Those Troublesome Chronic Diarrhea Cases

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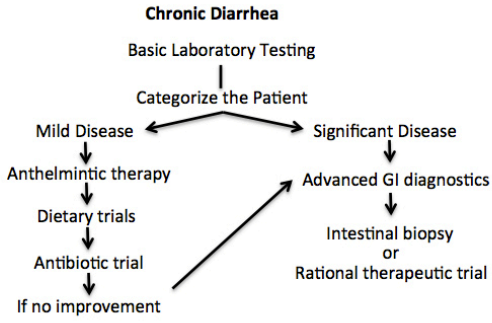
Chronic diarrhea is a common complaint, and the potential etiologies are extensive. Parasites, dietary intolerances, metabolic disease, pancreatic disease, bacterial causes, and inflammatory bowel disease are but a few etiologies of chronic diarrhea. Inflammatory bowel disease (IBD) is a common condition diagnosed in dogs and cats; however, it is not a specific disease but rather a term that describes animals having gastrointestinal (GI) signs with histologic evidence of inflammation within the intestine. IBD does not however describe the etiology, nor does the extent of inflammatory cells parallel the severity of clinical signs. Before beginning extensive diagnostics or obtaining an intestinal biopsy specimen from a patient with chronic diarrhea, there are a few diagnostic tests or trial therapies to consider. Obviously the course of action is predicated in part on a good clinical evaluation and based on the severity of the clinical disease.

Every patient with chronic GI signs should have a thorough history, physical examination, complete blood count, biochemical profile, urinalysis, and fecal examination. In many cases, this initial evaluation will determine if the etiology of the diarrhea is primary GI disease or secondary to other systemic or metabolic disease or if the diarrhea is predominately of small bowel or large bowel origin. For example, Addison's disease, liver disease, and renal disease can all be associated with secondary GI involvement. If the initial workup fails to provide a clue as to the etiology, then begin a specific GI evaluation. The fecal examination should include standard fecal flotation, wet mount preparation, and stained cytology. A stained Diff-Quick cytology may reveal such things as neutrophils, eosinophils, fungal organisms, or clostridial spores and may provide clues about the etiology. This is also the time to classify the patient based on the severity of disease: minimal signs and debilitation or those cases having severe disease obviously requiring an in-depth GI workup. For the animal with relatively mild diarrhea without weight loss or debilitation, I prefer to use trial therapy as part of the clinical evaluation. Trial therapy involves antiparasitic therapy, dietary food trials, and antibiotic therapy. If these trial therapies fail to resolve the diarrhea, further GI evaluation is indicated. Additional diagnostic testing may include imaging studies (ultrasonography is preferred as barium studies are rarely helpful), serology trypsin-like immunoreactivity, folate, cobalamin), and endoscopy or surgery for intestinal biopsies.



Always rule out parasites

Parasites must always be considered in any dog experiencing chronic GI signs.[1] *Giardia* and common nematodes are usually diagnosed using proper fecal examination techniques. Often it is difficult to find *Giardia* cysts on flotation, hence a more accurate way to diagnose *Giardia* is through fecal ELISA, which is highly sensitive and specific. It is important to know that *Giardia* also have antimicrobial sensitivity patterns like bacteria. Therefore, it is currently impossible to predict which anti-*Giardia* drug will be effective in an individual dog or cat. The treatment of choice for years has been metronidazole. Currently, metronidazole at a dose of 25 mg/kg orally twice daily for seven days is preferred; however, there are many different doses and durations of therapy reported (*Table***)**. Neurologic signs associated with toxicity occur at higher doses.

Other suggested *Giardia* therapies include febendazole or febantel for five days.[1] High-fiber diets may help lessen re-infection when given during the therapy. With treatment failure, one should make sure that *Giardia* is truly the problem and also that subsequent recontamination is not occurring. Infection with *Giardia* does not confer immunity. In resistant cases, combined febendazole and metronidazole therapy has been suggested. In difficult cases, bathing the animal before therapy and decontaminating the environment using quaternary ammonium compounds is also recommended. It is controversial whether to treat healthy dogs and cats that test positive for *Giardia* because *Giardia* is generally not considered a significant human health risk. I recommend treating the asymptomatic, positive dog and if on recheck evaluation the patient is still positive but subclinical, I will repeat therapy using a different agent. If the animal remains positive after two therapies, I simply recheck the patient again at the next yearly health evaluation. Some animals are chronic asymptomatic carriers and are very difficult to clear. It is a more significant concern when infected dogs live with immunocompromised individuals or young children.

