GASTROENTEROLOGY

Decoding Canine Protein-Losing Enteropathy

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Abstract

Protein-losing enteropathy is a life-threatening syndrome characterized by excessive loss of proteins into the lumen of the gastrointestinal tract, resulting in hypoproteinemia and other systemic sequelae. The most common causes of canine protein-losing enteropathy are chronic inflammatory enteropathy and intestinal lymphangiectasia, which may occur independently or concurrently. Successful management requires an individualized, multimodal approach that includes dietary management; correction of vitamin deficiencies; microbiome modulation; and, for some patients, immunosuppressive treatment. Nutritional management with a highly digestible, fat-restricted diet is the cornerstone of therapy, and dogs with chronic inflammatory enteropathy may benefit from a diet that is also hypoallergenic. This article reviews key concepts in the diagnosis and treatment of canine protein-losing enteropathy.

Take-Home Points

- Canine protein-losing enteropathy (PLE) is a heterogenous syndrome most commonly caused by chronic inflammatory enteropathy, intestinal lymphangiectasia, or a combination of both.
- Diagnosing PLE requires a systematic workup to exclude other causes of hypoalbuminemia and is most often accomplished by excluding nongastrointestinal causes rather than directly confirming intestinal protein loss.
- PLE is classified as food responsive, immunosuppressant responsive, or nonresponsive.
- The pathogenesis of PLE results from a complex interplay of environmental factors (e.g., diet, microbiota), genetic predisposition, and dysregulated immune response.
- Successful treatment targets 4 different areas: dietary management, correction of vitamin deficiencies, immune system modulation, and microbiome modulation.

Protein-losing enteropathy (PLE) is a life-threatening syndrome characterized by excessive loss of proteins into the lumen of the gastrointestinal tract, resulting in hypoproteinemia and other systemic sequelae. One literature review found PLE to be life-ending for 54% of dogs; thus, early identification and treatment are imperative.[1]

Although PLE may arise secondary to a variety of inflammatory, infectious, neoplastic, and endocrine disorders, the most common causes of PLE in dogs are chronic inflammatory enteropathy (CIE) and intestinal lymphangiectasia (IL). CIE describes gastrointestinal disorders characterized by ≥ 3 weeks of clinical signs (excluding infectious, neoplastic, endocrine, mechanical, and extragastrointestinal causes) and histopathologic evidence of mucosal inflammation. IL is characterized by variable intestinal lymphatic vessel dilation, lymphangitis, and/or lymphatic obstruction and rupture.[2] This article will review the diagnosis and treatment of PLE caused by CIE and IL.

Etiology and Signalment

The protein loss seen with PLE can result from lymphatic obstruction or dysfunction, increased vascular permeability, direct mucosal inflammation (nonerosive or erosive/ulcerative), or a combination of these mechanisms.[1] PLE has been identified as a consequence of a wide variety of diseases including infectious, neoplastic, endocrine, mechanical, and inflammatory conditions (**BOX 1**).

Although PLE can be diagnosed in dogs of any age and breed, some breeds are more frequently affected (**BOX 2**).

Clinical Presentation

Dogs with PLE most commonly exhibit chronic, relapsing, or progressive gastrointestinal signs, including vomiting, diarrhea, weight loss, and changes in appetite (e.g., anorexia, polyphagia). Many dogs also exhibit signs associated with decreased oncotic pressure secondary to hypoalbuminemia, such as peripheral edema, peritoneal effusion, and/or pleural effusion. In a small subset of dogs, gastrointestinal signs may be absent.[5] Dogs may also exhibit complications of PLE, including thromboembolic disease, dyspnea resulting from pleural effusion, tremors or seizures associated with hypomagnesemia, and hypocalcemia-associated signs such as facial rubbing, tremors, or seizures.[6-8]

Physical examination may reveal signs of malnutrition, including poor body condition and/or muscle wasting as well as poor hair coat.[9] Abdominal palpation may identify distension with a palpable fluid wave, consistent with effusion. Thoracic auscultation may

