INFLAMMATORY BOWEL DISEASE: A REVIEW OF DIAGNOSIS AND MANAGEMENT

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DIAGNOSIS & TERMINOLOGY

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 or weight loss) AND the exclusion of metabolic, infectious, neoplastic, and obstructive disorders of the gut (see Table 1). If biopsy samples also reveal mucosal morphologic abnormalities and inflammation (most commonly lymphoplasmacytic), a diagnosis of IBD is reached. However, a poorly defined number of animals (approximately ≥25% of dogs) lack substantial mucosal inflammation and continue to be referred to as CIE. A stricter definition of CIE and IBD includes failure to respond to an elimination diet ("*Food-Responsive Enteropathy or Diarrhea*") and failure to respond to antimicrobial therapy ("*Antibiotic-Responsive Enteropathy or Diarrhea*").

At this stage, categorizing animals with IBD vs. CIE is mostly academic, as these cases tend to be treated in a similar manner. However, as our knowledge of chronic enteropathies expands, it will likely become important to separate these syndromes for diagnostic and therapeutic purposes.

Table 1. Diagnostic tests to consider before reaching a diagnosis of CIE or IBD

Minimum data base
Complete blood count
Serum chemistries
Urinalysis
Fecal tests
≥ 2 Fecal concentration tests (e.g. centrifugation flotation)
± Giardia antigen (ELISA)
± Tritrichomonas fetus InPouch culture or PCR (cats)
± Rectal cytology
± Salmonella culture
± Clostridium perfringens toxin analysis
± Clostridium difficile toxin analysis
± E. Coli culture and typing
Empirical deworming
Additional serum tests
Trypsin-like immunoreactivity (especially dogs)
Cobalamin and folate (especially cats)
± Baseline cortisol or ACTH stimulation test (dogs)
± T_4 (older cats)
± FeLV/FIV (cats)
± Heartworm antibody (cats)
± Pancreatic lipase immunoreactivity
Imaging
Abdominal radiographs (plain ± contrast)
Abdominal ultrasound
GI Endoscopy
Gut biopsies
Endoscopic
Full thickness
± Gram stain biopsy, fluorescence in-situ hybridization (neutrophilic & granulomatous forms)
Diet trial
Strict hypoallergenic (elimination) diet
Highly digestible diets formulated for GI disease
High fiber diets (large bowel diarrhea)
Antibiotic trial
Metronidazole, Tylosin

NUTRITIONAL THERAPY

If the clinical presentation of dogs and cats with IBD or CIE is relatively mild, and the minimum database and histopathology supports this (e.g. no PLE, mild-moderate mucosa inflammation/injury), I personally prefer to begin management with an elimination diet without other therapies. Unfortunately, many pet owners are non-compliant with food trials because they do not always fully understand the importance of dietary restriction. If suspicion of food allergy is high (e.g. animals ≤ 12 months, concurrent atopy), I prefer to try at least 2 different elimination diets before concluding a dog or cat is not food-responsive. When clinical signs are more severe (e.g. canine IBD activity index ≥ 9, evidence of PLE), my preference is to use an elimination diet in conjunction with antibiotics or immunosuppressive drugs ± additional adjunctive nutritional therapy (see below).

Strict hypoallergenic (elimination) diets: A diet that is highly digestible, contains a single carbohydrate and protein source, the protein content is moderately restricted, and protein source is "novel" (the animal has not been previously exposed) or hydrolyzed. The diet should also be lactose and gluten free. There are several currently available commercial prescription diets that fit this description (Table 2) or a homemade diet can be used. The intention is to alter or reduce the antigenic load to the gut where primary or acquired food allergies may cause or perpetuate clinical signs.

Elimination diets are fed exclusively for a minimum of 3-4 weeks. Clinical response usually occurs within the first few weeks of therapy. Animals are said to be "*food or diet-responsive*" if their clinical signs resolve on dietary therapy alone, and "*food-sensitive*" if recrudescence of clinical signs occurs on a dietary re-challenge. Several reports suggest that as many as 50-60% of dogs and cats with IBD or CIE respond to elimination diets without the need for additional therapy.

Other highly digestible diets: Several prescription diets that are not "elimination diets" (as described above) are marketed for GI disease (Table 2). Although not well studied, it's possible these diets may perform as well as elimination diets for many pets. For example, one recent study revealed as many as 75% of cats (n = 60) with non-specific diarrhea responded favorably to a highly digestible poultry-based diet.

Table 2. Examples of some commercial diets appropriate for gastrointestinal disease

Strict hypoallergenic diets
Eukanuba Response FP & KO (KO may not be gluten-free), LB (feline)
Hills d/d & z/d
Purina HA & LA
Royal Canin Hypoallergenic HP & Novel ingredient diets
Other prescription diets
Eukanuba Low-Residue
Hills i/d
Purina EN
Royal Canin Intestinal HE

Fiber supplementation (see prebiotics below): Fiber (especially fermentable fiber) appears to be most beneficial for the treatment of chronic non-inflammatory large bowel diarrhea, but may also benefit pets with chronic colitis. Metamucil (psyllium) supplementation @ 1.3g/kg/day in conjunction with a highly digestible diet has been shown to resolve or greatly improve clinical signs in ≥ 85% of dogs with idiopathic large bowel diarrhea. Some dogs with large bowel diarrhea may also respond to high insoluble fiber diets.

