED READING:

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