Emerging Concepts in the Understanding and Treatment of Canine Protein-Losing Enteropathy

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KEYWORDS

• Protein-losing enteropathy (PLE) • Hypoalbuminemia • Intestinal permeability
• Intestinal lymphangiectasia (IL) • Chronic intestinal inflammation

KEY POINTS

- Protein-losing enteropathy (PLE) is a heterogeneous syndrome caused by intestinal lymphatic disease and dysfunction, increased intestinal permeability, and mucosal injury.
- Though intestinal inflammation is commonly documented in dogs with PLE, there are likely specific pathophysiologic mechanisms that distinguish dogs with PLE from their normoalbuminemic counterparts.
- Intestinal lymphangiectasia is frequently reported in dogs with PLE but is likely considerably underdiagnosed with current routine diagnostic methods.
- Dietary modification represents the most critical therapeutic intervention in dogs with PLE, with evidence showing diet monotherapy can result in remission and be instrumental in cases where medications fail.

INTRODUCTION

Protein-losing enteropathy (PLE) is a syndrome of excessive protein loss across a diseased or dysfunctional enteric mucosa.[1–3] Critically, PLE is not a discrete diagnosis, but rather occurs as a result of altered intestinal permeability and protein uptake, direct intestinal mucosal erosion or ulceration with secondary loss of protein, and/or altered intestinal lymphatic function and direct loss of protein-rich lymph (**Fig. 1**). Though causes are numerous (**Table 1**), most veterinarians use "PLE" to refer to non-neoplastic, non-infectious PLE, typically caused by intestinal lymphangiectasia (IL; the disease that results from distended and dysfunctional intestinal lymphatics) and idiopathic inflammatory small intestinal disease.

The most common clinical signs include chronic relapsing or progressive GI signs (diarrhea, weight loss, decreased appetite, vomiting) and signs associated with

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Abbreviations	
CIE	chronic inflammatory enteropathy
IL	intestinal lymphangiectasia
LEC	lymphatic endothelial cell
PLE	protein-losing enteropathy
TE	thromboembolic disease
VCE	video capsule endoscopy

hypoalbuminemia (ascites, pleural effusion, peripheral edema). Initial diagnostics must exclude other causes of hypoalbuminemia (most importantly, protein-losing nephropathy and liver insufficiency), then ideally identify the specific cause of PLE and screen for complications (most importantly, hypocobalaminemia, ionized hypocalcemia, and effusions). Despite limitations, intestinal biopsy is recommended in dogs with PLE syndrome where hypoadrenocorticism and infectious causes have been excluded, and a diagnosis was not achieved non-invasively. Biopsy can exclude infectious (eg, histoplasmosis) or neoplastic (eg, intestinal lymphoma) causes of PLE and help to determine whether intestinal inflammation or IL predominate in cases of PLE. Prior to

