Medical and Nutritional Management of Protein-Losing Enteropathy

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Terminology, causes and clinical features

Protein-losing enteropathy (PLE) describes a heterogeneous group of diseases in which plasma proteins are lost into the gastrointestinal (GI) lumen. Any GI disease, if severe enough, can lead to intestinal protein loss. A common example is canine parvoviral diarrhea. Clinically, however, the term PLE is applied to chronic, severe, diffuse small intestinal diseases of the dog that are accompanied by profound protein loss in the absence of anemia. PLE is very rare in cats. Features of PLE are hypoalbuminemia and hypoglobulinemia, (i.e.panhypoproteinemia), accompanied by variable degrees of ascites, pleural effusion, and/or less commonly) peripheral edema. Severe, diffuse, small intestinal inflammatory bowel disease (IBD is an important cause of PLE, occurring alone or in combination with lymphangiectasia. Another cause is GI lymphoma.

Lymphangiectasia (IL) is a condition characterized by dilation of the lymphatic vessels and leakage of lymph from the villi or from deeper portions of the intestinal wall into the lumen. The leakage of protein, lipid, and lymphocyte-rich lymph is responsible for the hypoproteinemia, hypocholesterolemia and lymphopenia that are characteristic of IL and induces secondary intestinal inflammation and edema. The intestinal inflammation contributes to clinical signs such as diarrhea, vomiting, and weight loss. It may be primary (idiopathic or congenital) or, much more commonly, secondary to another condition that increases hydrostatic pressure in the lymphatic vessels of the GI tract. Yorkshire terrier is the breed most often affected, but it is also reported in Rottweilers, Shar peis, Maltese and Norwegian Lundehunds, and is diagnosed sporadically in other breeds. Lymphangiectasia may be associated with unusual crypt lesions in which the intestinal crypts are severely dilated and filled with mucus, sloughed epithelial cells, and, sometimes, inflammatory cells. Crypt lesions are especially prevalent in Yorkshire terriers and Rottweilers.

The PLE syndrome associated with lymphangiectasia has been well described in Yorkshire terrier dogs. Clinical findings include diarrhea, vomiting, muscle tremors and even seizure activity due to hypocalcemia, hypomagnesemia, severe panhypoproteinemia with subsequent transudative uni- or bi- cavitary effusion, hypocholesterolemia, lymphopenia, and low serum vitamin D concentration. Surprisingly, 1/3 of cases lack any history of GI signs and present for abdominal distension or dyspnea due to pleural effusion. Hypocalcemia in dogs can cause facial pruritus, which can also be a sign described by owners. A unique sonographic feature described in some dogs with lacteal dilatation is mucosal speckling but is not pathognomonic.

Enteric protein loss can be directly measured by a commercially available fecal alpha$_1$ proteinase inhibitor assay (http://vetmed.tamu.edu/gilab/service/assays/alpha1). A working diagnosis of PLE in dogs with hypoalbuminemia or panhypoproteinemia is usually made by excluding renal protein loss via urinalysis and/or urine protein creatinine ratio, and by excluding decreased hepatic albumin synthesis via normal pre and post-prandial bile acids. Ultimately, intestinal biopsies are needed to identify GI histopathologic lesions that define IL and attempt to identify an underlying etiology for it. Dogs with hypoalbuminemia due to PLE of any cause are often poor surgical candidates; full thickness intestinal biopsies pose more risk than usual. Several studies have affirmed the adequacy of biopsies obtained endoscopically. Although the gross endoscopic appearance can be quite characteristic, this cannot be relied upon to make the diagnosis.

Dietary therapy

Dogs with PLE are in severe negative energy and protein balance. Nutritional therapy is a very important aspect of therapy both to provide adequate protein and energy, and for dogs with IL, to restrict fat intake. Although other dietary approaches may be used for IBD patients, in PLE a low fat diet is recommended. A recent manuscript confirmed the efficacy of this approach (Okanishi). The authors studied 24 dogs of a variety of breeds with biopsy-confirmed IL that were either refractory to >1 month of prednisone therapy or that were initially steroid-responsive but relapsed when the steroid dosage was reduced. One and 2 months after starting dietary fat restriction, 79% of dogs showed improvement in clinical activity score [an index of severity of GI signs], albumin, and total protein. It is believed that low dietary fat leads to improvement in clinical signs by reducing lymphatic pressure and removing one of the stimuli for intestinal inflammation (lymphatic leakage). Royal Canin Gastrointestinal Low Fat is a diet with one of the lowest fat contents currently available (7% fat of a DM basis), making it a good first choice for dogs with lymphangiectasia. The website < vet.**osu**.edu/vmc/nutrition-support-service> is a very useful one for comparing diets by specific nutrient class, such as low fat. Look for < diet search database>.

Nutritional therapy should provide a high energy-density diet (>3.5 kcal/g) that is highly palatable and ideally has a low fat content. Current recommendations are for a diet that provides <15% fat, >25%protein, < 5% crude fiber (dry matter [DM} basis), and >87 and >90% digestibility in the protein and carbohydrate/fat sources, respectively. A high fiber diet is not generally recommended, although the author has managed several Rottweilers with IL long-term with Hill's w/d dry (19.2% protein and 8.7% fat on a dry matter basis), which was one of the low fat diets used in the Okanishi study. A novel protein diet is sometimes used when IBD is associated with PLE. The fat content of the currently available dry novel protein diets ranges from 9-24% on a DM basis. Hydrolyzed

diets are a good source of highly digestible protein. Supplementation of the selected diet with cooked egg whites is an option to provide additional highly digestible protein (1-2 cooked egg whites /10 kg body weight daily or as needed to keep serum albumin above 2 g/dL). Small frequent meals are recommended to increase intake and improve nutrient absorption. Dividing feedings into at least two, and ideally three, meals per day will help maximize dietary assimilation.

