How to Manage Difficult Cases of Inflammatory Bowel Disease in Dogs and Cats

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A diagnosis of canine or feline inflammatory bowel disease (IBD) is reached after many other causes of chronic enteropathies have been ruled out. The prognosis of canine IBD is fair to guarded. In a retrospective study from Scotland, only 21 of 81 (26%) dogs with IBD were in complete remission after immune-suppressive treatment, while intermittent clinical signs were still present in 40 (50%), and 10 (13%) had to be euthanized due to refractory disease. Response to treatment was even worse in a prospective study of 70 dogs with chronic intestinal diseases from Switzerland, 11/21 dogs diagnosed with IBD (52%) were refractory to immune-suppressive doses of steroids. Nine of those (82% of refractory dogs or 42% of all dogs with IBD) were eventually euthanized due to treatment failure. A low serum albumin (< 2 g/dL) and/or cobalamin concentration were shown to be negative prognostic factors. However, a recent prospective study from the USA reported a remission rate > 80% in dogs with IBD after 3 weeks of treatment with prednisone or a combination of prednisone and metronidazole. The situation may not be as difficult in cats with IBD for which success rates of up to 80% were reported following immune-suppressive steroid treatment. However, definite differentiation between IBD and alimentary lymphoma, intercurrent illness or severe intestinal inflammation are challenges veterinarians are faced with in the feline species.

Objectives of the presentation

- To review the clinical approach of dogs and cats with IBD that are refractory to "routine" treatment
- To discuss available options for treatment of IBD cases refractory to immune-suppressive prednisone therapy

Approach of dogs and cats refractory to prednisone /prednisolone treatment

"Routine" immune-suppressive treatment with prednisone (dog) or prednisolone (cat) requires doses of 2-4 mg/kg/day PO (many clinicians opt to use 1-2 mg/kg BID). If dexamethasone is used, one eight (1/8) of the prednisone dose should be administered to account for the higher potency of dexamethasone (i.e. 0.25-0.5 mg/kg/day PO, SC, IV).

Generally, treatment failure should prompt the clinician to review the diagnosis and ascertain that no mistakes or erroneous assumptions were made in the diagnostic process. Only a subset of dogs and cats with chronic intestinal disease suffer from IBD, and systematic elimination of other causes is required before IBD can be a reasonable working diagnosis. Intestinal parasites (nematodes and protozoa), adverse food reactions, dysbiosis and antibiotic responsive disease (dogs), and low grade alimentary lymphoma (cat) are examples of diseases that must be ruled out. Schistosomiasis caused by Heterobilharzia americana can lead to vomiting, diarrhea, and weight loss among other signs in dogs from endemic areas. Diagnostic confirmation requires a specific parasitological test (saline sedimentation) or fecal PCR. Canine glucocorticoid-dependent hypoadrenocorticism may cause chronic intermittent GI signs similar to those of chronic enteropathies and must be ruled out (it responds well to prednisone treatment, but relapses when the treatment is discontinued).

In some cases immune-suppressive predniso(lo)ne treatment is initiated without documentation of intestinal histology due to financial constraints imposed by the owner. When steroid treatment trial fails, histologic evaluation of intestinal biopsies is strongly recommended, preferably after the medication has been weaned off and discontinued for a 2-4 weeks. The biopsy specimen can be collected endoscopically or during an exploratory celiotomy – both methods have advantages and disadvantages. The most important justification for histology is to rule out a neoplastic infiltrate (especially in cats). It is also useful to evaluate the magnitude of the intestinal mucosal inflammation based on the severity and type of the infiltrate and on the severity of the architectural mucosal changes.

Finally, refractory IBD patients must be examined thoroughly to detect intercurrent diseases that may be at the origin of the lack of response to treatment. A significant proportion of cats and dogs with IBD may develop hypocobalaminemia due to involvement of the distal jejunum and ileum, the site of cobalamin (vitamin B12) absorption. Cobalamin deficiency negatively impacts numerous processes in the intermediary metabolism and may cause a delayed or lacking response to adequately designed immune-suppressive treatment. Subcutaneous supplementation is essential in these animals. The weekly cobalamin doses range from 250 µg for cats to 250-1500 µg for dogs (depending on the size). Furthermore, concomitant inflammation of the biliary tree and pancreas may be observed in cats with IBD (triaditis syndrome). Additional evaluation of liver and pancreas using CBC, chemistry profile, abdominal ultrasound, cytological evaluation of fine needle aspirates, histological analysis of tissue biopsies, serum pancreatic lipase immunoreactivity etc. may be necessary. Finally, histoplasmosis is a systemic fungal disease that may cause clinical signs of chronic enteropathy in dogs. Cytological evaluation of rectal scrapings or ultrasound-guided aspirates of enlarged mesenteric lymph nodes may show organisms-laden macrophages.

The use of clinical scoring systems to evaluate the severity of disease and the response to treatment may be valuable in difficult cases of canine or feline IBD. Two systems have been proposed for dogs. They compute data from the history and physical exam

(CIBDAI – max 18 points) as well serum albumin (CCECAI – max 27 points) to grade the severity of disease. CIBDAI score > 9 or CCECAI score > 12 predicted negative outcome in one study. A similar system has recently been developed for cats as well which combines data from history and physical exam with endoscopic lesions, total serum protein and phosphorous concentrations as well as serum activity of ALT and ALP (FCEAI – max. 19 points). Details about the scoring indices are available in the literature and in recent textbook chapters.

