Advances in managing inflammatory bowel disease

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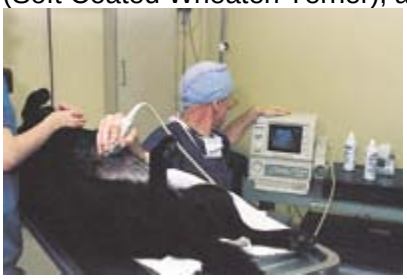
Inflammatory bowel disease (IBD) in dogs and cats older than 4 months of age occurs because of interactions between the mucosal immune system, host genetic susceptibility, and environmental factors. The proposed pathogenesis is the inflammation is caused by an abnormal immune response from host hypersensitivity caused by increased intestinal permeability, defective suppressor function of gastrointestinal-associated lymphoid tissue, and/or other primary immunologic events. Or, the inflammation is initiated by an appropriate immune response to a normal luminal constituent such as dietary antigen or resident enteric flora. The reported clinical signs are attributed to the mucosal cellular infiltrates and inflammatory mediators. There is also a strong genetic influence on the development of IBD as is appreciated in various recognized breed predispositions - lymphocytic-plasmacytic enteritis (Basenji, German Shepherd, Chinese Shar-Pei, and others), eosinophilic gastroenteritis (Rottweiler), gluten-sensitive enteropathy in Irish Setter, protein-losing enteropathy (Soft Coated Wheaten Terrier), and lymphangiectasia (Yorkshire Terrier).



Ultrasound can serve as an effective tool for diagnosing inflammatory bowel disease in older cats and dogs. This technology, along with radiographs, offer a clearer view to assess the progression of the disease.

Food allergy and feeding management

Adverse reactions to food may be due to a variety of causes, including food intolerance, poisoning, and idiosyncrasy, but a true food allergy is defined as an adverse reaction to food or food additive that has a proven immunologic basis. Skin testing and measurement of serum antibodies specific to food antigens are believed by many to have poor accuracy in detecting food allergies resulting in gastrointestinal signs. Intestinal biopsy specimens are not specific for food allergy even if inflammation is detected. Gastroscopic food sensitivity testing has been used as a method to diagnose food allergy in humans, dogs, and cats. Direct application of food antigen to the stomach mucosa results in localized swelling in allergic dogs. This technique may prove to be useful as a diagnostic tool for immediate hypersensitivity reactions in the future. Other techniques involving serology for mast cell degranulation products, measurement of cell mediated responses, and measurement of changes in intestinal permeability after exposure to an antigen may be helpful in the future but are in the experimental stages at this time.

It is also estimated that about 10 to15 percent of animals with food allergy dermatoses also have gastrointestinal signs. Allergic dogs may have resolution of their gastrointestinal signs on a hypoallergenic diet, and the gastrointestinal signs recur along with the dermatologic signs when challenged with the offending antigen.

Dogs and cats afflicted with IBD may be nutritionally deficient because of decreased food intake, impaired nutrient absorption, and/or increased exudation as seen with a protein-losing enteropathy. The most convenient dietary management for IBD-afflicted dogs and cats is feeding the hypoallergenic or fiber-enriched diets. The hypoallergenic diets are formulated with ingredients that the animal has not been fed before. These hypoallergenic diets contain a novel protein source of venison, rabbit, lamb, whitefish, or turkey or that is unlikely to evoke allergic responses such as potatoes. Diets enriched in omega-3 fatty acids are incorporated into biologic membranes resulting in decreased concentrations of pro-inflammatory omega-6 fatty acid metabolites (leukotriene B4, prostaglandins, and interleukin-1). Fiber-enriched diets are fed to mitigate signs

of large bowel diarrhea and tenesmus. Dietary fiber may increase fecal consistency, bind potential colonic irritants, improve abnormal colonic motility, and produce beneficial short chain fatty acids that influences large bowel structure and function. Commercial hypoallergenic or fiber-enriched diets should be fed for at least six to eight weeks to assess their efficacy.