BOX 1
Causes of Protein-Losing Enteropathy

Inflammatory
- Chronic inflammatory enteropathy

Neoplastic
- Intestinal lymphoma
- Intestinal adenocarcinoma

Ulcerative
- Intestinal ulceration

Infectious
- Fungal and oomycetes
  - Histoplasmosis
  - Pythiosis
- Viral
  - Parvovirus enteritis
- Parasitic
  - Hookworms
  - Giardiasis (*Giardia duodenalis*)
  - Schistosomiasis (*Heterobilharzia americana*)
  - Salmon poisoning disease (*Neorickettsia helminthoeca*)
- Bacterial (rare)
  - Campylobacteriosis
  - Salmonellosis

Chronic intestinal obstruction
- Foreign body
- Intussusception

Endocrine
- Hypoadrenocorticism

Lymphatic disease
- Primary intestinal lymphangiectasia
- Focal lipogranulomatous lymphangitis
- Secondary lymphangiectasia
  - Chronic inflammatory enteropathy
  - Right heart failure
  - Constrictive pericarditis
  - Portal hypertension

BOX 2
Predisposed Dog Breeds

Protein-losing enteropathy (irrespective of histopathologic findings)[1]
- Yorkshire terrier
- Border collie
- German shepherd
- Rottweiler

Primary intestinal lymphangiectasia[2]
- Soft-coated wheaten terrier
- Norwegian lundehund
- Yorkshire terrier
- Maltese
- Chinese Shar-Pei

Breed-specific chronic inflammatory enteropathy
- Immunoproliferative enteropathy ± concurrent protein-losing nephropathy
  - Basenji
- Lymphoplasmacytic enteritis ± lymphangiectasia and transmural lymphangitis ± concurrent protein-losing nephropathy
  - Soft-coated wheaten terrier[3]
- Lacteal and crypt dilation ± crypt abscesses with variable degrees of lymphoplasmacytic ± neutrophilic enteritis
  - Yorkshire terrier[4]

reveal decreased lung sounds secondary to pleural effusion. Peripheral edema and, less commonly, chemosis may also be observed as consequences of hypoalbuminemia.

Diagnostic Approach

The diagnostic approach to a dog suspected of having a PLE focuses on confirming gastrointestinal protein loss, excluding other causes of hypoalbuminemia, and identifying the underlying intestinal disease (**FIGURE 1**).

Confirming Gastrointestinal Protein Loss

Hypoalbuminemia is the hallmark biochemical abnormality of dogs with PLE, but it is not specific and can be secondary to many diseases. The gold standard test to confirm gastrointestinal protein loss, the 51-chromium-labeled albumin clearance test, is impractical for routine clinical use.[13] Fecal α_1 proteinase inhibitor can serve as a surrogate marker because it is lost into the intestinal lumen at a rate similar to albumin and resists degradation; however, the requirement of ≥ 3 fecal samples in preweighted fecal tubes and the potential for false-negative results limit its clinical utility.[14] Given these limitations, and because multiple causes of hypoalbuminemia may