Cobalamin supplementation: Cobalamin (Vitamin B_{12}) deficiency is common in cats, and occasionally occurs in dogs, where GI malfunction involves the ileum. Exocrine pancreatic insufficiency can also lead to cobalamin deficiency, especially in cats. If cobalamin deficiency occurs, it may be associated with a poor response to therapy unless parenteral supplementation is provided (e.g. cyanocobalamin @ 250ug/cat and 250-1500ug/dog SC once weekly for 6 weeks, then as required to keep serum levels normalized).

Omega (n-3) fatty acid supplementation: N-3 fatty acids can be administered orally in an effort to reduce proinflammatory cytokines synthesized from n-6 fatty acids. Their efficacy has been demonstrated in a number of species and inflammatory conditions, and they are commonly utilized as adjunctive therapy for canine atopy. Preliminary data on n-3 fatty acid use in rodent IBD models and in people is encouraging, although they have yet to be evaluated in dogs and cats for the ancillary treatment of IBD.

Prebiotics: Prebiotics are dietary components that promote the growth and metabolic activity of "beneficial" microbes within the gut. They include naturally occurring, non-digestible, fermentable substrates (e.g. fiber, oligosaccharides and resistant starch). They have been shown to alter the colonic flora and reduce inflammation in rodent models of colitis, but their potential role in the therapy of small intestinal disease is unclear.

A variety of prebiotics are used in commercial pet foods, although their specific benefits to dogs and cats with GI disease has not been well characterized.

Probiotics: Probiotics are live "beneficial" microbes (or their products) administered orally. Typically, these microorganisms transiently colonize the gut with beneficial properties for the host. Some microbial products (e.g. secreted proteins and DNA) may also exert beneficial effects. The beneficial properties are incompletely understood, but include inhibition of pathogenic bacteria, improvement of intestinal barrier function, immune modulation (e.g. induction of protective cytokines), and modulation of pain perception. *Lactobacillus* GG, *Enterococcus faecium* SF68 (Fortiflora®) and *Bifidobacterium animalis* AHC7 (Prostora™ Max) have received the most attention for use in dogs and cats to date, although probiotics have yet to be evaluated in dogs and cats with chronic diarrhea. Information from rodent models of IBD are encouraging, although data from human trials are less impressive but suggest probiotics may help to reduce disease relapse. It is important to be aware that not all probiotics exert the same effect, the effects are often species-specific, and the quality and viability of the many available commercial products is highly variable.

Glutamine: Glutamine is an amino acid that's a preferred fuel for enterocytes. It is a conditionally essential amino acid, in that during times of stress (e.g. certain illnesses including diarrhea) endogenous stores may be inadequate. In these situations glutamine can improve gut mucosal mass and healing, and help maintain mucosal integrity. Recommended oral supplementation is 0.5g/kg q 24h.

ANTIMICROBIAL THERAPY

The term "*Idiopathic Antibiotic-Responsive Diarrhea*" (ARD) is commonly used for animals that completely respond to antimicrobials, but relapse with diarrhea soon after the drug is discontinued. It appears to be more common in dogs, and the term ARD is preferred to "*Small Intestinal Bacterial Overgrowth*" (SIBO) as SIBO is poorly defined in dogs and cats.

Although a large number of dogs with ARD have yet to be described, as many as 30% of dogs with CIE or mild-moderate IBD may be antibiotic-responsive. In at least 1 report, dogs with ARD were typically young (average age of onset 1-6 years), medium-large breeds, with chronic persistent or intermittent diarrhea of mixed small and large bowel origin. Not surprisingly, German Shepard Dogs were overrepresented. The response to antibiotics was usually rapid (days to 1-2 weeks) and frequently required low doses to maintain its effect (e.g. 7-10 mg/kg of metronidazole q12-24h; 6-16 mg/kg of tylosin q12-24h). Upon discontinuation of the antimicrobial, most dogs relapsed with diarrhea in <30 days.

The exact mechanism by which antimicrobials exert their antidiarrheal effect on dogs with CIE or IBD remains unclear. However, it likely involves qualitative changes to the enteric flora (e.g. more "beneficial" and less "harmful" microbes), in addition to potential changes in bacterial adhesion properties, decreased bacterial tissue invasion and immune modulating effects. It is important to note that total small intestinal bacterial numbers do NOT appear to decrease with antimicrobial therapy, and there has been NO correlation of antibiotic response with bacterial numbers, serum cobalamin, folate, or unconjugated bile acid concentrations (direct and indirect measures of "SIBO"). At this point in time, it is also unclear if some cases of ARD are part of the spectrum of IBD (e.g. mild forms) or if this is an entirely separate syndrome. Studies and anecdotal evidence in people support a role for antibiotic use in some forms of IBD. In veterinary medicine, antibiotics are used commonly as an adjunctive therapy to prednisone or other immunosuppressive agents for dogs and cats with IBD. However, the only prospective study evaluating concurrent antibiotic and prednisone therapy in 19 dogs, found a high clinical response rate to both groups (89% to prednisone alone *vs.* 100% to prednisone and metronidazole).