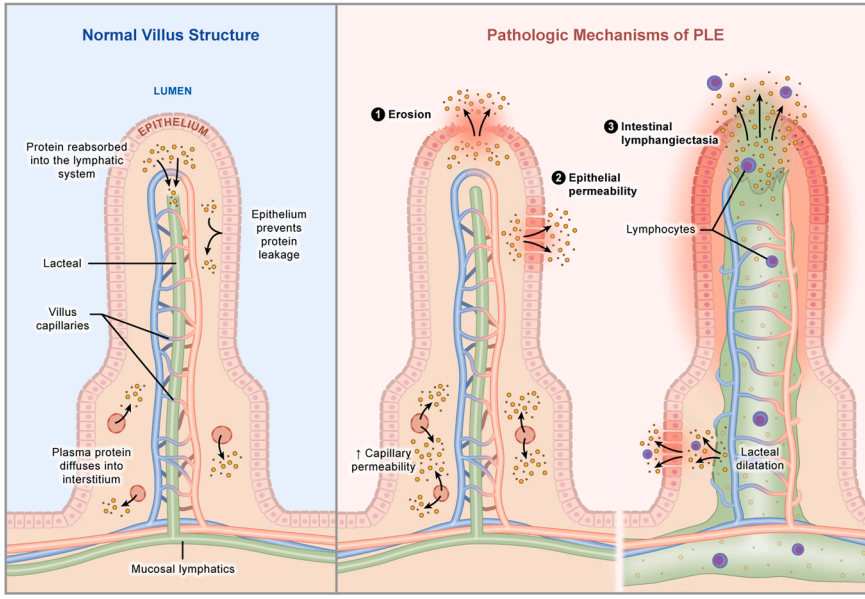

Fig. 1. The normal intestinal villus architecture and the pathological processes leading to protein loss are depicted. In healthy tissue, proteins and cells move from capillaries into the interstitial space, where lymphatic vessels and lacteals collect them for return to circulation. In disease, 3 mechanisms can contribute to protein loss. In erosive conditions, proteins diffuse from capillaries into interstitial tissue and are lost into the lumen through the damaged mucosa. In the absence of erosion, protein can be lost from the intestine due to increases in epithelial barrier permeability, IL, or both. In intestinal lymphangiectasia, enlarged lacteals may leak or rupture, and concurrent increases in epithelial barrier permeability may compound the issue. Additionally, when capillary permeability increases, fluid accumulates in the interstitium, exacerbating protein loss. IL, intestinal lymphangiectasia. (*From* The New England Journal of Medicine, Ahmet Ozen, M.D. et al.,Protein-Losing Enteropathy, VOL. 389 NO. 8, 733-748. Copyright © 2023 Massachusetts MedicalSociety. Reprinted with permission from Massachusetts Medical Society.)

Table 1
Causes of intestinal protein loss in dogs

Diseases that Alter Intestinal Permeability and/or Cause Mucosal Injury	Lymphatic Disease

• Intestinal inflammation (chronic inflammatory enteropathy/inflammatory bowel disease)
• Infectious enteropathies
  ○ Fungal (Histoplasmosis, Pythiosis)
  ○ Parasitic (Hookworm, Schistosomiasis)
  ○ Viral (Parvovirus)
  ○ Bacterial- RARE (Campylobacter, Salmonellosis)
• Chronic obstruction of the intestine
  ○ Foreign body
  ○ Intussusception
• Neoplasia
  ○ Intestinal lymphoma (solitary or diffuse)
  ○ Intestinal adenocarcinoma
• Intestinal crypt disease (unknown if primary disorder or secondary change)
• Hypoadrenocorticism (Addison's disease)
• Intestinal ulceration
	• "Primary" lymphangiectasia (suspected genetic predisposition)
	• "Secondary" lymphangiectasia
	  ○ Intestinal inflammation
	  ○ Intestinal neoplasia
	  ○ Theoretic causes (unconfirmed in veterinary medicine)
	  ■ Right heart failure
	  ■ Constrictive pericarditis
	  ■ Portal hypertension
	• Focal lipogranulomatous lymphangitis

biopsy, an empirical diet trial can be considered,[4–6] especially in mildly affected dogs with a good appetite.[6] Common histopathologic findings include lacteal dilation (LD), various inflammatory infiltrates, dilated cystic crypts, and mucosal edema.[1]

Why some dogs with idiopathic chronic inflammatory small intestinal disease develop PLE syndrome remains poorly understood. A fundamental question is whether PLE represents the severe end of a spectrum or constitutes a distinct pathophysiological entity. The lack of correlation between intestinal inflammation severity and clinical severity or hypoalbuminemia suggests this is not simply severe chronic enteritis.[7–9] Thus, specific pathophysiologic mechanisms likely distinguish dogs with PLE from normoalbuminemic counterparts.

Historical literature suggests over 50% of dogs with PLE are euthanized or die from their disease.[1] In one investigation, approximately 50% of Yorkshire terriers with PLE were "steroid-responsive," while the remainder did not respond.[10] Rather than accept these outcomes as inevitable, we should critically re-examine this disorder's etiopathogenesis and challenge current gold-standard approaches. A "one size fits all" approach is no longer acceptable for a disease with such heterogeneity in presentation and response to therapy. These proceedings review historical precedent while highlighting recent research advances and knowledge gaps in canine PLE etiopathogenesis and treatment.

ETIOPATHOGENESIS

Breeds commonly reported with PLE include Yorkshire terriers, border collies, rottweilers, Maltese, dachshunds, English springer spaniels, and soft-coated wheaten terriers. Basenji dogs have been described with a particular immunoproliferative enteropathy.[11] For IL, the breeds most often reported include Yorkshire terriers, Maltese, rottweilers, soft-coated wheaten terriers, Norwegian lundehunds, and Shar-Peis.[12] Genetic causes for PLE in dogs remain unidentified, though research is underway. The discovery of genetic variants related to particular breeds or subsets of dogs

with PLE could serve several important purposes, including helping to reduce or eliminate genetic defects from a specific breed or breeds, prediction of therapeutic responses, and the development and testing of new targeted therapies. A recent genomic discovery in humans known as CHAPLE syndrome (an autosomal recessive disorder caused by CD55 mutations resulting in both IL and inflammatory enteritis) led to the development of a specific successful treatment for affected individuals.[13]