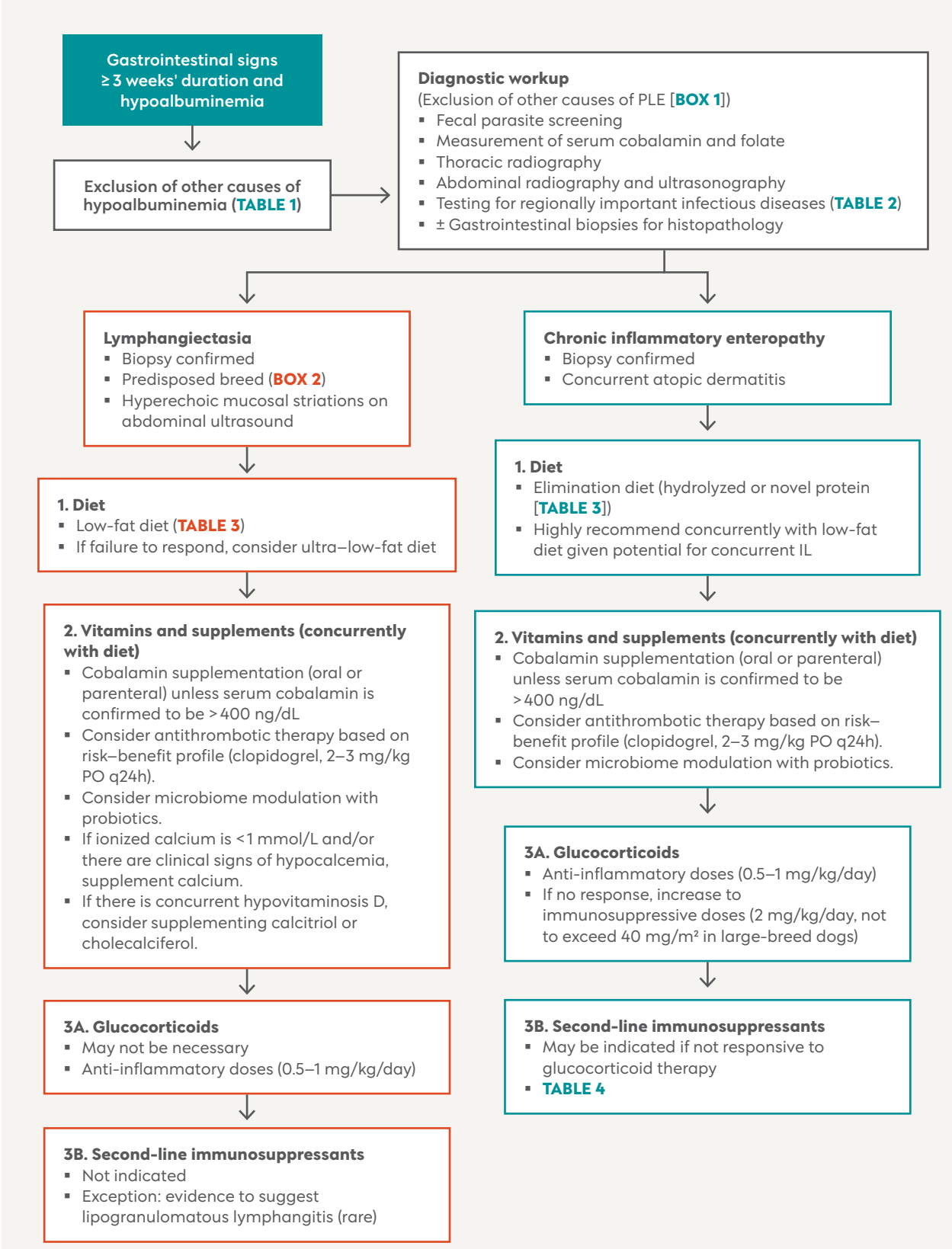

FIGURE 1. Diagnostic and therapeutic approach to canine protein-losing enteropathy (PLE). It is important to note that intestinal lymphangiectasia (IL) and chronic inflammatory enteropathy (CIE) can occur concurrently.

TABLE 1 Causes of Hypoalbuminemia

MECHANISM	DISORDER	TEST(S) FOR EXCLUSION
Albumin loss	▪ Protein-losing enteropathy	▪ Fecal α_1 proteinase inhibitor (false negatives can occur)
	▪ Protein-losing nephropathy	▪ Urinalysis ± urine protein:creatinine ratio
	▪ Hemorrhage	▪ Physical examination including rectal exam, evaluation for cavitary effusions
	▪ Exudative skin disease/burns	▪ Physical examination
	▪ Hypoadrenocorticism	▪ Baseline cortisol ± adrenocorticotropic hormone stimulation test
Decreased albumin production	▪ Liver dysfunction	▪ Bile acid stimulation test
	▪ Chronic systemic inflammation (negative acute-phase protein)	▪ Often concurrent hyperglobulinemia or elevated C-reactive protein concentration ▪ Identification of underlying inflammatory (e.g., pancreatitis) or infectious disease
Albumin sequestration	▪ Peritonitis, vasculitis/vasculopathy	▪ Physical examination, evaluation for cavitary effusions, histopathology for vasculitis lesions

coexist, diagnosing PLE is most often accomplished by systematically excluding nongastrointestinal causes rather than directly confirming intestinal protein loss.