Drug therapy of refractory IBD cases

Other corticosteroids: budesonide can be used to treat IBD. In humans, the drug is known to be locally efficient and undergo high first pass hepatic metabolism. Therefore, systemic complications of steroid treatment are less likely. It has been shown that the drug significantly influences the pituitary-adrenal axis in dogs, however it may cause less side effects than predniso(lo)ne, and has been used in large breed dogs which tend to be more prone to severe polyuria and polydipsia. To date, budesonide has not been evaluated critically for use in dogs or in cats with IBD, and there is no data available on its pharmacokinetics in pets. The recommended doses are 0.5-3 mg/dog daily (depending on the dog's size) and 0.5-1 mg/cat once daily. The drug must be formulated by a compounding pharmacist for use in cats and small dogs. Concurrent use with predniso(lo)ne is not recommended.

Antimicrobials: based on our current understanding, the intestinal microbiome and its interactions with the innate immune system play a central role in the pathogenesis of IBD. Modification of the intestinal microbiome with antimicrobials is therefore a logical choice in the treatment of IBD. Metronidazole is an antimicrobial effective against many obligate anaerobes. It is used successfully in the treatment of antibiotic responsive diarrhea and may have some immune-modulating effects on the intestinal mucosa. However, in a recent randomized controlled trial, dogs with IBD treated with prednisone and metronidazole did not have a better outcome than those treated with prednisone alone. Fluoroquinolones (e.g. enrofloxacin 10 mg/kg PO daily) are used in the treatment of histicoytic ulcerative colitis (HUC), a disease affecting mostly boxer dogs (see lecture on colitis). HUC is due to an infection with entero-invasive E. coli that cannot be efficiently cleared by the dog's macrophages. In cats with IBD, mucosa-associated bacteria (including Enterobacteriaceae and Clostridia) correlated with the severity of histological lesions and the number of clinical signs exhibited. Based on this information, cats with steroid-refractory IBD may benefit from treatment with fluoroquinolones. Furthermore, the author also considers antibiotic coverage if the inflammatory infiltrate in the intestinal mucosa consists mostly of neutrophils. However there is no scientific evidence to support these hypotheses and the potential side-effects of fluoroquinolones in cats must be considered before initiating treatment (marbofloxacin is preferable to enrofloxacin).

Thiopurines: azathroprine may be used in dogs with steroid-refractory IBD, and in those that relapse when prednisone treatment is weaned off. It may also be combined to prednisone in the initial treatment of severe cases of IBD. The drug is generally well tolerated, but side effects include bone marrow suppression, hepatotoxicity and pancreatitis. Regular monitoring of CBC and biochemistry profile is advisable during the first weeks-months of treatment. The initial dose is 2 mg/kg daily for 3 weeks, then 1-2 mg/kg every 48 h. Up to 3 weeks of treatment may be necessary for the drug to reach maximal effect.

Alkylating agents: chlorambucil is used with good success in conjunction with prednisolone in cats with low grade (small cell) alimentary lymphoma. It is a good addition to steroid treatment in cats with refractory IBD, and the dose is 2 mg/cat PO every 48 to 72 h. Side effects are rare and include bone marrow suppression. A CBC should be performed after a few weeks of treatment and repeated every 2-3 months or if the cat's condition deteriorates (look for neutropenia).

Cyclosporine is an inhibitor of T-cell function. In a 2006 study, pharmacokinetics of cyclosporine in dogs with IBD were not significantly different from those of normal dogs. Fourteen dogs with steroid-refractory IBD were enrolled, and 8 dogs (57%) went into complete remission within 4 weeks of cyclosporine treatment (5 mg/kg PO once daily). Additionally, 3 dogs experienced partial remission while 2 dogs did not respond and were euthanized. Furthermore, one dog relapsed after 14 weeks of initially successful treatment. Transient adverse effects were seen during the first 2 weeks of treatment in 5 dogs and included vomiting and loss of appetite in 4 dogs and hair coat changes and gingival hyperplasia in 1 dog. Most side effects responded to temporary discontinuation followed by dose-reduction. Cyclosporine treatment was discontinued in 8 of the 11 responders, which subsequently remained free of clinical signs. The owners of the remaining 3 dogs elected to continue treatment for several additional months, and the dogs remained apparently healthy. Cyclosporine has been anecdotically given to cats with refractory IBD as well with success (5 mg/kg once to twice daily).

Other immunosuppressive drugs such as mycophenylate mofetil, methotrexate and leflunomide have been used to treat immune-mediated or autoimmune diseases in dogs. Due to lack of data and possible side effects on the intestinal mucosa, their use for treatment of IBD in dogs cannot be recommended at this time.

Special dietary therapy: management of dogs with severe IBD including cases associated with significant protein loss (secondary protein-losing enteropathy or PLE) may be a serious challenge, particularly when their appetite is decreased. Elemental diets that only contain free amino acids (including glutamine), carbohydrates and reduced fat administered via feeding tube provide the necessary nutrients with minimal risk of disease flare up (e.g. Vivonex TEN ®, Peptamen HN ®). Attention should be paid to the osmolality of the product. There are currently no reports documenting the benefits of this dietary treatment in pets.

Conclusion

The morbidity and treatment failure rate in canine or feline IBD is not negligible. Reevaluation of the patient is the 1st step in the response to treatment failure. The objectives are to confirm the diagnosis of IBD and the lack of intercurrent diseases. A variety of treatment options are available for difficult cases of IBD in dogs and cats. However, the information available about many of these modalities is purely anecdotic and rigorous scientific studies are needed to identify the better options.

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