Medical therapy

Dietary management alone for advanced IBD is seldom successful and most dogs and cats will require additional therapy. Mild-to-moderate cases as determined by clinical signs, normal serum protein levels, and degree of inflammatory cell infiltrate on biopsy often respond to prednisone at a dose of 0.5-2.0 mg/kg divided twice daily for two to four weeks followed by a gradual decrease in 50 percent increments at two-week intervals. Alternate day or every third day treatment can often be reached by two to three months. Treatment may be discontinued altogether by three to six months in some cases. Moderate-to-severe cases and any cases in which the serum total protein levels are less than 5.5 g/dl should be treated more aggressively using an initial prednisone dose of 2.0 mg/kg per day for two to four weeks before an attempt is made to decrease the prednisone dosage. Dogs with this severity often require long-term therapy of months to years on an every-other-day or every third day basis to maintain remission of signs and maintain body weight.

If significant side effects are caused by prednisone, such as severe polyuria/polydipsia, panting, lethargy, pruritus, behavioral changes, and/or increasing serum liver enzymes activity, oral dexamethasone can be tried instead. In some dogs, dexamethasone is much better tolerated and side effects are minimal or nonexistent. If side effects are judged to be severe, prednisone is generally discontinued for 12-36 hours to allow for adequate metabolism and clearance. Prednisone may then be reintroduced at 25 to 50 percent of the previous dose or alternatively dexamethasone can be instituted at a conservative oral level of 0.005-0.01 mg/lb daily.

Alternative steroid medications characterized by good anti-inflammatory activity and first pass hepatic metabolism have been recently used in human IBD. These medications were developed to attain maximal therapeutic effect of conventional steroids while minimizing deleterious systemic effects. These medications are administered rectally (tixcortal pivalate and beclomethasone dipropionate) or orally (budesonide). The efficacy and potential toxicity of these new medications in dogs and cats remains to be proven; although, anecdotal evidence suggests budesonide may be of value in some dogs with lymphocytic-plasmacytic colitis.

Use of combination drug therapy, such as prednisone and metronidazole, in moderate-to-severe IBD cases at the outset is recommended to improve chances of controlling clinical signs more quickly and to slow progression of the disease. Metronidazole has antibacterial and anti-inflammatory effects and is useful in treatment of IBD in dogs as well as in cats. The metronidazole is generally administered at 10-20 mg/kg in dogs and 5.0-7.5 mg/kg in cats two times daily. When prednisone and metronidazole are used in combination, the dosage level of each drug is generally gradually decreased as the animal's condition improves, serum total protein levels attain 6.0 g/dl or higher, and white blood cell counts return to normal. Steroids are then decreased gradually for several months before any reduction is made with the metronidazole dosage. If there has been an excellent response, it may be also possible for the metronidazole to be discontinued after several months. Alternatively, if chronic therapy is required, metronidazole can often be administered on a once daily and eventually on an every-other-day basis. If it is not possible to discontinue medications altogether because of recurrence of signs when no medications are given, satisfactory control may be

maintained with prednisone and/or metronidazole given on an alternate day basis - giving prednisone on one day and metronidazole on the alternate day. Occasionally in dogs with moderate-to-severe IBD or in a case where both IBD and chronic bacterial overgrowth are present, it may be necessary to continue metronidazole on a long-term basis of months to years at 10-20 mg/kg twice daily.

Combination drug therapy is recommended early in severe cases of IBD or if a side effect to one drug requires that it be used at a lower dose. If steroids are poorly tolerated or if steroids and metronidazole are unable to achieve remission, then azathioprine should be added to the medications used. Azathioprine is started early in the course for cases of IBD that cause a severe protein-losing enteropathy with a serum total protein level less than 4.5 g/dl. The dog dosage is 2 mg/kg once daily until remission has occurred and then tapered to every other day administration. Note: there is significant difference in azathioprine dosage between dogs and cats. In cats, the dosage is 0.2-0.3 mg/kg once every other day. If azathioprine is used at the outset, the initial oral prednisone dosage may be decreased by as much as 50 percent. Subsequent decreases in the oral prednisone dosage can usually be made at monthly intervals until an alternate day schedule is reached. If azathioprine is started in any type of IBD case because of significant steroid side effects, the oral prednisone is initially decreased by 50 to 75 percent but is not stopped completely unless absolutely necessary because loss of remission might result.