Defects in intestinal epithelial permeability and intestinal lymphatic development or dysfunction would appear to be the most likely culprits to explain hypoalbuminemia that occurs in the setting of small intestinal disease (see **Fig. 1**). Increases in intestinal permeability have been documented in dogs with lymphoplasmacytic enteritis. Also, when measured by the dual sugar absorption test, permeability was significantly higher in dogs with lymphoplasmacytic enteritis and serum albumin below 2.5 g/dL.[14]

Multiple investigations suggest that the presence and degree of LD in dogs with PLE and intestinal inflammation may be an important finding that distinguishes them from normoalbuminemic dogs with intestinal inflammation. In 1 study, dogs with intestinal inflammation and hypoalbuminemia were 5 times as likely as normoalbuminemic dogs with intestinal inflammation to have LD identified via biopsy.[15] Additionally, in 94 dogs with lymphoplasmacytic enteritis, villous lacteal width was inversely strongly correlated with both albumin and cholesterol, suggesting that lower albumin and cholesterol correlate with greater lymphatic dilatation.[16] Though some literature suggests IL prevalence in dogs with PLE is roughly 50%,[1] substantial diagnostic limitations exist. In humans with IL, the lacteal changes are variably regional or focal, sometimes even treated with surgical resection of the affected bowel. In some dogs with PLE, the author has observed intestinal hyperechoic mucosal striations apparently limited to the jejunum on sonographic examination of the bowel (**Fig. 2**). When it is safe to perform, video capsule endoscopy (VCE) may be a helpful diagnostic modality in dogs with PLE. In some humans with PIL, VCE detected regional LD in intestinal sections not evaluated with traditional endoscopy.[17] In an ongoing study of the use of VCE in dogs with PLE (**Fig. 3**), preliminary data suggest that VCE is more sensitive for gross detection of LD than traditional endoscopy.

Immunohistochemical (IHC) labeling has revealed that intestinal lymphatic abnormalities extend beyond the mucosa in dogs with PLE.[18,19] Lesions can be detected in all intestinal layers including mucosa, submucosa, muscularis and serosa/mesentery.[19] In some cases, villous lacteal dilatation was absent when it was observed in the deeper layers,[18] possibly due to patchy disease, sampling error, or artifact.

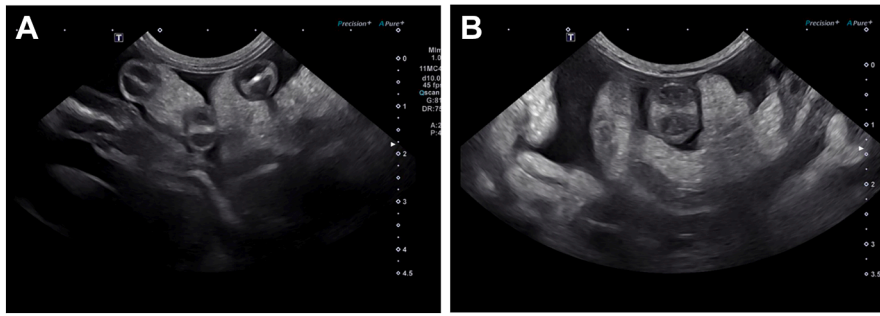

Fig. 2. Comparative transverse sonographic images of the duodenum [*left* (*A*)] and jejunum [*right* (*B*)] in a 11 year old, spayed female Maltese with PLE. Duodenal sonographic findings were unremarkable, while echogenic speckling and hyperechoic mucosal striations were present throughout the jejunum. PLE, protein-losing enteropathy.

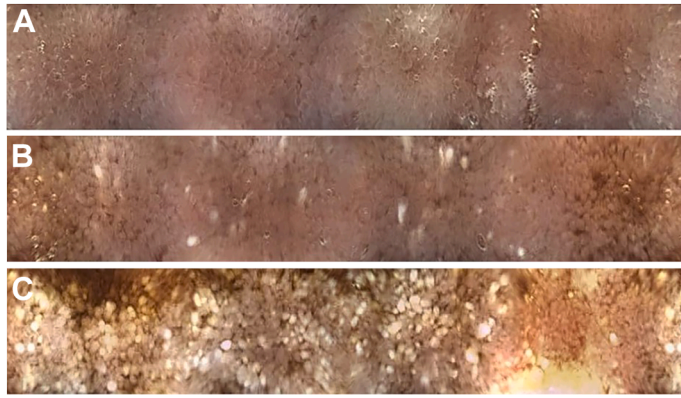

Fig. 3. Images of the small intestine obtained via VCE in an 8 year old, spayed female Newfoundland with PLE. VCE revealed patchy IL [no "white spots" observed in the top image (*A*) versus mild "white spots" in the middle image (*B*) versus marked "white spots" observed in the bottom image (*C*)]. Histopathology of both the duodenum and ileum revealed only mild, rare lacteal dilatation. IL, intestinal lymphangiectasia; PLE, protein-losing enteropathy; VCE, video capsule endoscopy.

