CHRONIC SMALL BOWEL DIARRHEA: IBD IS NOT THE MOST COMMON CAUSE

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Inflammatory Bowel Disease

Inflammatory bowel disease (IBD), depending upon how you define it, is not the most common cause of chronic small or large bowel diarrhea in dogs and may not be as common in cats as was once believed. In this discussion, we will define IBD as "idiopathic inflammation of the intestines". This means that you cannot diagnose IBD just by histopathology. You diagnose IBD by finding intestinal inflammation and showing that it is idiopathic by eliminating diet, parasites, bacteria and fungal agents as the cause. You cannot eliminate dietary causes and bacterial causes by histopathology or blood tests; therapeutic trials are necessary. This is very important because diagnosing IBD generally results in anti-inflammatory or immunosuppressive drugs being used. However, if the patient has dietary-responsive or antibiotic-responsive disease, then these drugs are generally unnecessary. I stress this point because many patients have been erroneously diagnosed, improperly treated, and significantly harmed because IBD is a "fashionable" or "trendy" diagnosis. IBD is a real syndrome and is important for the veterinary practitioner to understand. However, it often degenerates into an excuse of convenience rather than a real diagnosis. More and more evidence is accumulating that shows that bacteria are probably a major source of the inflammation in dogs and cats with this disease. See below, under Antibiotic-responsive enteropathy.

Dogs With Chronic Small Bowel Diarrhea (Not Ple)

Once parasites, protein-losing enteropathy, and maldigestion are eliminated (i.e., you have determined that the patient has a non-PLE malabsorptive disease), the question is whether to recommend therapeutic trials or a major diagnostic work up. If the patient can tolerate a possible delay of 4-8 weeks without undue risk, then therapeutic trials are reasonable. If therapeutic trials are performed, they must be designed such that even if they fail, useful information is obtained and the clinician is further ahead than previously. Always ask yourself: "If this therapy fails, will I really know more about what the patient probably has, or will I be as confused as I was before treating it?".

An elimination diet for dietary responsive disease is often useful for non-protein-losing malabsorptive disease. There is no such thing as a commercial diet which is an appropriate elimination diet (i.e., is hypoallergenic and appropriate to look for non-allergic intolerance) for all dogs. We often see cases in which the right thing was done (i.e., an elimination diet was used); but, it was done in such a poorly planned or implemented fashion that the effort was wasted. One must carefully investigate the history and see what the patient has eaten in the past. However, even when you have determined what dietary ingredients the patient has previously been exposed to, it is sometimes difficult to find a diet that works for that particular patient. In some cases, all of our well-planned hypoallergenic diets fail but a chance try at some commercial brand works.

When starting the patient on an elimination diet, one may use a homemade diet or a commercial diet. There are many excellent commercial diets, and they usually work. Home-made elimination diets sometimes work when commercial diets do not; however, this is very uncommon. Therefore, you will have to decide which is most appropriate in the patient that you

are treating. The hydrolyzed diets are usually good but are not always the best choice for every patient. Some animals respond better to a novel protein diet than a hydrolyzed diet, and vice-verse. Which ever elimination diet is used, one must be prepared to feed it and it alone for an absolute minimum of 3-4 weeks before its efficacy can be accurately determined. Rare cases need to be feed a diet for 6-8 weeks before they respond, but this is probably well less than 5% of cases. If a diet seems to be effective (i.e., weight gain plus resolution of diarrhea) then continue it for at least another 3-4 weeks to be sure that it was the diet that made a difference as opposed to the patient having some transient improvement due to any number of causes.

Antibiotic-responsive enteropathy (ARE) seems to be a relatively common problem in dogs. It can best be described as a syndrome in which there are substantial numbers of bacteria in the upper small intestines AND the host responds to them in such a manner as to cause intestinal dysfunction. These bacteria are not usually obligate pathogens. Rather, they can be of any species, and *E. coli, Staph, Strep,* and *Corynebacterium* are particularly common aerobic/facultative anaerobic bacteria found in the upper small intestines, while *Clostridium* and *Bacterioides* are especially common anaerobic bacteria. These bacteria are probably commensals or they may represent contamination from ingested material which is not eliminated by normal host defense mechanisms. The signs they produce, if any, seemingly depend upon at least two factors: a) which bacteria are present and b) how the host responds to them. The relationship of ARE to IBD is unclear, but it seems very possible that bacteria could be responsible for either initiating and/or perpetuating the intestinal inflammation we call IBD. The term "dysbiosis" has been suggested as the bridge between ARE and IBD – that is to say that having bacteria that are somewhat prone to cause problems (i.e., usually enterics such as E. coli) as opposed to having overt pathogens.

