How I Treat: Inflammatory Bowel Disease

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The inflammatory bowel diseases (IBD) 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 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 successful management of IBD is predicated on the proper diagnosis of the syndrome. The diagnosis of "chronic idiopathic enteropathy" (CIE), which includes inflammatory bowel disease (IBD), is based on the presence of compatible clinical signs (chronic diarrhea, vomiting, weight loss, with or without borborygmus and flatulence), and the exclusion of metabolic, infectious, neoplastic, and obstructive disorders of the gut. Gastrointestinal biopsies must show histological evidence of a moderate to marked infiltration of the gastrointestinal mucosa by inflammatory cells (predominantly lymphocytes and plasma cells) and changes in mucosal architecture for a diagnosis of IBD to be rendered.

MANAGEMENT OF IBD

The importance of dietary intervention in the management of dogs and cats with chronic idiopathic enteropathies (CIE) cannot be overemphasized. A new term of "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 40–60% of dogs and cats with chronic enteropathies will benefit from an elimination or hydrolyzed protein diet, underscoring the importance of dietary elimination trials in stable animals with chronic GI disease prior to undertaking more invasive diagnostic procedures**.

Dogs and cats with suspected IBD or CIE that are deemed to be stable based on the history, physical examination findings, and laboratory work-up (i.e., no evidence of hypoalbuminemia, fever, etc.) should be managed with an elimination or hydrolyzed diet alone before other therapeutics are attempted. The elimination diets are typically fed for 2–3 weeks prior to determination of the need for antimicrobial administration and/or the need for additional diagnostics such as gastrointestinal 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.

PRINCIPLES OF NUTRITIONAL MANAGEMENT

Regardless of the underlying etiology for any given patient, exaggerated responses to dietary antigens are often suspected in patients with IBD. This is assumed to be the result of the increased permeability and increased expression of co-stimulatory molecules on antigen-presenting cells (APCs) that commonly accompanies IBD.

Elimination Diets

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. In one study, Guilford *et al*. (2001) found that in 16 feline cases of elimination-challenge proven dietary hypersensitivity with chronic gastrointestinal signs, all 16 had mild to severe inflammatory infiltrates in at least one region of the bowel. The infiltrates were lymphocytic, lymphocytic-plasmacytic (most cases), or eosinophilic (2 cases). All cases responded completely to the elimination diet alone and offending foods were identified in all cases. In a report of 13 dogs with lymphocytic-plasmacytic colitis, clinical signs resolved in all 13 with the introduction of an elimination diet, and of 11 dogs re-challenged with their original diet, 9 relapsed. In a further report of 6 cats with lymphocytic-plasmacytic colitis, all 6 responded completely to an elimination diet.

Hydrolyzed Protein Diets

The theoretical basis for the use of protein hydrolysate diets is that a reduction in immunogenic epitopes being presented to the mucosal immune system, whilst 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 immunological response is suspected to be present or not. The ability to induce an antibody-mediated hypersensitivity response appears to be dependent upon the size and structure of the protein. The allergens in soybean protein, for example, are between 20 and 78 kilodaltons, suggesting that soybean proteins with a molecular weight below this threshold would be less likely to illicit an immune-mediated response. Hypoallergenic 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.

Experience with protein hydrolysate diets is increasing, and anecdotally they appear to be very effective adjuncts to pharmacological therapy, even as sole therapy. Clinical resolution with histological improvement has been reported in 4 of 6 dogs with refractory IBD when treated with a hydrolyzed soy-protein diet alone. In addition, the administration of a hydrolyzed diet to 18 dogs with chronic enteropathy was shown to be superior to the administration of a highly digestible control diet for the long-term management of the chronic small-bowel enteropathy. However, it is possible that nutritional factors other than protein hydrolysis were responsible for the improvement. These could include dietary digestibility, correction of vitamin or mineral deficiencies, a lowered n-6:n-3 fatty acid ratio, and the potential for an immunomodulatory effect of soy isoflavones within the hydrolyzed diets.

Dietary Fiber

The gelling and binding properties of fatty acids and deconjugated bile acids in soluble fibers may be beneficial in certain gastrointestinal diseases. The use of soluble (fermentable) fiber in preference to insoluble (non-fermentable) 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. The health benefits derived from dietary supplementation of **prebiotics** have been documented in humans and feeding oligofructose to dogs decreased the concentrations of fecal ammonia and amines and increased the numbers of bifidobacteria in dog feces.

Polyunsaturated Fatty Acids

Fish oil has been reported to be beneficial in ulcerative colitis and Crohn's disease patients, but the results are controversial. Only a few studies found significant decreases in rectal leukotriene B_4 (LTB_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.

Fat

Avoiding excessive fat can be instrumental in the management of various gastrointestinal diseases, because fat delays gastric emptying in dogs and high-fat foods may contribute to osmotic diarrhea. Malabsorbed fatty acids are hydroxylated by intestinal bacteria and stimulate colonic water secretion, exacerbating diarrhea, as well as gastrointestinal protein and fluid losses. A recent study in 60 cats with chronic diarrhea showed that dietary management can be helpful in cats with chronic diarrhea, but dietary fat content did not appear to affect outcome. The cats were randomized to receive one of two dry diets containing 23.3% or 10.5% fat on a DM (dry matter) basis for 6 weeks. Fecal scores improved significantly within the 1st week, and maximized within 3 weeks, with 78.2% of cats improving by at least 25 points on the 100-point fecal scoring chart or having a final fecal score of at least 66. Over one third of the cats developed normal stools. There were no differences in clinical responses between the diets. These results show that dietary management can be helpful in cats with chronic diarrhea, but dietary fat content does not appear to affect the outcome.

