PROTEIN-LOSING ENTEROPATHIES: LOW ALBUMIN DOES NOT HAVE TO BE A DEATH SENTENCE

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Basic Approach To Hypoalbuminemia

When concerned with protein loss of any cause, one should measure serum albumin concentrations as opposed to the serum total protein concentration. Do not use human clinical pathology laboratories because their technology sometimes does not detect canine albumin; this means that they routinely report serum albumin concentrations of < 1.5 gm/dl in clinically normal dogs. If the patient has hypoalbuminemia (especially less than 2.0 gm/dl), the next step is to examine the skin for obvious lesions which can cause protein loss. Cutaneous lesions sufficient cause such hypoalbuminemia are obvious; you should be able to just look at the patient and know if this is the problem or not. Next, hepatic function testing (e.g., resting and post-prandial serum bile acid concentrations) and a urinalysis are requested. Never consider "panhypoproteinemia" as a good criteria to determine if protein-losing enteropathy is or is not present. It is insensitive and non-specific. If there is any doubt regarding the amount of protein being lost in the urine, then a urine protein:creatinine ratio will quantify the magnitude of urinary protein loss. Severe hypoalbuminemia (i.e., < 2 gm/dl) in an animal with diarrhea suggests a protein-losing enteropathy (PLE); however, diarrhea (even when severe) in no way is sufficient to eliminate hepatic disease as the cause of the hypoalbuminemia. Hepatic disease can at times cause such profuse diarrhea that it perfectly mimics intestinal disease. To further complicate matters, a very substantial number of dogs and cats with protein-losing enteropathy do not have vomiting or diarrhea; remember the diarrhea is nothing more than excess water in the feces. As long as the colon can absorb the excess water, the feces appear normal. That is why some dogs with PLE are asymptomatic while others (maybe 10-15%) have ascites as the only sign of a protein-losing enteropathy. This seems to be especially true of dogs with primary intestinal lymphangiectasia.

In general, once severe, exudative cutaneous disease, protein-losing nephropathy, and hepatic insufficiency are eliminated, then PLE is becomes a diagnosis of exclusion in patients with a serum albumin < 2.0 gm/dl. Fecal examinations for parasites are obviously appropriate in all such patients. Although parasites are an uncommon cause of PLE in adult animals, pets in select environments (e.g., confined areas where patients can reinfect themselves) may incur substantial parasitic loads. In the southern US, we have seen adult large breed dogs literally exsanguinated by hookworms.

Hypocholesterolemia

The serum cholesterol can be very helpful in determining the cause of hypoalbuminemia. Most dogs with either protein-losing enteropathy or hepatic insufficiency sufficient to cause hypoalbuminemia also have hypocholesterolemia. In contrast, most dogs with protein-losing nephropathies sufficient to cause marked hypoalbuminemia typically also have hypercholesterolemia. In patients with low urine specific gravities and large amounts of proteinuria, it is not hard to figure out what is happening. However, a patient with a 1.034 urine specific gravity and a 1+ protein and a urine protein:creatinine ratio of 1.34 may be confusing.

Fecal Alpha-1 Protease Inhibitor Testing
Fecal concentrations of alpha-1 protease inhibitor can be used as a means of confirming PLE if there is confusion because of concurrent hepatic or renal disease. The major use for this test in clinical medicine seems to be the hypoalbuminemic patient in which you strongly suspect PLE (e.g., based upon it having severe diarrhea or having hypocholesterolemia), but which also has PLN and/or hepatic disease. However, there are several nuances about this test, especially collecting samples, that make it potentially difficult to interpret. We seldom need this test in clinical practice. Finally, contrary to what the textbooks say, PLE may be associated with a low, normal or increased serum globulin concentration – personally, finding "panhypoproteinemia" is not very helpful in my patients.

