

Focus on Refractory Protein-Losing Enteropathy

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Introduction

Protein-losing enteropathy (PLE) is a syndrome of excessive protein loss across the enteric mucosa. PLE has been identified as a consequence of a wide variety of disorders in the canine including infectious (parasitic enteritis, fungal enteritis), neoplastic (alimentary lymphoma, gastrointestinal adenocarcinoma), mechanical (foreign body obstruction, intussusception), miscellaneous (intestinal erosions/ulcerations) and inflammatory processes. In clinical practice the most commonly diagnosed disorders resulting in PLE are chronic inflammatory enteropathies (CIE) and intestinal lymphangiectasia (IL).

Traditional management of CIE with PLE involves adjustment of diet (hydrolyzed, novel protein, fat-restricted, highly digestible), administration of glucocorticoids at anti-inflammatory to immunosuppressive doses, variable administration of immunosuppressive agents, correction of nutritional deficiencies, and supportive care therapies. Traditional management of IL with PLE may be similar, but dietary fat-restriction is emphasized, and more conservative doses of glucocorticoids are typically recommended.

Compared to dogs with CIE and normal serum albumin concentrations, dogs with CIE and PLE are reported to have a poorer prognosis.¹⁻³ Short-term responses to prednisolone or budesonide in dogs with CIE without PLE have ranged from 69-88% with follow up times ranging from 21-42 days.^{4,5} In Yorkshire terriers with PLE, response to prednisolone was 53%, with follow up times up to 80 months.⁵ Median survival times reported from 8 different studies of dogs with PLE ranged from 1 to 28 months,³ which suggests that response to treatment is highly variable. It is not uncommon for dogs with refractory PLE to be treated with a varied combination of commercial diets, glucocorticoids, and immunosuppressant medications, with little to no clinical or clinicopathologic improvement. In these cases we must consider a variety of factors that may be contributing to the lack of response including owner compliance, the accuracy/validity of the diagnosis, and the possible contribution(s) of concurrent disorders or complicating factors. Following these considerations, alternatives to traditional management strategies can be pursued.

Initial considerations for refractory cases

Prior to attributing clinical signs and clinicopathologic abnormalities to refractory disease, we must consider inadequate owner compliance, the possibility of misdiagnosis or incomplete diagnosis, concurrent disease, or complicating factors.

Owners of dogs with PLE may have trouble adhering to all your recommendations. If this is the case, prioritize which medications are most necessary, and consider ways to create variations in

their diet without compromising your recommendations (e.g. baking canned food to create dog treats). Consultation with a board-certified veterinary nutritionist can be very useful in these cases. If owner compliance is acceptable, failure to respond to therapy should next prompt the clinician to re-evaluate the diagnosis and look for concurrent or complicating disorders.

Next, it is important to consider whether you have the correct and complete diagnosis. In addition to enteric protein loss, hypoalbuminemia can be the result of liver insufficiency, renal disease, hemorrhage, exudative skin disease, exocrine pancreatic insufficiency, dilution or redistribution of albumin in the body, and systemic inflammatory disorders. Care should be taken to exclude these causes of hypoalbuminemia before a clinical diagnosis of PLE is made.

Following a clinical diagnosis of PLE, identification of the underlying cause or causes will optimize treatment. For this reason, intestinal biopsy is still recommended in the diagnostic work-up of PLE. When evaluating a refractory case of PLE that has not undergone intestinal biopsy for full evaluation, it would be important to consider whether the dog could have an infectious or neoplastic disorder that may not respond well to traditional therapies for PLE. Additionally, recent studies have shown that many hypoalbuminemic dogs with chronic inflammatory enteropathies may also have concurrent lymphangiectasia⁶⁻⁸, which may necessitate a change in therapeutic management. Thus, if a dog is not responding to therapy and an intestinal biopsy has not yet been performed, this should be considered.

In cases of refractory PLE, evaluation or re-evaluation for concurrent disease should also be performed. Concurrent disease may include parasitic infection, pancreatic disease, bacteremia secondary to a compromised intestinal barrier and enteric bacterial infections, among others. Hypoadrenocorticism can cause chronic gastrointestinal signs and hypoalbuminemia but would be expected to respond to glucocorticoid therapy. Concurrent liver or renal disease contributing to hypoalbuminemia should also be considered, if not already excluded by appropriate testing. Diagnostic tests that should be performed or re-evaluated in refractory PLE cases include fecal parasitology screens and serum trypsin-like immunoreactivity concentrations for evaluation of exocrine pancreatic insufficiency. In addition, depending on the level of suspicion for concurrent hematologic or enteric infection, blood cultures, fluorescent *in situ* hybridization of the intestine, and fecal culture and sensitivity for enteric pathogens can be considered. Fecal culture and sensitivity need to be interpreted with caution as isolation of a particular bacterium does not always provide cause for a patient's clinical signs.