Excluding Other Causes of Hypoalbuminemia

Other causes of hypoalbuminemia must be excluded in dogs with suspected PLE (**TABLE 1**). Although not present in all dogs with PLE, concurrent hypoglobulinemia that causes panhypoproteinemia, particularly in the absence of hemorrhage or exudative skin disease, is highly suggestive of PLE because it cannot be explained by renal or hepatic causes of hypoalbuminemia. Additional laboratory abnormalities noted in dogs with PLE may include lymphopenia, hypocholesterolemia, hypocalcemia, and hypomagnesemia.[11] Some dog breeds (e.g., soft-coated wheaten terrier) are prone to the development of PLE with concurrent protein-losing nephropathy.[3] Consequently, the initial diagnostic workup should evaluate other causes of hypoalbuminemia including proteinuria, liver dysfunction, and hypoadrenocorticism.

A urinalysis is indicated for every dog to evaluate for proteinuria. If proteinuria is detected, it should be quantified via a urine protein:creatinine (UPC) ratio to determine if it is clinically significant. A bile acid stimulation test should be considered to exclude hepatic dysfunction, particularly for dogs with concurrent hypoglycemia, hypocholesterolemia, and/or low blood urea nitrogen.

Because of the role of cortisol in enterocyte function, hypoadrenocorticism can cause PLE. Dogs may exhibit eunatremic, eukalemic hypoadrenocorticism, meaning

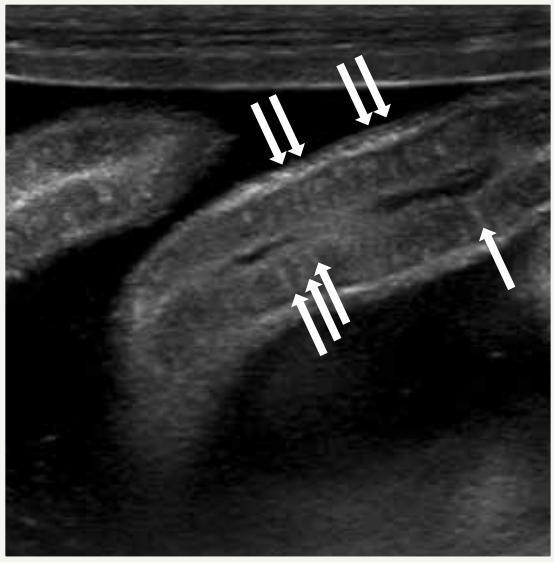

FIGURE 2. Longitudinal axis view of a segment of small intestine of a dog diagnosed with histopathologically-confirmed lymphangiectasia. Note the perpendicularly oriented hyperechoic striations within the mucosal wall **(arrows)**. These hyperechoic striations represent dilated lacteals. The intestinal segments are surrounded by a moderate volume of anechoic abdominal effusion.

TABLE 2 Infectious Causes of Protein-Losing Enteropathy by Geographic Region

INFECTIOUS DISEASE	REGION	TEST
Histoplasmosis (*Histoplasma capsulatum*)	Midwestern and southern United States	Cytology, urine *Histoplasma* enzyme immunoassay, histopathology
Schistosomiasis (*Heterobilharzia americana*)	Gulf coast, southern Atlantic, midwestern and southwestern (lower Colorado River basin) United States	Fecal sedimentation, fecal PCR, histopathology
Salmon poisoning disease (*Neorickettsia helminthoeca*)	Western coast of United States	Fecal sedimentation combined with zinc sulfate centrifugal fecal flotation, cytology, blood or fecal PCR

they do not develop the electrolyte changes expected with mineralocorticoid deficiency.[15] Consequently, every dog with suspected PLE should be screened for hypoadrenocorticism using either an adrenocorticotropic hormone stimulation test or a baseline cortisol concentration.