The azathioprine is generally maintained as alternate day therapy for three to nine months in most dogs afflicted with severe IBD. Side effects are uncommon in dogs but may include anorexia, icterus from active hepatic damage, poor hair growth, and bone marrow suppression. In addition, it is suspected that azathioprine has the potential to cause pancreatitis. A complete blood count should be done to monitor for evidence of anemia or leukopenia at three-week intervals for the first two months and then once every several months. Routine monitoring also includes once every four to six weeks initially of the serum total protein levels and serum liver enzyme activity where increases in serum liver enzyme activity may be caused by steroids and occasionally azathioprine.

Sulfasalazine is considered by many veterinarians to be the preferred drug in dogs for treatment of colitis. The recommended oral dosage in dogs is 12.5 mg/kg q8h up to a maximum of one gram q8h in refractory dogs or those having severe IBD. It is important to continue initial therapy with sulfasalazine for a minimum of four weeks before modifying drug dosage. With resolution of signs, sulfasalazine dosage is gradually decreased by 25 percent at two-week intervals and eventually discontinued while maintaining the dietary management. Caution is advised in using sulfasalazine in cats because of their sensitivity to salicylates. Other oral medications of potential use in dogs include olsalazine and mesa-lamine. Olsalazine (Dipentum) consists of two molecules of mesalamine linked by an azo bond. The enteric-coated products of mesalamine (Pentasa and Asacol) release the active drug in the distal small intestine and colon, respectively. The use of olsalazine or mesalamine for treatment of IBD in dogs and cats has not been critically evaluated, but there are substantial anecdotal reports of their efficacy. The proposed dosage is about one-half that of sulfasalazine.

A variety of other drugs, such as cyclophosphamide, cyclosporine, and tylosin, are occasionally of value in treating refractory IBD. Cyclosporine acts primarily by inhibiting interleukin-2 release from helper T-cells, which prevents T-cell recruitment and amplification and inhibits the release of gamma-interferon. Preliminary observations in humans with IBD suggest that cyclosporine may act

synergistically with steroids and produce a more rapid response than the classic immunosuppressants drugs. The use of 5-lipoxygenase inhibitor drugs, such as Zileuton, may also offer a new type of treatment for IBD in the future.

If mast cell instability leads to food hypersensitivities and subsequent development of IBD, affected animals may benefit from therapeutic measures that stabilize mast cells. Sodium chromoglycate (Gastrocrom) inhibits mast cell degranulation and decreases gastrointestinal permeability. It is minimally absorbed from the intestinal tract and has a low incidence of side effects in humans. Feeding a hydrolysate diet and treating with sodium chromoglycate have shown some favorable responses in dogs afflicted with IBD. The hydrolysate diets contain hydrolyzed proteins that are presumed to be non-antigenic because they are too small to cross-link surface IgE and trigger mast cell degranulation.

Summary

Inflammatory bowel disease in dogs and cats older than 4 months of age occurs because of interactions between the mucosal immune system, host genetic susceptibility and environmental factors. A diagnosis of IBD is one of exclusion and requires ruling out other diseases that may cause intestinal inflammation. The most convenient dietary management for IBD-afflicted dogs and cats is feeding the hypoallergenic or fiber-enriched diets. Dietary management alone for advanced IBD is seldom successful, and often requires additional medical therapy. Most drug therapies interrupt the amplification sequence of inflammation in IBD, explaining why maintenance therapy by way of dietary management and/or medical therapy are important. Anecdotal evidence supports the use of oral steroids, azathiopurine, metronidazole, sulfasalazine, or similar drugs in IBD therapy. The combination drug therapy appears warranted in animals with severe IBD and multi-organ involvement and to reduce systemic effects of steroids.

Suggested Reading:

- Baez JL, Hendrick MJ, Walker LM, et al: Radiographic, ultrasonographic, and endoscopic findings in cats with inflammatory bowel disease of the stomach and small intestine. JAVMA 215:349-354, 1999.
- Guilford WG: Idiopathic inflammatory bowel diseases. In Guilford WG, et al (eds): Strombecks Small Animal Gastroenterology. Philadelphia: WB Saunders, 1996, pp 451-486.
- Jergens AE: Inflammatory bowel disease: Current perspectives. Vet Clin North Am Small Anim Pract 29:501-521, 1999.