Diagnostic Approach To The Dog With Protein-Losing Enteropathy
Hypoalbuminemia has been reported to be a poor prognostic sign in patients with chronic GI disease; however, there may be one or more subset(s) of patients that respond well to appropriate therapy if diagnosed in a timely fashion. Therefore, diagnosing PLE is not necessarily cause for despair. Aggressive diagnostics are typically an appropriate recommendation in PLE patients. Although therapeutic trials can be chosen in place of classic diagnostic tests in many of the more common alimentary tract diseases (e.g., dietary allergy, dietary intolerance, antibiotic-responsive enteropathy, parasites), such an approach is generally ill-advised if the serum albumin concentration is less than 2.0 g/dl. This is true because hypoalbuminemic patients tend to be more ill, and perform an antibiotic and/or dietary therapeutic trial for 3-6 weeks in order to ascertain if it is being effective may allow the patient to become markedly worse if the serum albumin concentration is falling rapidly. Furthermore, failure to respond to a dietary trial for lymphangiectasia does not eliminate it. And, if you live where histoplasmosis or heterobilharzia or pythiosis exists, doing therapeutic trials with anti-inflammatories or immunosuppressive drugs may be very ill advised.

Any GI disease can cause protein-losing enteropathy if it is severe enough. Many acute GI diseases cause protein-losing enteropathy (e.g., parvoviral enteritis); however, these diseases typically are comparatively easier to treat than the chronic GI disease causing protein-losing enteropathy. Therefore, the focus in this lecture is PLE in animals with chronic GI disease. The major causes of protein-losing enteropathy in adult dogs tend to be intestinal lymphangiectasia, alimentary tract lymphoma (LSA), intestinal fungal infections (i.e., histoplasmosis and pythiosis), and severe inflammatory bowel disease (IBD. Other causes include alimentary tract ulceration/erosion, severe disease of intestinal crypts, antibiotic-responsive enteropathy, and parasites. The major causes of protein-losing enteropathy in juvenile dogs tend to be parasites and chronic intussusception. Cats with protein-losing enteropathy usually have IBD or alimentary tract lymphoma.

Diagnosis Of Cause of Protein-Losing Enteropathy
Once protein-losing enteropathy has been diagnosed, intestinal biopsy is usually the ultimate means of establishing a diagnosis. Biopsy can be done via laparotomy, laparoscopy, or endoscopy. Feeding a small, fatty meal (use canned food, not dry, and add in cream or corn oil) the night before the procedure might (?) make it easier to diagnose lymphangiectasia. Flexible endoscopy, when done by someone who is trained in how to take diagnostic tissue samples and

submit them, is usually more than adequate to obtain diagnostic samples. However, if endoscopy will be used to biopsy the small intestines, it is preferable to first ultrasound the abdomen to make sure that there are no focal infiltrates that are out of reach of the endoscope, or which might be more easily diagnosed by ultrasound-guided fine needle aspiration. Furthermore, there are ultrasonographic changes (streaks in the submucosa) that can be nearly diagnostic for lymphangiectasia (i.e., about 95% confidence). Feeding fat the night before an ultrasound exam is clearly indicated as it has been shown to increase the sensitivity of ultrasound for making this diagnosis. Radiographs and barium series are seldom as sensitive as ultrasound. If flexible endoscopy will be done, one should biopsy the duodenum and ileum and, if at all possible, the proximal jejunum. There have been numerous cases in which lymphangiectasia, IBD or LSA were obvious in the ileum but not in the duodenum. It is not necessary to enter the ileum with the endoscope to obtain a good tissue sample of the ileal mucosa.

Laparotomy and laparoscopy are good means of obtaining diagnostic samples, but it is surprisingly easy to procure non-diagnostic samples with these techniques (i.e., "full-thickness sample" is not synonymous with "diagnostic sample"). Endoscopy does have the advantage of allowing one to visualize mucosal lesions that are "invisible" when looking at the serosa. In some cases, the diagnosis can only be obtained by biopsying these focal lesions. If full-thickness biopsies are obtained in severely hypoalbuminemic animals, then serosal patch grafting will minimize the risk of suture line leakage. A nonabsorbable or a poorly absorbable suture (PDS) should also be used.