Thus, consideration should be given to more widespread use of lymphatic endothelial cell (LEC) labeling in dogs with PLE. Non-invasive biomarkers may also prove useful, as serum C-reactive protein, bacterial lipopolysaccharide, cleaved cytokeratin 18, and both serum and fecal zonulin were recently found to be elevated in dogs with IL compared with other gastrointestinal conditions.[20]

Even within a segment of bowel, LD can often be patchy within the mucosa, therefore biopsies could miss an affected section.[21–23] Lymphatic abnormalities are also not limited to LD. Generalized intestinal lymphatic hypoplasia has been reported in 3 dogs with PLE where immunohistochemical labeling of LECs revealed a lack of villous lacteals in these dogs compared with healthy controls,[24] with additional cases reported anecdotally. Because this condition requires intestinal biopsies and IHC labeling, it is likely underdiagnosed.

A complete understanding of PLE etiopathogenesis is critical to advancing therapeutic approaches. Determining whether increased inflammation and increases in intestinal permeability and/or lymphatic disease and dysfunction predominate in individual cases should theoretically guide treatment selection. The following section highlights how given the current gaps in our understanding and the limitations of available diagnostics, treatment strategies should balance evidence-based approaches with individualized patient strategies and prioritize interventions with the strongest safety profiles and proven efficacy.

TREATMENT

The Initial Treatment Approach

Diet

Dietary modification represents the most critical component of therapy in dogs with PLE. This assertion is supported by substantial evidence demonstrating that dietary intervention can succeed as monotherapy and when pharmacologic therapies fail.[4–6,25,26] In the author's experience, the selection and optimization of dietary therapy frequently determines whether a dog achieves remission or continues to deteriorate despite aggressive interventions.

The first reports of PLE in dogs in the 1960's and 1970's largely described IL as the cause, and treatment was heavily focused on dietary management, as it is in humans.[27–30] Over subsequent decades, the therapeutic paradigm shifted toward aggressive immunosuppressive protocols, with corticosteroids and other immunomodulatory drugs becoming the dominant treatment strategy. More recently, the pendulum appears to be swinging back toward a more balanced approach, with renewed appreciation for the role of dietary modification.

Multiple studies have shown that dogs with PLE can achieve remission with dietary therapy alone. Beyond the early reports of successful dietary management,[28,31] more recent work has demonstrated remission in Yorkshire terriers with presumptive PLE using diet as monotherapy.[4] Another study found that dogs with PLE, especially those with lower disease severity (CCECAI <8), responded well to dietary intervention alone.[6] A prospective trial of low-fat diet monotherapy in dogs with presumptive PLE reported that nearly half (6/14) achieved clinical remission without any additional treatment.[5]

Dogs with PLE are not a homogeneous population, and dietary management must be tailored to the individual patient. The selection process should be guided by a comprehensive nutritional assessment, a thorough dietary history, and careful consideration of diagnostic findings. More than 1 dietary trial is often necessary to find the optimal approach. For dogs with chronic inflammatory enteropathy (CIE) driving their PLE, the source and form of dietary protein are important considerations. Novel protein or hydrolyzed diets may be beneficial, though the amount of protein provided must be balanced against the risk of excessive fermentation if malabsorption is severe. Dietary fat restriction is the mainstay of therapy for humans with IL, with the majority of cases able to be managed with dietary therapy alone. Thus, the author considers that dietary fat restriction is also paramount for dogs with IL and often also appears to be beneficial even when CIE is the predominant lesion with secondary lymphatic involvement. While there is no universal consensus on definitions, commercially available "low-fat" diets typically contain 16 to 25 g fat/1000 kcal (1.6 to 2.5 g/100 kcal), while "ultra low-fat" diets contain $\leq$15 g fat/1000 kcal ($\leq$1.5 g/100 kcal). Some dogs with IL may require fat restriction beyond what commercial diets can provide, necessitating veterinary nutritionist-formulated home-cooked diets. Dogs with PLE may also benefit from fiber-enriched diets or those with mixed fiber sources; however, this varies.