Complications of PLE are common and can result in persistence of clinical signs and clinicopathologic abnormalities if not identified and treated appropriately. Examples of complications of PLE include hypocobalaminemia, ionized hypocalcemia, hypomagnesemia, low vitamin D status, thoracic and abdominal effusions, peripheral edema and thromboembolism. To the degree possible, complicating factors need to be identified and treated appropriately as they can impede responses to therapy. For example, if cobalamin deficiency goes unrecognized and/or untreated, signs of poor intestinal tract function including weight loss and diarrhea can persist. Additionally, severe ionized hypocalcemia can result in clinical signs including weakness, lethargy, vomiting, muscle twitching or tremors, and facial rubbing. Patients with PLE displaying these signs should be screened for ionized hypocalcemia and treated if significant hypocalcemia is recognized. It is important to remember that hypomagnesemia can impair calcium absorption so treatment with oral magnesium supplementation may be necessary in patients with refractory hypocalcemia. Though decreased vitamin D concentrations are a known complication of PLE, an

optimal treatment protocol for low vitamin D status in dogs with PLE has not yet been determined. Commonly used therapies include calcitriol and vitamin D3. Draining of abdominal or thoracic effusions is only recommended when the effusion is resulting in discomfort or respiratory difficulty. In general, the use of diuretics is discouraged as they are often ineffective and can promote dehydration. Colloids, such as hydroxyethyl starches, are likely to be the most useful for improving edema. Administration of canine albumin can also be considered. If a previously stable dog with improving albumin suddenly develops new or recurrent ascites, portal hypertension secondary to a thrombus in the portal vein should be considered, as thromboembolism is a known complication of PLE.

Options for confirmed refractory cases

Once the diagnosis of refractory PLE is confirmed, concurrent disorders ruled out or addressed, and complicating factors identified and treated if possible, alternative therapeutic approaches should be considered. In examining options for refractory cases, we should consider the underlying pathophysiologic mechanisms that result in protein loss and whether we are addressing all of these mechanisms with current management strategies. The main pathophysiologic mechanisms suspected to be responsible for protein loss across the enteric mucosa include an increase in intestinal permeability to protein, direct loss of albumin due to erosions or ulcerations of the intestinal mucosa and altered lymphatic function.

Dietary Adjustment

Dietary modification can result in significant improvement in clinical signs and clinicopathologic parameters. In the authors practice, cases of PLE considered refractory to traditional management protocols are routinely managed with a tapering of their glucocorticoid and immunosuppressive agents (or at least not escalating these therapies) and a prioritization of dietary therapy. This may involve a switch to a different commercially available diet suitable for dogs with PLE, however, since many of these dogs have already been treated with a variety of commercially available prescription gastrointestinal diets, we commonly recommend that dogs be fed a home cooked diet formulated by a board-certified veterinary nutritionist. For cases of PLE, these diets are generally formulated to be both fat restricted beyond what is found in commercially available prescription gastrointestinal diets and novel in their protein source. The fat content in these diets is generally prescribed to be <15 g/1000 kcal. The more stringent dietary fat restriction would seem particularly important for dogs that have had intestinal lymphangiectasia diagnosed endoscopically or histologically with or without concurrent inflammatory enteritis and have not responded well to the commercially available low-fat diets. In those cases, ongoing protein loss may be secondary to continued lymphatic dysfunction. In fact, in a retrospective study of 24 dogs with intestinal lymphangiectasia that had either not responded to prednisolone or had relapsed once their prednisolone dose was decreased, 19/24 (79%) responded satisfactorily to further dietary fat restriction (with either a home cooked diet, or a combination of a commercial low fat diet and a home cooked diet) allowing for their prednisolone dose to be decreased without relapse.⁹ Additionally, we documented improvement in clinical signs and serum albumin in a prospective study that evaluated a dietary change in dogs with steroid-refractory PLE.¹⁰ In dogs with both CE and IL, it would also make sense that the most ideal approach to dietary therapy would be a diet that could provide both a novel protein source and dietary fat restriction. However, some dogs that do not seem to have significant lymphangiectasia histologically also seem to improve in response to a homecooked diet. The apparent dietary response in these cases may be due to fat restriction improving lymphatic function, a reduction in ongoing immune reactions or inflammation, improved digestibility of the diet or a combination of these benefits. Veterinary nutritionist-formulated home

cooked diets typically contain just a few ingredients, so it could also be considered that the absence of certain ingredients could be responsible for the improvement. Regardless of the reason for the response, it is strongly recommended to consider a switch to a veterinary nutritionist formulated further fat-restricted and novel protein sourced diet in cases of canine PLE refractory to traditional therapies including commercially available diets. In these cases showing clinical responses, some response is typically seen within 1-2 weeks of full dietary modification, and in many of these cases tapering or cessation of glucocorticoids and immunosuppressive therapies is possible. A temporary diet to test for response could be a lean novel protein such as cod or tilapia combined with white rice and sweet potato in 3 equal parts by body weight. If the dog is responsive, follow up with a board-certified veterinary nutritionist will be necessary for long-term management.