Antibiotic-responsive enteropathy is hard to definitively diagnose with laboratory tests. Histopathology and cytology of the intestinal mucosa are extremely insensitive at detecting ARE. Serum cobalamin and folate concentrations have been used for diagnosis, and finding both a low serum cobalamin and an increased serum folate concentration has been considered to be relatively specific for ARE. Measuring serum cobalamin and folate concentrations is relatively insensitive and non-specific for detecting ARE. There are many dogs with chronic GI disease that respond to antibiotic administration but which have normal cobalamin and/or normal folate concentrations. It would seem that treatment for ARE is justified regardless of whether the serum cobalamin and folate concentrations are normal or abnormal, leading one to ask whether there is any benefit to measuring them to diagnose this disorder. Finding hypocobalaminemia or low serum folate levels is beneficial when looking for otherwise occult gastrointestinal disease. Supplementing cobalamin can clearly make cats feel better and diarrhea diminish. In fact, it is almost getting to the point where it is never wrong to give any sick cat cobalamin injections, regardless of blood values of the vitamin. Severe hypocobalaminemia has been suggested to be a poor prognostic signs. While the value of supplementing cobalamin to cats is clear (in fact, it is almost never wrong to give any sick cat supplemental cobalamin), the clinical value of administering cobalamin to dogs with low serum cobalamin concentrations is very uncertain.

Culture of the small bowel was once considered the "gold standard", but this test is fraught with problems. First, it is technically hard to do it correctly. Samples must be obtained without contaminating them with oral secretions. Then they must be processed correctly in an expedient

manner so as not to lose any anaerobic bacteria while not allowing the numbers of aerobes to increase. Many investigators have snap frozen fluid samples to culture them later, but such freezing appears to kill large numbers of bacteria, especially anaerobic bacteria. We now know that culture only detects about 30% of the bacteria in the gut; the other 70% cannot be cultured. This makes one seriously question the value of culture unless one is searching for a specific pathogen, and even then there are culture-less methods (e.g., PCR) that may be better. Finally, as has already been said, just culturing bacteria from the small bowel does not allow one to make a diagnosis of a bacterial disease of the small intestines. Large numbers of bacteria (i.e., $> 10^7$ CFU/ml) can be present in dogs without any evidence of any clinical disease. For these reasons, we very rarely culture the small intestine of dogs with chronic GI disease. However, there are rare patients that appear to have ARE and yet are resistant to treatment with commonly used antibiotics. Seemingly, these dogs may have one or two very resistant bacteria in their GI tracts, and culture may be required to determine what antibiotic will be effective. However, we have only seen this scenario twice, and we believe it to be very rare.

Because of the apparent difficulty in diagnosing ARE with lab tests, empirical antibiotic therapy is often chosen as a means to diagnosis instead of laboratory tests. The obvious drawbacks to this approach are a) clinical "response" of the patient to the administered antibiotics may be due to the antibiotics or may be due to something else, b) if the patient did not respond to the antibiotic, it may be that you used the wrong antibiotics, and c) even if the patient does have ARE, there may be yet another disease present (e.g., a tumor causing a partial intestinal obstruction) which predisposed the patient to the ARE.

Because any bacteria can be present in the upper small intestine, the species of bacteria in the upper small intestine may change from week to week, and we seldom know which bacteria we are treating, broad spectrum antibiotics designed to lessen bacterial numbers seem to be indicated. You can never sterilize the GI tract. However, because clinical signs are due to a combination of large numbers plus an altered host response, simply lessening the numbers of bacteria often seems beneficial. Oral aminoglycosides were generally considered a poor choice to treat ARE because anaerobic bacteria (which have been suggested to be more of a problem) are resistant to aminoglycosides. However, this opinion is not clearly correct as there are occasional patients that clearly improve when given amikacin orally. Tetracycline is often effective; but, giving tetracycline is inconvenient. Tetracycline must be administered alone (i.e., without any food) and yet be washed down with water to ensure that the capsule to tablet does not stick in the esophagus and cause esophagitis. Tylosin powder has also been useful and is revered by many clinicians. Some clinicians like metronidazole; however, I have not been impressed with the efficacy of metronidazole for ARE. Metronidazole seems to have real benefit in many GI disorders, probably because it is so effective in eliminating many anaerobic bacteria. For patients that are EXTREMELY ill in which we need to know RIGHT NOW whether or not it will respond to antibiotics (i.e., that patient is so ill that you cannot take a chance of being 2-3 weeks from now and not having a response to therapy), I use a combination of enrofloxacin and metronidazole. I did not say that I used this combination for long periods of time. I use this combination when I absolutely MUST know whether or not I will have a clinical response within the next 2-3 weeks or take a chance on losing the patient.