A significant advance in the dietary management of canine PLE occurred in 2024 with the release of several multifunctional diets that are both hydrolyzed and comparatively low in fat. These products represent an ideal choice for dogs with both CIE and IL (which appears to be the majority of dogs), as well as for dogs being treated empirically when the underlying etiology is unclear or histopathology is unavailable. These diets should be prioritized in clinical practice for dogs with PLE of mixed or unknown etiology. However, these diets might contain comparatively lower amounts of total dietary fiber than could be necessary for adequate stool quality in some dogs; therefore, a switch to a different diet or the addition of supplemental fiber might become necessary.

Though combination hydrolyzed/low-fat diets could represent the most ideal initial choice of diet for many dogs with PLE, when histopathology is available, dietary recommendations should be tailored accordingly. For example, if histology demonstrates severe LD and dietary history demonstrates a lack of response to a low-fat diet, it would be prudent to consider that the ideal initial diet might be considered "ultra-low fat" and therefore a fresh frozen commercial diet that is lower in fat or a veterinary-nutritionist formulated ultra-low-fat, home-cooked diet might be preferred. In the absence of histopathologic data, breed predisposition, clinicopathologic

findings (particularly the degree of hypocholesterolemia), and imaging results (such as intestinal hyperechoic striations on ultrasound) can guide empiric diet choice. The patient's previous dietary history also provides critical information about the degree of fat restriction that may be required. It should also be noted that some dogs may achieve equally good disease control on veterinary prescription novel protein low fat diets, of which there are several options, and these may offer improved palatability in some cases.

Diets should be strict to start. Providing a list of safe and suitable vegetables and fruits for treats would be acceptable. Medications can be given in vegan marshmallows if necessary. Clients should be strictly advised that high-fat items (eg, peanut butter) and animal protein-based treats/snacks should be aggressively avoided. Improvement in gastrointestinal clinical signs typically occurs within 7 to 14 days when a dietary trial will be successful, with many dogs with PLE demonstrating improvement related to a specific dietary change within 3 to 5 days. Practitioners should be prepared to modify the dietary recommendation if no improvement is observed within this time period.

Glucocorticoids

The underlying mechanisms driving chronic intestinal inflammation in dogs remain incompletely characterized, though evidence points toward dysregulated immune responses to luminal antigens, whether dietary, bacterial, or environmental in origin. Additionally, lacteal dilation and dysfunction with subsequent lymph leakage induce secondary mucosal inflammation. Given these pathophysiologic considerations, glucocorticoid therapy has historically formed the cornerstone of initial PLE management and is beneficial in many dogs.

Prednisone or prednisolone are the most commonly prescribed glucocorticoids. Typical starting doses have ranged considerably over time, with many choosing immunosuppressive doses (1 to 2 mg/kg, PO, daily) as the initial dose. However, the author has not found considerable benefit in exceeding 1 mg/kg/day, PO, in dogs. To that point, an interesting abstract at the ACVIM Forum 2025 reported that prednisolone pharmacokinetics did not differ at 1 mg/kg versus 2 mg/kg in dogs with various immune-mediated diseases.[32] Individual dosing decisions should also reflect the presumed dominant disease process. Dogs that have IL as the predominant process may warrant more conservative initial doses around 0.5 to 0.75 mg/kg/day. Maximum daily doses should not exceed 60 mg per dog.

Importantly, glucocorticoids can worsen muscle catabolism and exacerbate the hypercoagulable state already present in many PLE patients. Additionally, high-dose immunosuppression carries theoretical risks in dogs with compromised intestinal barrier integrity who may be susceptible to bacterial translocation and sepsis. Thus, care should be taken to use the lowest dose possible. A recent pharmacokinetic investigation found that prednisolone absorption in dogs with PLE did not differ from that of healthy controls.[33] This indicates that intestinal malabsorption of steroids is unlikely in dogs with PLE, and, consequently, selecting higher doses or administering steroids parenterally appears unwarranted based on currently available evidence.

Secondary immunosuppressive agents

The use of secondary immunosuppressive medications at the initiation of PLE therapy lacks robust supporting evidence and is generally not recommended.