Altering or Initiating Immunosuppressive Therapy

Ongoing inflammatory and immune processes may result in the persistence of increased intestinal permeability and ongoing erosions and ulcerations to the intestinal mucosa, resulting in continued protein loss and clinical signs. Therefore, in patient's refractory to appropriate doses and durations of glucocorticoid therapy, adjunctive immunosuppressive medications are often considered.

In one study of dogs with steroid-refractory inflammatory bowel disease, treatment with cyclosporine (5 mg/kg, po, q 24 h) induced clinical remission in 12/14 dogs. Ten of these dogs had PLE, 7 of which had long-term survival.¹¹ In another study of seventy dogs with chronic enteropathies, 9/18 dogs with steroid-refractory CIE were rescued with cyclosporine.¹ The reason that some dogs with PLE will be refractory to glucocorticoids but responsive to immunosuppressive medications is not well understood. *While some dogs with steroid-refractory PLE may respond to initiating or adjusting immunosuppressive medications, a significant percentage of these dogs will be unresponsive to a variety of immunosuppressive medications despite trial treatment with several different protocols at appropriate dosages given for adequate durations.*

Octreotide

A recent publication described the use of octreotide in 18 dogs with PLE.¹² Octreotide is a somatostatin analogue thought to inhibit triglyceride absorption, decrease lymphatic flow, inhibit GI vasoactive peptides, and stimulate the autonomic nervous system. It was most commonly prescribed for dogs with PLE with a clinical suspicion or confirmed diagnosis of IL that were refractory to standard therapies. The median dose of octreotide prescribed was 20 µg/kg, SQ, daily with a range of 4-39 µg/kg, SQ, daily (divided into q8 or q12 dosing). Adverse effects (urgent diarrhea, pain with administration) were noted in 3/18 dogs; discontinuation of the drug was necessary in one dog. Clinical improvement was assessed in 12 dogs; improvement in clinical signs was noted in 6/12. Though a benefit to PLE dogs could not be confirmed by this case series, octreotide was well tolerated by most of the dogs at the doses prescribed, thus it could be considered for use in dogs with PLE suspected or confirmed to be caused by IL.²⁰ The recommend starting dose is typically 10 µg/kg, SQ, q8, though some recommend starting with a lower dose or frequency and dose escalating if it is well tolerated.

CONSIDERATIONS FOR THE FUTURE OF PLE MANAGEMENT

The main challenge in the treatment of CIE and PLE stems from an incomplete understanding of the etiopathogenesis of these disorders, as well as the varied responses of individuals to traditional therapies. It is likely that cases of canine PLE require individualized treatment, rather than a cookbook approach. In addition to resolving inflammation, promoting mucosal healing, improving

intestinal permeability and improving lymphatic function should be targets for therapy in cases of PLE. A variety of novel compounds to address these specific goals are being evaluated in the context of human IBD and may be applicable to veterinary patients in the near future.

In the treatment of gastrointestinal disease we tend to focus on dietary therapy early in the course of disease or in cases that have more mild clinical presentations. It is the author's opinion that the importance of dietary therapy may be overlooked when the clinical presentation is more severe. It has recently been demonstrated that in some Yorkshire terriers and other breeds with PLE, dietary therapy may be all that is required.¹³ In other cases, adjusting the dietary therapy may allow for improved clinical responses and spare the need for long-term high doses of glucocorticoids or immunosuppressive therapies. The ability to manage PLE dogs without the use of glucocorticoids or with lower doses of glucocorticoids is certainly attractive, as glucocorticoids can have substantial side effects including exacerbation of hypercoagulable states. Interestingly, a study evaluating dogs with PLE saw a survival benefit in dogs treated without the use of glucocorticoids¹⁴, or with lower doses of glucocorticoids. Additionally, a recent retrospective study found that treatment with steroids + immunosuppressives offered no survival advantage when compared to steroids alone in dogs with PLE.¹⁵ Long-term use of immunosuppressive drugs in these patients can also increase the risk of opportunistic infections and development of lymphoproliferative disorders. Finally, preliminary data from a study the author just completed found that dogs with PLE have immunodeficiency at the time of diagnosis.

Importantly, the author has found that some dogs with PLE failing to respond to steroids and immunosuppressive drugs will improve considerably with just tapering or discontinuing these therapies, suggesting that in some cases immunosuppression may be detrimental.

We need carefully planned prospective clinical trials to determine which specific therapeutic approaches are best in relation to clinical, clinicopathologic and histologic characteristics of individual dogs with PLE. ***Until more information is available, it is the author's opinion that in cases of PLE not responding to traditional management with glucocorticoids and immunosuppressive medications, we should consider an alternative approach with dietary modification (as described above) and de-escalation of immunosuppressive therapies in addition to the more traditional approach of escalating immunosuppressive strategies. In the future we may discover that approaching these cases more conservatively may lead to better outcomes in certain cases of canine PLE.***

This information is provided by the Center for Canine Protein-Losing Enteropathy. For more information please contact us at centerforcanineple@gmail.com or request a consultation.

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