Identifying the Underlying Intestinal Disease

A thorough diagnostic workup for a dog suspected of having PLE includes a CBC, chemistry panel (including cholesterol, globulin, and electrolytes), urinalysis (as well as UPC ratio, if proteinuria), fecal parasite screening, geographically relevant infectious disease testing, thoracic radiography, abdominal radiography, and abdominal ultrasonography.

Thoracic radiography is useful to screen for evidence of pleural effusion, metastatic disease, or disseminated fungal disease. Abdominal radiography is primarily used to rule out obstruction and evaluate for macroscopic intra-abdominal abnormalities and peritoneal effusion. Abdominal ultrasonography can help identify focal or extraluminal lesions that can be sampled via fine-needle aspirate, which may change the diagnostic approach. In 1 study, 92% of dogs with PLE had abnormalities of the intestinal wall (e.g., stippling, striations, loss of wall layering) on transabdominal ultrasonography.[16] Hyperechoic mucosal striations (**FIGURE 2**) are associated with the histologic finding of lacteal dilation and are 75% sensitive and 96% specific for IL, whereas hyperechoic mucosal speckles are a nonspecific finding that do not reliably distinguish among disease categories (e.g., IL-associated PLE, food-responsive nonhypoalbuminemic CIE, steroid-responsive nonhypoalbuminemic CIE).[17,18]

Infectious disease testing should be performed according to exposure risk, clinical suspicion, and geographic history, including the dog's travel history and origin (**TABLE 2**). In general, a fecal flotation and *Giardia* species antigen testing are recommended for all dogs with suspected PLE.[19]

A definitive diagnosis of PLE requires histologic evaluation of intestinal biopsy samples. Biopsies are often performed earlier for dogs with PLE in comparison to dogs with nonhypoalbuminemic chronic enteropathies. This enables an earlier definitive diagnosis and targeted therapy before a dog's anesthesia risks may be increased due to severe and progressive hypoalbuminemia. Severely hypoalbuminemic dogs may require interventions such as transfusions of canine albumin or plasma to support oncotic pressure and blood pressure during anesthesia.

Histopathology enables the exclusion of infectious and neoplastic causes and helps determine whether a dog is affected by CIE, IL, or both. Although surgical exploration provides the opportunity to biopsy other tissues beyond the gastrointestinal tract (e.g., liver, lymph node) and collect full thickness samples that can be assessed for lesions deeper in the intestinal wall, endoscopy is often preferred. Endoscopy enables direct visualization of the intestinal mucosa and documentation of intestinal mucosal abnormalities (e.g., increased granularity, ulceration, increased friability, dilated lacteals) as well as targeted sampling. Furthermore, given the concern for underlying CIE and the role of albumin in tissue healing, surgery may carry a risk for dehiscence.[20]

In CIE, mucosal inflammation is most often characterized by lymphoplasmacytic infiltrates; granulomatous and eosinophilic infiltrates are rarely

seen. The finding of granulomatous infiltrates should prompt testing for geographically relevant infectious causes, if those have not already been performed.

Classification

PLE is subclassified based on response to dietary intervention (food-responsive PLE), immunosuppressive therapy (immunosuppressant-responsive PLE), or lack of response to dietary or immunosuppressive therapy (nonresponsive PLE).[19] Although biopsies are helpful for ruling out neoplastic and infectious causes as well as determining the predominate disease process (IL or CIE), a diagnosis of CIE does not indicate which subtype of PLE is present and, therefore, what treatment will be effective.