Antimicrobial therapy with 2-3 weeks of tylosin (20 mg/kg q 12h initially) or metronidazole (10 mg/kg q 12h initially) is a good option for dogs and cats with mild-moderate IBD (canine IBD activity index < 9) or CIE that fail or only partially respond to nutritional therapy. If a complete response to antibiotics occurs, I typically continue the course for 4-6 weeks. If the diarrhea recurs after withdrawal of the antibiotic, a longer-term course (e,g, 2-3+ months) using the lowest effective dose *vs.* trying immunosuppressive therapy should be considered. Unfortunately some dogs require antibiotic therapy for years to remain diarrhea-free.

IMMUNOSUPPRESSIVE THERAPY

Immunosuppressive therapy (glucocorticoids ± a second agent) should always be considered for cases that fail to respond to nutritional and antimicrobial therapy. They are also recommended as part of the initial therapy for cases with more severe clinical disease (e.g. CIBDAI ≥ 9, evidence of PLE). Due to the difficulty in differentiating IBD from small cell lymphoma, combination prednisolone and chlorambucil should be considered as initially therapy for older cats with moderate to severe IBD.

Prednisone or prednisolone (initial dose 1-2 mg/kg q 12h): Corticosteroids remain the immunosuppressive drug of first choice for most cases of IBD. Typically the initial dose is reduced to once daily dosing in 2-4 weeks, then gradually tapered over the following1-3 months. Recent reports evaluating dietary therapy ± antibiotics in dogs and cats with IBD or CIE suggest that only 20-50% require immunosuppressive therapy. Although data is scarce, approximately 10-20% of dogs with IBD may be refractory to steroid therapy.

Azathioprine (dogs: initial dose 2 mg/kg q 24h) or chlorambucil (cats: initial dose 2 mg/cat q 48h): These drugs are commonly introduced when glucocorticoid therapy is ineffective or cannot be reduced without relapse, if the systemic effects of glucocorticoids are unacceptable, or as part of the initial immunosuppressive protocol in animals with severe clinical disease. Animals should be monitored regularly (e.g. every 2 weeks) for bone marrow suppression and hepatotoxicty (azathioprine) during the first few months of use.

Budesonide (3 mg/m^2 q 24h): Budesonide is a potent glucocorticoid (15-20 x more potent than prednisone) that exerts mostly topical effects on the GI mucosa since it undergoes extensive first-pass hepatic metabolism. It is readily available as a slow release enteric-coated formulation (Entocort®) that dissolves in a pH dependent manner. In people, most of the drug activity occurs within the ileum and colon, but since GI pH and transit times differ for dogs and cats, it is currently unknown where most of the drug activity occurs in these species. The main advantage of budesonide over prednisone is reduced systemic side effects (although these can still occur). The main disadvantage is the increased cost and current lack of pharmacokinetic and clinical information in animals. However, there are many anecdotal reports that budesonide is effective for treating canine and feline IBD. Efficacy of budesonide in human IBD appears to be similar or slightly worse to prednisolone, and both are poor at maintaining long-term remission. For treatment of small intestinal disease in dogs or cats, a non-enteric coated formulation an be obtained from a compounding pharmacy or the enteric-coated beads within the Entocort® capsule can be crushed in an attempt to maximize drug activity in the small intestine.

Cyclosporine (initial dose 2.5-5 mg/kg q 12h): Cyclosporine has been used with some success in steroid refractory IBD in humans, and was recently evaluated in 14 dogs with moderate-severe IBD that were non-responsive to 10+ weeks of prednisone. A significant long-term clinical improvement was seen in 78% of cases (57% complete response, 21% partial response) and occurred within the first 4 weeks of therapy. However, it is unknown how well these dogs may have responded to a cheaper immunosuppressive drug such as azathioprine.

Mycophenylate mofetil: Mycophenylate is a potent immunosuppressive drug that is gaining popularity within veterinary medicine for treating a variety of immune-mediated disorders. However, it should be used with caution (and probably avoided) for the treatment of IBD at this time as it has been shown to induce enteritis and colitis in healthy dogs as well as lesions resembling IBD in people.

Methotrexate & Leflunomide: Little to no information is currently available regarding the use of these drugs in animals with IBD.

OTHER THERAPIES

Time permiting, other therapeutics including the aminosalicylates (e.g. sulfasalazine, mesalamine, olsalazine) and sodium chromoglycate will be briefly discussed during the presentation.

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