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HOW I TREAT INFLAMMATORY BOWEL DISEASE IN DOGS

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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.[1] 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.

Although the etiology of canine IBD is poorly understood, there is provocative evidence from clinical observations and animal models to incriminate normal luminal bacteria or bacterial products in the initiation and perpetuation of canine and feline IBD. Evidence of the role of enteric microflora in the pathogenesis of IBD in people is supported by clinical responses to fecal stream diversion treatment in patients with Crohn's disease (CD)[2] and antimicrobial therapy in CD and ulcerative colitis (UC) patients.[3] Additionally, there are increases in circulating and intraluminal humoral and T-cell responses to the enteric microflora in human IBD patients. Furthermore, genetic mutations in NOD2/CARD15[4] and TLR-4 (Toll-like-receptor-4) in IBD patients make them less able to detect bacterial components, resulting in defective responses to enteric microflora.[5] Studying the composition of the intestinal microflora has been a challenge to researchers; however, recent work has focused closely on the bacteria associated with the mucosal lining. A study of adherent mucosal bacteria in IBD patients concluded that *Bacteroides fragilis* comprised >60% of the biofilm mass in patients with IBD.[6] Dietary factors also appear to play a role in the etiopathogenesis of IBD in dogs and cats based on the clinical response to elimination or "hypoallergenic" diets in many of these animals.

MANAGEMENT OF IBD

PRINCIPLES OF NUTRITIONAL MANAGEMENT

Elimination / Novel Protein Diets

Antigenic determinants on proteins are incriminated in many cases of IBD, implying that the feeding of select protein diets containing a single, highly digestible, novel protein source might be beneficial for managing dogs and cats with IBD.[9]

Hypoallergenic diets

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.[10]

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 principle 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.[11] 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.[12]

Polyunsaturated fatty acids

Fish oil has been reported to be beneficial in ulcerative colitis and Crohn's disease patients,[13] but the results are controversial. Only a few studies found significant decreases in rectal 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.[14]

Vitamins and Minerals

Water-soluble vitamins are often depleted by the fluid losses associated with diarrhea and fat-soluble vitamin loss can be significant in animals with steatorrhoea. Magnesium deficiency has been well documented in Yorkshire Terriers with severe inflammatory bowel disease and lymphangiectasia.[15] Cats with severe IBD frequently have subnormal serum cobalamin concentrations.

Patients with mild-to-moderate IBD can often be successfully managed with dietary modification and antimicrobial (tylosin or metronidazole) administration. Dogs and cats with lack of response to more conservative therapy or patients with severe IBD based on activity index scores or histologic findings should be managed with immunomodulatory therapy.

PHARMACOLOGIC MANAGEMENT

Most dogs and cats with moderate to severe IBD will require adjuvant pharmacologic therapy in combination with dietary management. 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 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 to 2 mg/kg q 12 hours. 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 reducing the dose of prednisone. Parenteral corticosteroid therapy is reserved for vomiting patients, or animals with severe non-responsive disease.

Budesonide, 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 up to 2 mg BID 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.[16] 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 dug 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 prednisone) 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.[17] 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).

Antimicrobials

Metronidazole (Flagyl), an inhibitor of cell-mediated immunity,[18] has been frequently used as an adjunctive agent for the management of IBD. The dose of metronidazole is 10 to 15 mg/kg q 8 to 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).[19] 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 40 mg/kg q 12 hours.

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.[20,21] 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-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.[22]

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.[23] 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).

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