DIET	FAT (g/100 kcal)	PROTEIN (g/100 kcal)	CALORIC DENSITY (kcal/cup)
Royal Canin LF (dry)	1.7	6.4	229
Royal Canin LF (canned)	2.0	9.2	-
Hill's i/d Low Fat (dry)	2.0	7.1	331
Hill's i/d Low Fat (canned)	2.3	6.9	-
Hill's i/d (dry)	3.3	6.3	379
Hill's w/d (dry)	2.6	5.9	243
Royal Canin Hypoallergenic Hydrolyzed Protein (canned)	3.9	6.3	-
Royal Canin Hydrolyzed Protein Moderate Calorie	3.2	6.1	302
Purina EN (dry)	3.2	6.6	399
Purina Fit & Trim (dry)	1.7	8.7	320

Parenteral supplementation with fat-soluble vitamins may be necessary due to chronic fat malabsorption. This may be manifest clinically as symptomatic hypocalcemia (vitamin D malabsorption along with other factors, especially hypomagnesaemia) and coagulopathy (vitamin K malabsorption). In any dog with chronic small intestinal enteropathy there may be subnormal serum concentrations of cobalamin. Determination of current status and weekly supplementation (250-1000 µg/dog depending on body weight) as indicated is important, as cobalamin deficiency is associated with decreased villous length and health.

Medical therapy

There is no practical way to provide long-term oncotic support to PLE dogs with profound hypoproteinemia. Before anesthesia, such as to perform intestinal biopsies, intravenous oncotic support can be provided by hydroxyethyl starches (dextrans) at a one-time dose of 20-30 mL/kg/day. Plasma can also be used to temporarily raise oncotic pressure but poses the problem of hypervolemia in some cases.

Abdominal and thoracic cavity transudates need not be drained unless they induce respiratory difficulty. The potassium-sparing aldosterone-antagonist, spironolactone (0.5–1 mg/kg PO once or twice daily), can help limit fluid accumulation, especially during the first month of therapy. Furosemide is not recommended as a first-line drug as it may induce dehydration and further activate the renin-angiotensin axis. In cases with refractory ascites or pleural effusion, it may be combined at very low doses (1 mg/kg once or twice daily) with spironolactone. Diuretics are rarely needed after the first 3-4 weeks of therapy, during which the albumin can be expected to rise significantly.

Because of the presence or risk of effusive disease, severe PLE cases (serum albumin is less than 2.0 g/dl) should be treated using a combination of dietary and immunosuppressive therapy. A low fat diet is prescribed and the author starts therapy with a combination of prednisone (or budesonide) and cyclosporine (5 mg/kg once daily initially; can be used at 5 mg/kg twice daily if needed). Dosing for budesonide is: dogs 3-7 kg: 1 mg/day PO, 7-15 kg: 2 mg/day PO, 15-30 kg: 3 mg/day PO, >30 kg: up to 5 mg/day PO. Budesonide is a corticosteroid that is largely extracted on its first pass through the liver, and 90% is converted to metabolites with low corticosteroid activity. It thus provides local effect in the GI tract while minimizing side effects seen with systemic absorption of steroids. Treatment is once a day. If prednisone is used, an initial dose of 2 mg/kg per day (usually divided twice daily) is used until in remission for 2-4 weeks, then the dose is tapered to 0.5 mg/kg every 48 hours or lower. Doses for large dogs should not exceed 30 mg/m^2 q12 hr (or 30 every 12 hours regardless of weight). Some dogs require long-term therapy (months to years) on an every other day or every third day basis to maintain remission. If a dog fails to respond to prednisone, consider failure to absorb oral prednisone and switch to injectable corticosteroids. Once serum albumin levels increase, the dose of each drug can be modified and alternate day therapy achieved for both drugs in most cases.

Azathioprine is another choice for adjunctive immunosuppression to reduce the dose of steroids needed or if cyclosporine results in diarrhea, mucosal hyperplasia, or other side effects that limit its use. The dose of azathioprine is 2.2 mg/kg daily for about 7 days, then every other day. Mycophenylate is usually avoided due to the high incidence of GI side effects with this drug. If azathioprine is used at the outset, the prednisone dose is decreased by 50% after three to four weeks or based on clinical improvement (i.e., remission of signs and increase in albumin level) and degree of tolerance of this dose of prednisone. Subsequent decreases in the prednisone dose 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 corticosteroid side effects, the prednisone is initially decreased by 50% to 75% but is not stopped completely unless absolutely necessary because remission failure might result. Side effects of azathioprine are uncommon in dogs but may

include anorexia, jaundice (hepatic damage), poor hair growth, and bone marrow suppression. In addition, azathioprine is sometims incriminated in the induction of pancreatitis. A complete blood count should be performed 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 periodic (once every 4 to 6 weeks initially) evaluation of hepatic enzymes (increases may be due to corticosteroids and occasionally azathioprine) as well as albumin concentration.

Dogs diagnosed with PLE are prone to sudden death from thromboembolic disease. This may occur even once albumin levels are stabilized using the above therapies. Either low dose aspirin (0.5 mg/kg/day PO) or clopidogrel (1-3 mg/kg/day PO) are recommended as platelet aggregation inhibitors but efficacy data for prevention of thromboembolic events is lacking for both drugs.

Prognosis

The prognosis for dogs with PLE is variable. The clinical outcomes have been reported in a series of Yorkshire terriers with IL. Approximately 50% of dogs had complete or acceptable control of clinical signs and a median survival of 44 months. 50% failed to respond and survived a median of 12 months with 4/11 of these dogs experiencing peracute death, presumably due to thromboembolism.

Selected readings

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