Regardless of which drug is used, such a therapeutic trial should be performed for at least 3

weeks before a decision is made as to its efficacy. Remember, you must not only suppress the numbers of bacteria, but you must also allow the intestinal mucosa time to heal. Finally, it appears that concurrently feeding a high quality elimination diet can substantially enhance the efficacy of the antibiotic therapy. Therefore, we now routinely use both in our therapeutic trials.

If the patient appears to respond to this therapeutic trial of elimination diet and antibiotics, then it appears best to continue everything unchanged for an additional 2-4 weeks to be sure that the patient responded to this therapy (as opposed to the patient having some fortuitous, transient response to who-knows-what). If the patient is still doing well at that time, then you either a) stop the antibiotics and see if they diet alone is sufficient to control signs or b) slowly wean the antibiotics to their lowest effective dose (e.g., once a day or even once every other day). It all depends upon how frequently the clinical signs occur. If the signs occur once every 2+ months, then it obviously makes sense to only treat when the patient is symptomatic. If the signs consistently recur within a few days of stopping the antibiotics, then you are probably stuck with treating almost constantly. In some cases, the patient will breakthrough and re-develop clinical signs after several weeks or months, and a different antibiotic must be used. If the decision is made to stop administering the antibiotics, then the owners should be warned that it is possible that the signs are likely to recur at some point. For ARE to occur, there is probably some defect in host defense mechanisms that allowed the commensal bacteria to cause the clinical signs, and this defect is unlikely to disappear. The question is how severe is the defect (i.e., is the dog likely to have problems continually or only once in a while)?. You should warn the clients that they are likely to have to deal with this problem repeatedly and you need to explain the difference between “cure” and “control”.

It may be a good idea to routinely treat all dogs with chronic small intestinal disease for ARE, even if you have histologic evidence of IBD or other disease. I will treat for ARE almost every time I diagnose a dog with a malabsorptive disease since there is no test for ARE that is reliable in ruling this disorder out, including cobalamin and folate determinations.

Other options that are becoming increasing more interesting are prebiotic and probiotic therapy. In particular, these therapies are being looked at as possible alternatives to protracted antibiotic therapy.

If the patient is so sick that you cannot chance a 3 week therapeutic trial that may fail; or if the owners insist upon obtaining a diagnosis, then tests are the next step. If, based upon history, physical examination, laboratory data, fecal examination and/or abdominal ultrasonography you are sure that the small intestine is involved, then the best next step is usually intestinal biopsy.

Intestinal biopsy may be accomplished two ways: endoscopy and surgery. CBC, serum chemistry profile, and urinalysis are useful and may point out systemic manifestations of the disease which will aid in correctly diagnosing and prognosing the problem (e.g., hypoalbuminemia due to histoplasmosis), but are also useful as a preanesthetic work up before endoscopy. Ultrasound is useful to look for enlarged mesenteric lymph nodes, focal intestinal/gastric lesions, and loss of mucosal layering. Focal enlargements may suggest a tumor (e.g., alimentary lymphoma or carcinoma), as may lymphadenopathy. However, animals with severe IBD may also have mesenteric lymphadenopathy (as may dogs with histoplasmosis or

pythiosis). If the lymph nodes are enlarged, it is reasonable to aspirate them percutaneously with ultrasound guidance. Mesenteric lymph nodes are typically reactive, making it more difficult to interpret cytology from them. However, finding obvious sheets of lymphoblasts or fungal organisms (e.g., histoplasmosis) allows diagnosis. Sonographic examination of the intestines is important (i.e., you may make a diagnosis), but it does not detect intestinal mucosal disease in many patients that are afflicted with such disease. If loss of mucosal layering is seen, then severe infiltration is likely (either inflammatory or neoplastic), but normal-appearing mucosa may have marked disease present. Most of the time, ultrasound's major use is to help you decide whether to perform intestinal biopsy using endoscopy or laparotomy. If there is an obvious lesion where an endoscope cannot reach, it is best to perform laparotomy instead of endoscopy.