A recent study of 31 dogs with inflammatory PLE found that adding second-line immunosuppressants to glucocorticoid therapy did not reduce time to albumin normalization or improve outcomes compared with glucocorticoids alone.[34] Although it was

not the objective of the study to evaluate this, a retrospective analysis of 43 dogs demonstrated that those treated with dietary therapy alone achieved significantly better outcomes than those receiving immunosuppressive treatment.[35] Chlorambucil is often touted as a secondary immunosuppressive agent that should be considered in dogs with PLE, as a retrospective study comparing chlorambucil-prednisolone versus azathioprine-prednisolone reported that dogs in the chlorambucil group improved faster and had better outcomes.[36] However, this study did not compare glucocorticoid therapy alone to combination therapy. Additionally, the chlorambucil group received significantly lower steroid doses (median 1.7 mg/kg/day, range 1.0–2.4) than the azathioprine group (median 2.0 mg/kg/day, range 1.3–3.8),[36] thus consideration could be given to the possibility that positive outcomes were attributable to lower steroid dosing.

A clear immune-mediated pathogenesis has not been established for IL, which appears to affect many dogs with PLE. At the current time, when lymphatic pathology predominates, broad-spectrum immunosuppression lacks rationale. Some primary IL cases in humans have been linked to genetic mutations,[37] and humans with IL show deficiencies in immunoglobulins and T-cell subsets. Broad immunosuppression is not utilized to treat primary IL.[38,39] A recent study found significant reductions in serum immunoglobulins and certain T-cell subsets in treatment-naïve dogs with PLE compared with healthy controls.[40] These findings highlight the importance of case selection when considering aggressive immunosuppression in dogs with PLE, and encourage vigilance for secondary infections.

Treating and preventing complications

Decreases in vitamins and minerals. Hypocobalaminemia occurs in 43% to 75% of dogs with non-neoplastic, non-infectious PLE and should be treated.[41] Evidence demonstrates oral supplementation can be equally effective as parenteral in dogs with intestinal disease.[42] Hypofolatemia can be safely treated, though a benefit has not been reported.

Multiple studies have documented decreased serum 25-hydroxyvitamin D (25[OH]D) in dogs with PLE.[35,43,44] Recently, a prospective, double-blind, randomized, placebo-controlled trial evaluated cholecalciferol supplementation (400 IU/kg/day) in dogs with PLE and 25(OH)D below 50 nmol/L in the absence of severe ionized hypocalcemia.[45] This level of supplementation exceeded the National Research Council's safety standards for vitamin D in dogs. Dogs receiving cholecalciferol achieved significantly higher 25(OH)D at 4 weeks compared w placebo. However, no significant differences occurred in clinical variables or biochemical parameters between groups. Notably, 50% of placebo-treated dogs achieved normal 25(OH)D by 4 weeks, and approximately 80% normalized by study completion, suggesting that treating underlying disease may resolve hypovitaminosis D without supplementation. Five dogs (18%) developed hypervitaminosis D, though no ionized hypercalcemia occurred. Dietary vitamin D intake was not controlled, and all dogs received glucocorticoids, which may have confounded results.[45]

In dogs with ionized hypocalcemia and clinical signs (muscle twitching, tremors, facial rubbing, seizures), immediate treatment with 10% calcium gluconate (0.5 to 1 mL/kg IV slowly over 10–30 minutes while monitoring heart rate) may be necessary. Oral calcium carbonate (25 to 50 mg/kg/day elemental calcium, PO, once daily or divided every 12 hours) can also be beneficial. Calcitriol is often prescribed in these cases with an initial dose of 20 to 30 ng/kg PO every 24 hours for 3 to 4 days, followed by maintenance of 5 to 15 ng/kg PO every 24 hours. Calcitriol is best administered

apart from glucocorticoids, and serum phosphorus and ionized calcium should be monitored closely during therapy.

For dogs with hypovitaminosis D and normal ionized calcium, the approach should be individualized. A conservative approach involves monitoring 25(OH)D while treating underlying PLE, based on the findings of the study mentioned above. However, studies suggest that 25(OH)D3 supplements raise vitamin D status more rapidly and efficiently than D3 in adult dogs,[46] therefore 25(OH)D3 might be more successful in impacting the dogs clinically. Additionally, when dogs have persistent hypovitaminosis D despite attempts at disease management, supplementation might be appropriate.

Thromboprophylaxis. According to the 2022 CURATIVE guidelines, dogs with PLE fall into the "high risk" category for thrombotic events.[47] While both evidence of hypercoagulability[48] and thromboembolic disease (TE)[49] have been reported in dogs with PLE, our understanding remains limited regarding which patients face elevated risk, what underlying mechanisms drive TE development, and the incidence of morbidity and mortality secondary to TE in dogs with PLE. A prospective study using CT angiography found thromboembolism in 13.6% (3/22) of dogs with PLE, with 2 cases being subclinical.[50] Unpublished work from an ongoing study found that 11/51 (22%) had thromboemboli diagnosed by CT scan with angiogram of chest and abdomen at the time of initial diagnosis. Most of these thromboemboli were also subclinical. Data from this ongoing study are still being analyzed to determine if any clinical, biochemical or histologic findings were correlated with the presence of thromboembolism.