Management

Management of PLE begins with addressing the underlying disease. CIE represents a dysregulated and multifactorial immune-mediated disorder arising from complex interactions among diet, intestinal microbiota, genetic susceptibility, and aberrant mucosal immune responses.[21] Treatment of IL is directed at reducing intestinal lymphatic pressure and minimizing fat malabsorption.[2] Despite these distinct pathophysiologic drivers, management of PLE secondary to CIE and IL overlaps considerably. This convergence reflects the frequent interplay between the 2 processes: Severe CIE can induce secondary IL through inflammatory disruption of the intestinal lacteals; primary IL can promote lymphatic leakage and intestinal inflammation, further amplifying intestinal immune activation.[1,2]

The pathogenesis of PLE results from a complex interplay of environmental factors (e.g., diet, microbiota), genetic predisposition, and dysregulated immune response.[21] Consequently, successful treatment targets 4 different areas: (1) dietary management, (2) correction of vitamin deficiencies,

TABLE 3 Commercial Diets Used in the Management of Protein-Losing Enteropathy

CLASS	DIET	FAT (G/MCAL)	PROTEIN (G/MCAL)	CARBOHYDRATE (G/MCAL)
LF, CP	Royal Canin Gastrointestinal Low Fat dry	20.6	64.6	154.3
LF ± NP* (pork)	Royal Canin Gastrointestinal Low Fat loaf	21.2	79.6	140.1
LF, CP	Hill's i/d Low Fat dry	21	72	163
LF, CP	Purina EN Gastroenteric Low Fat dry	19.5	80.8	157.5
LF, CP	Purina EN Gastroenteric Low Fat wet	24.5	120.5	105.9
ULF, CP (turkey)	Just Food for Dogs Sensitive Stomach fresh frozen	19	56	151
HP (soy), LF	Hill's z/d Low Fat dry	21	77	158
HP (soy), LF	Hill's z/d Low Fat wet	25	81	143
HP (soy), LF	Royal Canin Gastrointestinal Low Fat + Hydrolyzed Protein dry	19.8	70.7	146.1
HP (soy)	Purina HA Hydrolyzed Protein Vegetarian dry	28.1	57.4	159.3
HP-like (amino acids)	Purina EL Elemental dry	26.5	69.7	154
NP* (whitefish)	Royal Canin Selected Protein PW Moderate Calorie dry	29.9	77.3	132.8
NP* (cod), LF	Just Food for Dogs Hepatic Support Low Fat fresh frozen	17.5	52	158

CP = common protein; HP = hydrolyzed protein; LF = low fat; NP = novel protein; ULF = ultralow fat.
[a]Novel protein designation should be determined based on a thorough dietary history, ensuring the protein source has not been previously consumed by the dog. Note: Because of periodic reformation of therapeutic diets, the values presented in this table are intended for general reference only. Macronutrient composition should be verified using the most current manufacturer product guide at the time of diet selection. The Mark Morris Institute Nutrition Guide (markmorrisinstitute.org/nutrition_guide) is a recommended resource for macronutrient information on Hill's, Purina, and Royal Canin diets as well as for sorting diets by a given disease.
[b]This product only has crude fiber listed, not total dietary fiber; therefore, crude fiber is 4.4 g/Mcal.

(3) immune system modulation, and (4) microbiome modulation. Furthermore, these areas can influence each other; for example, diet can alter microbiota and microbiota can influence immune system response.

Dietary Management

Dietary therapy is the cornerstone of PLE management.[22-26] In addition to addressing the underlying intestinal pathology, nutritional intervention is critical as most dogs with PLE are in a catabolic state with negative energy and protein balance resulting from ongoing gastrointestinal protein loss; malabsorption; systemic inflammation; and, frequently, reduced dietary intake. Dietary management alone has been shown to be successful for Yorkshire terriers with PLE as well as various other breeds.[5,22,25] Furthermore, response to diet can be seen quickly, occurring 7 to 30 days following diet change with a median of 15 days for dogs with food-responsive PLE.[5,26,27]

TOTAL DIETARY FIBER (G/MCAL)	CALORIES (KCAL)
24.7	263/cup
27.6	345/can
14	300/cup
17.8	290/cup
29.8	363/can
5.6	39/ounce
26	317/cup
27	342/can
16.7	236/cup
12.4	287/cup
5.8	411/cup
47.3	257/cup
4.4[b]	25/ounce

Dietary management of PLE typically consists of a highly digestible, low-fat diet with adequate protein content. The diet may also need to be hypoallergenic (e.g., novel protein, hydrolyzed) if concurrent CIE is suspected or confirmed. When feasible, dietary selection is guided by the underlying histopathologic diagnosis of IL or CIE, recognizing that they can occur concurrently.