Intestinal lymphangiectasia seems particularly common in Yorkshire terriers and Soft-Coated Wheaten terriers, but may occur in any breed. Sometimes these dogs have distinct ultrasonographic findings: "streaks" in the mucosa that represent dilated lymphatics. While histopathology is obviously the desired means of diagnosis, one can sometimes make a definitive diagnosis based upon grossly visible endoscopic findings (i.e., numerous, erratic, grossly engorged lacteals seen as large white blebs on the mucosa). These lesions are "fragile" and apparently may be destroyed by biopsying them (both endoscopically and surgically) if the endoscopist or surgeon is not careful. It is important to note that lymphangiectasia can be a relatively localized disease in the intestines, being present in only the ileum or only the jejunum or only the duodenum; therefore, it is important to biopsy as much of the intestinal tract as possible. Furthermore, if one biopsies the intestines and cannot find a cause of PLE, sometimes lymphangiectasia can be tentatively diagnosed by eliminating IBD, lymphoma, parasites, intussusception, fungal infections, etc.

Diagnosis by means of endoscopic biopsy is certainly possible if the endoscopist is trained in taking high quality tissue samples. However, recent work has demonstrated that poor quality mucosal biopsies (e.g., primarily villus tips or substantial "squash" artifact) makes is much more difficult or even impossible to find the lesions. If one is taking high quality tissue samples (i.e., total length of the villi plus subvillus mucosa down to the border of the mucosa and muscularis mucosa), it typically takes about 6-7 tissue samples to have 90-99% confidence in finding lymphangiectasia. However, it can take 5-7 times as many tissue samples to have the same assurance if you are obtaining poor quality tissue samples that primarily consist of villus tips.

When doing endoscopy, it is important that ileal biopsies be taken in addition to the typical duodenal biopsies. We are finding that ileal biopsies often reveal lesions not found on duodenal biopsies. This is true for lymphangiectasia as well as lymphoma and other lesions. With basic training, an endoscopist should be able to obtain ileal biopsies endoscopically at least 85%+ of the time. Typically, ileal biopsies are often of higher quality than duodenal biopsies.

Therapy For Lymphangiectasia – Ultralow Fat Diet

Therapy for intestinal lymphangiectasia revolves around an ultra-low fat diet. Please note that "low fat" is NOT acceptable; it needs to be ULTRALOW FAT (i.e., less than 2 grams fat/100 kcal). Feeding homemade diets that are highly digestible and ultra-low in fat (e.g., white turkey meat plus potato or rice) is fine, but now there are commercial ultralow fat diets that are often very successful in these patients. Dogs that are in the earlier stages of lymphangiectasia often show a marked increase in serum albumin concentration (i.e., an increase of 0.5 gm/dl or more) within 7-14 days of starting such a diet. Dogs that are diagnosed later in the course of the disease may not have such a dramatic response, which is one reason why failure to respond to an ultralow fat diet is not grounds for eliminating lymphangiectasia as a diagnosis.

Supplementation with medium chain triglyceride oil (MCT) used to be recommended. Don't use it. It is unnecessary and expensive. Pancreatic enzymes were often added to the diet to ensure digestion of the medium chain triglyceride oil. It too is no longer recommended.

Therapy For Lymphangiectasia – Dealing With Lipogranulomas

Lipogranulomas in the intestinal wall and mesentery appear to be very important to the ultimate prognosis of the patient. We hypothesize that most patients that fail to respond to appropriate dietary therapy do so because of formation of very large or excessive numbers of lipogranulomas that so completely obstruct the intestinal lymphatics that even an ultra-low fat diet cannot prevent lacteal rupture. Therefore, once a diagnosis of lymphangiectasia is made (either by histology, grossly at endoscopy, or tentatively by response to an ultra-low fat diet), we routinely use anti-inflammatory therapy designed to prevent granuloma formation and/or enlargement. Prednisolone (NOT prednisone) is commonly used, but I do not like prednisolone simply because of all the side effects it has in these patients.

I like cyclosporine, but be aware that it is critical that you measure blood levels of the drug if the patient is not responding within 10 days. Not only is there a major difference between patients in how much cyclosporine they absorb, but the bioavailability of the same product may change as the intestine heals. Remember that hyporexia is the main sign of overdose.

Because cyclosporine is so expensive, many clinicians opt for prednisolone but add in chlorambucil or azathioprine. If you use azathioprine (2.2 mg/kg PO), be very careful not to overdose the patient lest hepatic failure, acute pancreatitis, and/or bone marrow suppression occurs. Be careful to give the correct dose, meaning that you should be willing to have the drug recompounded, if necessary. Most people give azathioprine daily for 7 days and then every other day. I often give azathioprine every other day from the start to lessen the chance for toxicity, but it takes 4-5 weeks for it to work if you start giving it every other day.