Young cats with diarrhea

The organism *Tritrichomonas foetus* (TTF) has been identified as a cause of chronic diarrhea in young cats.[2] This organism appears to be genetically similar to that associated with bovine venereal disease. Most of the affected cats are under 1 year of age and are

reported to have a watery to sometimes mucoid diarrhea. It is most often observed in cats from humane shelters or catteries, and Abyssinians and Bengal cats appear to be over-represented or to have a more resistant disease. There are several ways to diagnose TTF. In some cases, a diagnosis can be made by performing a wet mount fecal prep and identifying the organism. A small amount of stool is thinned with warm saline solution, a coverslip applied, and the feces examined at 40X. It is important that the stool is fresh for examination. A colonic flush of saline can also be used to obtain fecal material for cytology and culture. TTF is identified by its progressive forward motion. (In contrast, *Giardia* has a falling leaf motion.) Feces can also be cultured in your practice using the bovine TTF culture technique employing an In Pouch TF™ culture method (Biomed Diagnostic Labs) (*Figure 3*). With these pouches, a very small amount of stool is placed in the broth and cultured at room temperature. The bag is then examined under a microscope 24 to 72 hours later for evidence of motile organisms. Fecal PCR for TTF is offered by many commercial labs and is considered the test of choice for confirming the infection. Ronidazole is the only antimicrobial shown to have efficacy in treating TTF infection.[3] Ronidazole is given at 30 mg/kg q24h PO for up to 14 days. Ronidazole has a very narrow therapeutic range; higher doses or a longer duration can result in neurotoxicity. Ronidazole is not approved for use in the United States and must be obtained through a reliable compounding pharmacy. It is very bitter and therefore should be given via capsule; liquid solutions are not recommended. Treatment failure can occur, and a fecal PCR should be performed if a cat fails to respond to therapy because a negative PCR result means TTF is a less likely cause of the diarrhea. When left untreated many cats eventually become normal, especially young cats under 1 year of age. In one study, 88% cats with TTF infection were reported to undergo spontaneous resolution of diarrhea within two years of a diagnosis; however, most remained infected based on PCR results when retested as long as two to five years after the initial diagnosis.[4] The role of these asymptomatic carriers in disease transmission remains unclear.

When the diet works

Over the years, I have become more and more impressed to see GI signs resolve simply by changing a patient's diet. It is my impression, which is supported by a number of clinical studies, that possibly 30% to 50% of dogs and cats with nonspecific GI disease may respond to diet alone.[5-7] A positive response to a diet trial is referred to as a food-responsive diarrhea (FRD). FRDs include both true dietary allergies and dietary intolerances. Allergies result from a reaction with a protein antigen, whereas intolerances occur in response to some substance in the diet, such as a preservative or food coloring. Dietary trials using a test diet generally require two weeks or less to appreciate a response; the GI signs seem to respond much faster than dermatologic signs, which that may take eight weeks or more to improve. There is no ideal diet that will consistently resolve diarrhea. My personal favorite is the use of a hydrolyzed diet, such as Purina HA®. Hydrolyzed diets are single-protein sources (usually soy-, rice-, or potato-based) and have undergone digestion, producing low-molecular-weight protein derivatives that are thought to be highly digestible with low antigenic potential. Their benefit might actually be because they are pure and contain little else that might contribute to a dietary intolerance. These diets have now become the ideal initial trial diet. If a positive response is observed, then the patient's GI signs can be controlled with a diet. The patient can either continue on the test diet or you can attempt to find another long-term diet that works well for both the client and patient. Some clinicians recommend if there is a diet response that the patient to be fed that diet exclusively for at least three months, at which time the diet can be changed or even the original diet reintroduced. Only a small percentage of dogs with GI signs (~8%) relapse on challenge and are thus truly food allergic.[7] Feeding novel-protein diets with a single protein antigen would be an alternative approach. If using the novel antigen diets, one should prescribe only veterinary diets because many over-the-counter novel-protein diets are not all that novel and have been shown to contain many other antigens not listed on the label.[8] Highly digestible gastrointestinal diets such as Purina EN® may improve assimilation, promote gastrointestinal health, and modify the microbiota. Diets containing highly fermentable fibers such as those containing fructooligosaccharides (also referred to as prebiotics diets) are often useful for colonic disease because fermentation products are shown to benefit mucosal function and modify enteric microbiota, promoting "good" bacteria and inhibiting certain pathogenic bacteria.[9] If a diet trial is unsuccessful, with no improvement in clinical signs after 10 to 14 days, the next step is to institute an antibiotic trial.