Given the role of intestinal lymphatic vessels in transporting dietary fats, nutritional management of IL focuses on reducing lymphatic pressure by minimizing chylomicron formation through dietary fat restriction (<30 g fat/Mcal of metabolizable energy [ME], ideally <26 g fat/Mcal ME). However, the composition of dietary fat is also important. Diets with slightly higher total fat contents that contain a greater proportion of medium-chain triglycerides (e.g., Purina Pro Plan HA Hydrolyzed Protein Vegetarian) may still be effective for managing PLE. Unlike long-chain triglycerides, which are transported via the lymphatic system, medium-chain triglycerides are more water soluble and can be absorbed directly through enterocytes into portal circulation, bypassing the lymphatic system.[28]

If histopathology is not available, ultrasonographic identification of small intestinal hyperechoic linear striations—suggestive of lymphangiectasia—can support low-fat diet strategies. In a prospective study of 14 dogs with PLE and the ultrasonographic findings, 6 dogs achieved remission with a commercial common protein, low-fat diet alone; an additional 5 dogs entered remission when prednisone was subsequently added.[22] In addition, breed predisposition can be a helpful consideration for diet selection. Yorkshire terriers, which are predisposed to primary IL, can often be managed successfully with a low-fat diet alone, and a novel or hydrolyzed protein source is often not necessary.[24]

For dogs with CIE, an elimination diet—such as a hydrolyzed diet or limited-ingredient novel-protein diet—is often recommended to eliminate dietary antigens and reduce the enteric inflammatory response. Given that 76% of dogs with CIE have concurrent lacteal dilation, a fat-restricted elimination diet is often needed to manage both pathologies concurrently.[29] Notably, IL can be segmental, focal, or only affect the deeper parts of the intestinal wall, which increases the risk for underdiagnosis by routine

mucosal biopsies.[30] Therefore, the author favors prioritizing a highly digestible, low-fat diet for all dogs with PLE and incorporating a concurrent hydrolyzed/novel-protein diet when histopathologic or clinical features (e.g., concurrent skin allergies) support a diagnosis of CIE. Regardless of the strategy, a dog's dietary history should always be carefully reviewed to optimize diet selection.

Several low-fat diets, some with common protein sources and others with novel protein sources, are commercially available (**TABLE 3**). The fat content of most commercially available low-fat diets ranges from 19 to 28 g fat/Mcal ME, which is an appropriate initial choice for most dogs with PLE. However, insufficient dietary fat restriction can be a cause of treatment failure.[23,26] Furthermore, dogs with PLE refractory to prednisone or dependent on high doses of prednisone have shown improvements of clinical signs and biochemical abnormalities after switching to home-prepared ultra–low-fat diets.[23] Therefore, a home-prepared ultra–low-fat diet (<15 g fat/Mcal ME) is recommended for dogs with marked IL or dogs with PLE that are refractory to treatment. Ultra–low-fat diets can be deficient in essential fatty acids; these diets should be balanced, ideally through a board-certified veterinary nutritionist.[2]

Correction of Vitamin Deficiencies

B Vitamins

Hypocobalaminemia is reported in 43% to 75% of dogs with PLE.[31] Cobalamin (vitamin B_{12}) plays a critical role in cellular metabolism, modulation of gut microbiota composition, and mucosal immunity.[32] Consequently, hypocobalaminemia can cause gastrointestinal clinical signs and has been associated with a negative prognosis.[1]

Serum cobalamin concentrations should be assessed in all dogs with PLE. Concentrations <400 ng/dL warrant supplementation, which may be administered orally (cyanocobalamin) or parenterally (cyanocobalamin or hydroxocobalamin). Further information regarding dose, frequency, and administration of cobalamin can be found on the Texas A&M Gastrointestinal Laboratory website (go.navc.com/4ndAxCu). If financial constraints preclude measurement of serum cobalamin, empiric cobalamin supplementation is recommended given its potential benefit, safety, and relatively low cost.