Chlorambucil is safer and probably more effective than azathioprine, and I recommend it instead. Given at 4-6 mg/M2 PO daily or every other day, it can take 3-5 weeks for it to take effect. Even though it is an alkylating agent, it seems to be much safer than azathioprine.

If the serum albumin is very low (e.g., < 1.3 gm/dl), one is often tempted to administer a plasma transfusion while waiting to see what effect the diet will have. However, it is exceedingly difficult to increase the serum albumin concentration by transfusing patients that are losing protein with plasma because so much of the albumin is quickly lost out the gut. You would probably have to give at least two and possibly three units of plasma to a 15 lb dog in order to raise the serum albumin from 1.0 gm/dl to 1.6 gm/dl, and sometimes you would have to give more. However, any benefit will probably be so short lived that it is not cost-effective. If it is critical to raise the plasma oncotic pressure, then administering hetastarch may be preferred because it costs less than plasma, and it stays in the intravascular compartment longer than albumin.

These patients may be a increased risk for hypomagnesemia which may potentiate the problem of hypocalcemia. At this time, we do not know how important it is to supplement magnesium to patients, but severe hypomagnesemia can be resolved by a constant rate infusion of magnesium sulfate.

Intestinal Crypt Lesions

Lesions of the intestinal crypts have been recognized as being associated with PLE in dogs. We have identified two different lesions of the small intestinal crypts that can cause PLE. One type is characterized by crypts (usually duodenal) that are filled and somewhat distended with proteinaceous fluid and necrotic inflammatory cells. While such dilated crypts can be found in many animals, including clinically normal dogs, finding large numbers of them in multiple tissue samples seems to be consistently associated with PLE. We do not know if this is a cause-and-effect relationship, or if the dilated crypts are simply a marker for some other process but are not causing the protein loss themselves. Several of these patients have responded to therapy with elemental diets, total parenteral nutrition, prednisolone, azathioprine, and/or metronidazole. We have seen this lesion associated with IBD as well as lymphangiectasia (especially in Yorkshire terriers).

A second type of crypt lesion that appears to be less common than the first, is characterized by focal accumulations of mucus causing massive distention of the intestinal crypts. This has been reported once before, and we have seen a few such cases. The most important aspect of diagnosis seems to be the fact that the lesion may be very focal, almost appearing as ulcers when looking at the intestinal mucosa through an endoscope. Therapy similar to that used on animals with the other form of crypt lesion may be helpful. We have used cyclosporine, but do not know if it is helpful, or if the clinical response is due to the other drugs that the patient is receiving.

These lesions have not been commonly reported. Recent work has shown that these lesions are extremely easy to miss if poor quality endoscopic biopsies are performed. While 7-12 high quality tissue samples (i.e., full length of villi plus subvillus mucosa down to the level of the

muscularis mucosa) will find these lesions 90-99% of the time, about 7 times as many tissue samples will be needed if poor quality samples primarily consisting of villus tips are submitted.

Chronic Intussusception And Other Causes Of Protein-Losing Enteropathy

Chronic intussusception is a relatively important, and often missed cause of PLE in juvenile animals. The classic history is one of acute enteritis (e.g., parvoviral enteritis) which does not resolve as expected. The patient feels somewhat better, but continues to have diarrhea, and the serum albumin concentration gradually diminishes. It can be very hard to palpate an ileo-colic intussusception; abdominal ultrasound is clearly the preferred way to diagnose intussusception. Therapy is surgical.

Although uncommon, nematodes may cause PLE in adult animals if there are large numbers of them. Whipworms and hookworms in particular may occasionally be responsible for PLE in older dogs. However, giardiasis has been reported to cause PLE in people.

We believe that we are starting to recognize antibiotic responsive enteropathy (now commonly called dysbiosis) as a cause of protein-losing enteropathy in dogs. We now have several patients that appeared to have marked increases in their serum albumin concentration associated with antibiotic therapy. However, because dietary change is often performed simultaneously with antibiotic therapy in these patients, cause-and-effect is not clearly established. However, since we believe that bacteria (i.e., ARE or dysbiosis) is probably the ultimate cause of IBD, it makes sense that treating ARE may resolve some cases of protein-losing enteropathy.