Given the suspected pathogenesis, thromboprophylaxis might be particularly important for dogs with markers of heightened inflammation (hyperfibrinogenemia, elevated platelet counts), low antithrombin and/or profound hypoalbuminemia. The author's standard approach involves clopidogrel at 2 to 3 mg/kg orally once daily. However, factor Xa inhibitors (rivaroxaban or apixaban) are believed to offer superior protection against venous thromboembolic events, making them perhaps preferable for very high risk patients or those with confirmed venous thromboembolism.

Dysbiosis. The prevalence and impact of intestinal dysbiosis in dogs with PLE is currently not well understood. However, clinical observations suggest a potential benefit from treatments directed at correcting dysbiosis in some cases. There are anecdotal reports of dogs with PLE (particularly those exhibiting notable large bowel signs such as severe flatulence, and frequent, urgent defecations) improving with probiotics, fecal microbial transplant, or with antibiotics (in some cases when being used to treat co-morbidities rather than the PLE itself). More work is necessary to identify the dogs who could most benefit from these therapies and the best treatment approach.

Providing supportive care. Removing effusions is only recommended when they are causing discomfort or respiratory difficulty. Diuretics are discouraged as they are often ineffective and can promote dehydration. If crystalloid fluid therapy is needed, it should be judicious. The volume of plasma needed to increase albumin is substantial and typically not practical; thus, plasma administration is not recommended. Colloids, such as hydroxyethyl starches, are most useful for improving edema, though contraindications exist. Concentrated human albumin is not recommended. A canine albumin product is available and can be useful in dogs with severe consequences of hypoalbuminemia. Dogs with PLE can often benefit from other supportive care, such as medications to reduce vomiting and nausea and support appetite. Because of the critical importance of dietary treatment, assisted feeding might be necessary

and life-saving[51] to provide adequate nutrition and dictate the diet type if the dog is unwilling to eat the recommended diets.

Ongoing Treatment

Steroid-responsive

When dogs respond well to initial diet and corticosteroid therapy, the author typically tapers steroids by about 25% after initial 3 to 4 weeks, with subsequent 25% reductions every 3 to 4 weeks until a dose less than 0.5 mg/kg PO daily or every other day is reached. This dose is typically continued for at least 3 to 4 months before attempted discontinuation, which will determine if diet alone can manage the condition. If relapse occurs during taper, prednisone/prednisolone can be increased back to the previous effective dose and continued long term if tolerated (typically <0.5 mg/kg PO daily with limited adverse effects). If the dog cannot tolerate an effective corticosteroid dose, a transition to oral budesonide for long-term management can be successful. Cyclosporine could also be considered to replace the prednisone/prednisolone, though the author prefers budesonide when effective and tolerated. Some dogs who relapse during steroid tapering respond better after switching to a lower-fat diet. To assess the effect of each change independently, it is recommended to avoid adjusting steroids within 5 days of any dietary modification.

Non-steroid responsive (or incomplete response)

A subset of dogs has minimal improvement in clinical signs and hypoalbuminemia despite anti-inflammatory or immunosuppressive steroid doses and initial dietary changes. Failure may occur because the disease is not primarily immune-mediated (lymphatic disease is the primary issue), other management factors are inadequately addressed (diet worsening IL or triggering immune response), or the condition is immune-mediated but steroid-refractory.

Studies show significant improvement in steroid-refractory cases with dietary modification alone. Okanishi *and colleagues* reported that 19/24 dogs with steroid-refractory IL improved when dietary fat content was lowered.[26] In another study, 8/10 dogs with steroid-refractory inflammatory PLE responded to dietary change.[25] Many dogs failing commercial diets and immunosuppressive drugs have been rescued by specifically formulated, often novel protein and ultra-low-fat, home-prepared diets. There is no one-size-fits-all approach. Supplemental oils should be avoided initially, as the additional fat can worsen lymphatic congestion and diarrhea. Although several other options exist, a temporary trial diet of lean novel protein (cod or tilapia) combined with white rice and sweet potato in equal parts by weight can assess initial response. If improvement occurs, follow-up with a board-certified veterinary nutritionist is essential for complete and balanced long-term diet formulation, which may require the addition of essential fatty acids once the dog is more stable. Some dogs achieving a response to a home cooked diet can eventually be transitioned back to a commercially available diet once their condition is improved.