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 TNF-α, IL-6, IL-12p70 and IL-23. 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 anti-inflammatory pattern of cytokines (IL-10^{high}, TGF-β^{high}, IL-$12p70^{low}$, IL-23^{low}, TNF-αlow). 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.

Probiotics have also been utilized to facilitate eradication of intestinal parasites. A recent study documented the ability of the probiotic organism *Enterococcus faecium* SF68 (FortiFlora, Nestle-Purina, St. Louis, MO) to antagonize *Giardia intestinalis* infection in mice. Oral feeding of *E. faecium* strain SF68, starting 7 d before inoculation with *Giardia* trophozoites, significantly increased the production of specific anti-*Giardia* intestinal IgA and blood IgG. This humoral response was mirrored at the cellular level by an increased percentage of $CD4^+$ T cells in the Peyer's patches and in the spleens of SF68-fed mice. The improvement of specific immune responses in probiotic-fed mice was associated with a diminution in the number of active trophozoites in the small intestine, as well as decreased shedding of fecal *Giardia* antigens (GSA65 protein).

Magnesium

Hypomagnesaemia has been identified in approximately a third of canine and feline admissions to intensive care facilities, when intestinal disease was the primary complaint. Whether hypomagnesaemia is a common feature of IBD on presentation has not been reported. However, the combination of malabsorption, anorexia, and therapy with magnesium-free fluids (e.g., lactated Ringer's solution), is predicted to lead to hypomagnesaemia. The possibility of hypomagnesaemia should be suspected in cases if cachexia and hypokalaemia are concurrently present, and if intestinal ileus or hypocalcemia cannot easily be rectified.

Cobalamin

Low serum B12 or cobalamin has often been regarded solely in the context of its diagnostic utility in identifying dogs with small intestinal bacterial overgrowth. However, low serum B12 has been described in cats in association with a wide variety of gastrointestinal disease including IBD. It is likely that mucosal repair is impeded in the initial management of IBD when B12 is deficient and its absorption impaired; however, this has not been investigated. Consideration should be given to B12 assays in the initial evaluation of dogs and cats with chronic intestinal disease, and parenteral administration during the initial management of IBD if low serum cobalamin is identified. Dogs and cats are typically supplemented with B12 at a dose of 250–1,500 µg per dose (depending on weight of animal), subcutaneously, for 6 weeks on a weekly basis, with supplementation continued on an as-needed basis.

Other Vitamins and Trace Elements

Vitamin and trace-element deficiencies can occur in canine and feline patients with IBD. Vitamin K deficiency, leading to coagulopathy, has been reported to occur in cats in association with IBD and may also occur in dogs. In the cats reported, the coagulopathy responded to parenteral vitamin K administration.

PHARMACOLOGIC MANAGEMENT

Patients with mild-to-moderate IBD can often be successfully managed with dietary modification (elimination diet or hydrolyzed diet) and antimicrobial administration (tylosin or metronidazole). 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 diarrhea" (ARD) 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 (1–6 years), medium-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 is currently uncertain, although qualitative changes in the intestinal microflora (intestinal dysbiosis) appear to play an important role.

Metronidazole (Flagyl), an inhibitor of cell-mediated immunity, has been frequently used as an adjunctive agent for the management of IBD. The dose of metronidazole is 10–15 mg/kg q 12 hours. Metronidazole tablets have a sharp, unpleasant, metallic taste when scored that can cause severe salivation. Side effects are rare, although metronidazole has been associated with a peripheral neuropathy in humans and animals. Less common side effects include inappetence, nausea, vomiting, seizures, and reversible neutropenia.

Tylosin (Tylan) is a macrolide antibiotic that has been reported to be effective and safe in managing canine IBD and antibiotic-responsive diarrhea (ARD). Although the drug's mechanism of action is unknown, it appears to be effective in some dogs' refractory to other forms of therapy. The current recommended dose is 5–10 mg/kg q 24 hours.

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).

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 q 12 hours, not to exceed a total dose of 40 mg per dog q 12 hrs. The drug is gradually tapered over a 6- to 12-week period once clinical remission is attained. Most cats are started on prednisolone at 5 mg q 12 hrs (for average size cat), with a gradual taper over the ensuing 8–12 weeks. Combination therapy with dietary therapy, metronidazole, and azathioprine (dogs only), is undertaken with the goal of reducing the dose of prednisone. Parenteral corticosteroid therapy is reserved for vomiting patients or animals with evidence of severe malassimilation.

Budesonide

Budesonide is an orally administered corticosteroid, structurally related to 16-hydroxyprednisolone, 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.

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 immunological 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 the adverse effects of prednisone are unacceptably high. The dose for dogs is 50 mg/m^2 or 1–2 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.

Chlorambucil

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

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 q 24 hrs and the drug was 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. 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 q 8 hours for 3 weeks, followed by 20 to 40 mg/kg q 12 hours for 3 weeks, and 10 to 20 mg/kg q 12 hours for 3 weeks. The most common side effects of sulfasalazine include anorexia, vomiting, cholestatic jaundice, allergic dermatitis, and keratoconjunctivitis sicca (KCS).

It is important to emphasize that IBD is a disease of control, and relapses are possible depending on the severity of disease. Client education is therefore pivotal to avoid frustration and to maximize dietary and medical compliance.

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