GI drugs and bugs

There are many dogs with chronic large or small bowel disease that have an antibiotic-responsive diarrhea (ARD). An old term for ARD is *small intestinal bacterial overgrowth (SIBO).* However, SIBO is a poorly defined syndrome in dogs, and we currently have no way to adequately and convincingly diagnose bacterial overgrowth or to know in which cases antibiotics would be beneficial short of a therapeutic trial. More recently the term *gastrointestinal dysbiosis* has been given to conditions associated with an abnormal GI bacterial ecosystem.[10] In simple terms, GI dysbiosis refers to an imbalance in GI bacteria with the loss of the "good bacteria" coupled with an increase in the so-called "bad bacteria." For chronic diarrhea cases that do respond to antibiotic therapy, it is likely the antibiotics are not eliminating a specific pathogen but rather changing the overall bacterial ecosystem, promoting a more normal bacterial makeup. Some cats and dogs with gastrointestinal dysbiosis have decreased serum cobalamin (vitamin B_{12}) concentrations.[11] The cobalamin deficiency can be due to lack of intrinsic factor production, abnormal increased intestinal bacterial utilization, or ileal disease causing inadequate cobalamin absorption. Serum folate concentrations are usually variable in cases having dysbiosis.

Metronidazole is frequently used in GI cases but long-term administration and potential side effects make it less desirable than other options. Metronidazole has been shown to cause DNA damage to feline lymphocytes in vitro. There is also evidence in laboratory animals that it has some carcinogenic potential.[12] A suggested GI dosage for metronidazole in cats and dogs is 7.5 to 10 mg/kg given orally twice daily. A commonly used alternative, and my first choice, is tylosin. Tylosin was first reported to be useful for chronic diarrhea in the early 1970s and there has been a recent resurgence in interest and use of the antibiotic. Tylosin is a macrolide, bacteriostatic antibiotic that is currently marketed over the counter for the treatment of respiratory disease in chickens. Tylosin has activity against most gram-positive and gram-negative cocci, gram-positive rods, and *Mycoplasma*; however, the gram-negative bacteria *Escherichia coli* and *Salmonella* species are intrinsically tylosin-resistant.[13] Tylosin works by transiently changing the GI enteric bacterial population, probably by promoting the growth of beneficial commensal bacteria while suppressing deleterious bacteria. Once tylosin is discontinued, the original bacterial population often returns to its pretreatment state. There is also a suggestion that tylosin may have anti-inflammatory properties.[13] Tylosin appears to have almost no systemic or toxic side effects. The initial dose recommendation for tylosin in both dogs and cats is 15 mg/kg orally, twice a day, mixed with the food (has a bitter taste) or given via gelatin capsule. (Note: it comes as a powder and a #3 gelatin capsule holds 130 mg, a #1 capsule holds 240 mg, a #0 capsule holds 345 mg, and a #00 capsules hold 430 mg.) For cases that respond, the long-term dose can be reduced to as low as 5 mg/kg/day.[13] Tylosin is effective for most *Clostridium perfringes* and is considered by many to be the treatment of choice for suspected clostridial diarrhea.[14]

Probiotics

To date, there have been very few controlled clinical studies evaluating probiotic success. However, a large double-blinded placebo control study of shelter dogs and cats developing diarrhea found significantly fewer cats that received *Enterococcus faecium* (FortiFlora®, 2.1 x 10^9 cfu/day) developed diarrhea for greater than a two-day duration.[16] Probiotics exert their effects as long as they are being given but once stopped the GI flora generally returns to the pretreatment state. It may seem counterintuitive to give antibiotics with probiotics, but clinical improvement is often seen when they are given in combination. Probiotics are considered a safe adjunctive therapy and are commonly used for both acute and chronic diarrhea in dogs and cats as well as for the prevention of stress induced diarrhea.[15-17] Recommendations for the ideal probiotic, containing an adequate type and number of viable organisms for specific GI disorders, become difficult to make. Some over-the-counter preparations have been found not to contain the label claims.[18] My recommendation is to use a product produced by a reputable veterinary company that has done research on their product.

German shepherds with chronic diarrhea

A clinical syndrome frequently encountered in German shepherd dogs is chronic GI signs and weight loss. Exocrine pancreatic insufficiency is common in the breed, requiring pancreatic enzyme supplementation, and it must first be ruled out. The diagnosis is made by documenting a subnormal trypsin-like immunoreactivity (TLI) concentration followed by improvement with pancreatic enzyme replacement. A second group of German shepherd dogs with similar clinical signs have normal TLI concentrations. Many of these dogs turn out to have an antibiotic-responsive diarrhea due to GI dysbiosis. Testing should include measurement of folate and cobalamin (serum B_{12}) concentrations. Low cobalamin and high folate levels are characteristic of both exocrine pancreatic insufficiency and GI dysbiosis. Dogs with subnormal cobalamin concentrations will require parenteral supplementation (initially, about 500 µcg subcutaneously weekly) as part of the therapy. The cause of the GI dysbiosis in German shepherds is unknown. Researchers have investigated IgA concentrations, suggesting the possibility of an inherent deficiency leading to altered GI immunity. More recently researchers have measured toll-like receptors (TLR) in the GI tract of these dogs with a documented abnormal expression of the receptors. Using candidate gene analysis, polymorphisms in TLR4 and TLR5 were recently shown to be significantly associated with IBD in German shepherds.[19] Furthermore, the same polymorphisms in TLR5 were also associated with IBD in a heterogeneous population of dogs consisting of 38 different breeds.[19] These mutations could well play an important role in the pathogenesis of IBD in dogs, as a mutated receptor will lead to misrepresentation of commensal bacteria as pathogens, therefore signaling “danger” to the host and initiating the characteristic inflammatory response seen in this disease. Management of affected German shepherds involves diet, antibiotics, and cobalamin supplementation. Prebiotics and probiotics are also often given as additional adjunctive therapy. This condition tends to require life-long management.