Some practitioners add secondary immunosuppressive agents (commonly cyclosporine or chlorambucil) after initial treatment failure. Since glucocorticoids are typically effective and broad-spectrum immunosuppressives, there must be a specific rationale for why other medications would be more effective. As previously noted, oral prednisolone absorption was recently demonstrated to be similar in dogs with PLE versus healthy controls, thus malabsorption of the steroid would not appear to be a major cause of treatment failure.[33] The possibility of glucocorticoid receptor polymorphisms exists but seems unlikely in such a large subset of dogs. Perhaps in dogs

with highly T-cell-driven disease, cyclosporine could be more effective, as speculated by authors of a study reporting that 12/14 dogs with inflammatory enteritis non-responsive to glucocorticoids had a positive response to cyclosporine.[52] Importantly, only 5 cases had hypoalbuminemia, and though some IL was reported, inflammatory enteritis predominated. Thus, applying these findings to all dogs with PLE could be inappropriate. Chlorambucil is an alkylating agent that is particularly effective against diseases with severe B-cell over-activity; thus, it would be expected to be most beneficial in cases of lymphoma or lymphocytic leukemias. Though some clinicians report anecdotal success with chlorambucil in some cases of steroid-refractory PLE, there are no clinical studies evaluating its use in steroid-refractory dogs.

While there is potential rationale for secondary immunosuppressive agents in some non-steroid responsive dogs, there is concern that if the dog suffers from intestinal lymphatic disease primarily, or if diet promotes ongoing inflammation, they will be similarly unresponsive and at increased risk of opportunistic infections, most commonly intestinal bacterial translocation and sepsis. Based on previous publications, anecdotal experience, and unpublished data, upward of 80% to 90% of dogs with PLE failing immunosuppressive steroid doses and initial diets can achieve clinical remission with targeted diet change, often to ultra-low-fat, home-cooked diets. Therefore, the author feels strongly that this should be recommended prior to adding secondary immunosuppressive agents. Additionally, the author's anecdotal experience is that some dogs will not have maximal clinical or biochemical improvement in response to the home-cooked diet until glucocorticoid doses are tapered (usually to 1 mg/kg/day or below) and secondary immunosuppressive agents are discontinued.

The author views the use of secondary immunosuppressive agents as steroid-sparing therapy differently from the scenario described above. When a dog is steroid-responsive but experiencing steroid side effects severe enough to negatively affect its clinical status, there is clearer rationale for introducing a second agent to reduce steroid dependence.

What is an acceptable response?

Effective management of PLE should not always be defined by achieving completely normal serum albumin. Instead, the goal should be to establish clinical remission and prevent life-threatening complications. If therapy controls clinical signs without adverse effects and albumin concentration is maintained at a level unlikely to cause serious complications, the author considers this successful management. This approach acknowledges the complexity and difficulty that sometimes come with managing this condition and prioritizes the patient's quality of life and long-term stability over complete normalization of laboratory values.

SUMMARY AND LOOK TOWARD THE FUTURE

The author agrees with *Craven and colleagues*[1] that until we better understand the pathophysiology and why our current immunosuppression strategies fail in so many cases, PLE management should favor "the safest approach." The future of PLE management would optimally include the prevention of PLE in susceptible breeds through the discovery of specific genetic variants. Furthermore, our care of these dogs must advance to include better ways to differentiate which dog is most likely to respond to what therapy based on a critical examination of all potential clinical, imaging, and laboratory biomarkers, which may require the discovery of new predictors. Novel therapies ideally might target intestinal lymphatic dysfunction, increased intestinal permeability, or unique immune disorders. Any time the current management of a medical condition fails to work well, we should critically examine the underlying pathophysiology and current

practices rather than simply accepting the poor outcome. There are countless examples in both human and veterinary medicine where once-fatal or untreatable conditions now have highly effective treatments or cures, and we must aim for the same breakthroughs for dogs suffering from PLE.

CLINICS CARE POINTS

- Protein-losing enteropathy (PLE) is a heterogeneous syndrome requiring individualized management.
- Dietary modification is the most critical therapeutic intervention in canine PLE and should be addressed in all cases.
- When dogs with PLE fail to respond to glucocorticoids, initial dietary modification(s), +/- secondary immunosuppressive agents, the author has found de-escalating immunosuppression and implementing a targeted dietary change (often to an ultra-low-fat home-cooked diet) to be more successful than adding or intensifying immunosuppressive therapy.

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