When is it inflammatory bowel disease?

A diagnosis of IBD requires a complete laboratory evaluation to rule out other diseases. A complete blood count, biochemical profile, urinalysis, fecal cytology, and parasite evaluation are required in all cases. An eosinophilia or hypoproteinemia may provide clues to IBD. Abdominal radiographs or ultrasonography may be helpful. However, ultrasound images showing increased wall thickness are neither specific nor sensitive for the diagnosis of IBD.[20] Specific testing may include measurement of serum folate and cobalamin concentrations. Cobalamin deficiency is a common complication of feline GI disorders, and complete improvement in GI function is not possible until cobalamin deficiency is corrected.[11]

An overall impression is that most cases of IBD can be managed; however, unless the underlying etiology can be identified and removed, it can become a long-term proposition. A retrospective study demonstrated that only 26% of canine IBD cases progressed to complete remission, with intermittent clinical signs remaining in about half of the cases, 4% being completely uncontrolled, and 13% resulting in euthanasia because of poor response to treatment.[21] Another study found 18% of the dogs were euthanized because of their disease.[6] Poor prognostic indicators are hypoalbuminemia and hypocobalaminemia.[6]

Treatment of IBD

Patients that do not respond to a diet or an antibiotic trial are usually administered glucocorticoids. It is estimated that about 30% of the dogs that fail to respond to a change of diet and antibiotics will respond to corticosteroids. Generally oral prednisolone is given to dogs and cats once daily at a starting dose of 1 to 2 mg/kg, and then the dose is tapered over an eight-week period. However, the side effects of glucocorticoids can be marked, and I try never to exceed a total of 40 mg per day in large-breed dogs. Budesonide is a novel glucocorticoid that is reported to have high first-pass hepatic metabolism and exerts a “local effect” on the intestine with minimal systemic effects. An enteric-coated formulation is used for people with IBD but a non-enteric coated formulation made by a compounding pharmacy should be used. Despite apparent efficacy of budesonide in dogs and cats, the systemic steroid effects are present and consequently, its use may have no benefit over traditional corticosteroid therapy in most cases. The recommended dose is 1 mg once daily in cats and toy breeds and up to 2 mg once daily for large-breed dogs.

If there is poor response to glucocorticoids in dogs after the first three to four weeks or if the side effects are severe, then I recommend oral cyclosporine at 5 to 10 mg/kg once daily for at least two months. Many dogs with IBD that are steroid refractive are reported to respond to cyclosporine.[22] In cats, the use of chlorambucil (2 to 6 mg/m^2, q24h, PO, or 2 mg/cat three times a week) with prednisolone is preferable, if there is inadequate response to glucocorticoid treatment alone. If chlorambucil is used, hematologic parameters should be monitored regularly. Cyclosporine blood concentrations do not need to be monitored regularly, unless side effects induced by the cyclosporine treatment are suspected or an inadequate response to treatment is observed. If measuring cyclosporine serum concentrations, it is recommended to take blood samples one to two hours after giving the medication to ensure that peak concentrations are measured. If the cyclosporine serum concentration is above 700 ng/ml at peak level, then halving the dosage for the first two weeks can reduce the side effects.[22] If the patient responds to cyclosporine, then the medication can either be tapered slowly or stopped after 10 weeks. Sulfasalazine (20 to 50 mg/kg orally three times daily for three to six weeks) and related drugs are often used in dogs when IBD is limited to the large intestine. However, side effects include keratoconjunctivitis sicca, so tear production should be monitored regularly when using these drugs. I rarely prescribe sulfasalazine for large bowel disease because, in my experience, most patients get better with diet and antibiotics. Other novel or adjunctive therapies could include omega 3 fatty acids for anti-inflammatory effects and various antioxidants. Probiotics have also been suggested to be beneficial for treating IBD due to the multiple mechanisms described above.

References upon request