Folate (vitamin B_9) may be below, within, or above the reference range in dogs with PLE.[11] A benefit of supplementing folic acid has not been clearly demonstrated; however, oral supplementation may be considered.

Vitamin D

Biochemistry panels of dogs with PLE may reveal decreased total serum calcium and/or magnesium.[11,33] Although a decrease in total calcium is expected from the reduction in protein-bound calcium with hypoalbuminemia, ionized hypocalcemia is frequently present in dogs with PLE.[34,35] Ionized hypocalcemia in dogs with PLE occurs secondary to decreased serum 25-hydroxyvitamin D concentration, which has been well-documented in dogs with PLE.[33,36] Although incompletely understood, the pathogenesis of hypovitaminosis D in PLE is likely multifactorial and related to malabsorption, systemic inflammation, and gastrointestinal loss.[33,37] Hypovitaminosis D can lead to clinically significant ionized hypocalcemia, which may manifest as muscle tremors, stiff gait, facial rubbing, biting or licking the paws, or seizures. A lower 25-hydroxyvitamin D concentration at diagnosis has been associated with a worse outcome.[38]

Calcium supplementation should be considered for patients with clinical signs and/or an ionized calcium <1 mmol/L.[39] Oral supplementation with calcium carbonate (25 to 50 mg/kg/day) is sufficient for most patients. However, for critically ill dogs or dogs unable to tolerate oral administration of medications (e.g., seizing), parenteral administration of 10% calcium gluconate (0.5 to 1 mL/kg IV, given slowly over 10 to 30 minutes while monitoring heart rate and, ideally, electrocardiography) is recommended.

The indications, dosing strategy, and benefits of vitamin D supplementation of dogs with PLE have yet to be clearly established. In a randomized, double-double blinded, controlled trial of dogs with PLE and hypovitaminosis D, cholecalciferol supplementation conferred no observed clinical benefit; 80% of placebo-treated dogs had normalization of 25-hydroxyvitamin D concentrations by the end of the study, suggesting that successful treatment of the underlying intestinal disease alone may resolve hypovitaminosis D.[40] The

author considers oral vitamin D supplementation with cholecalciferol (300 to 400 IU/kg q24h) or calcitriol (20 to 30 ng/kg q24h for 3 days, followed by a maintenance dose of 5 to 15 ng/kg q24h) for dogs with documented hypovitaminosis D and an ionized calcium <1 mmol/L. Given the risk for hypervitaminosis D documented with this supplementation dose, serial monitoring of serum vitamin D and ionized calcium concentrations is essential. Repeated assessment of vitamin D concentrations and ionized calcium may be financially burdensome or impractical for some clients, which should be considered when developing a supplementation plan.

Immune System Modulation

Although the pathogenesis of CIE is not fully understood, an immune response to dietary, microbial, or environmental antigens is likely a factor. Of the dogs with CIE, including those with and without hypoproteinemia, 38% to 89% respond to dietary modification.[19] For those that fail to respond to diet alone, immunomodulatory treatment is indicated. Primary IL is a diet-responsive disease with no evidence of an immune process. However, IL can be associated with lymphangitis and lymph leakage, which can induce secondary CIE. Therefore, immunomodulatory treatment may be indicated for a subset of dogs with IL.

Immunosuppression is not benign. The adverse effects of glucocorticoid therapy for dogs with PLE can be profound and, in some dogs, worsen the catabolic and hypercoagulable state.[12,41] The lowest effective dose to achieve clinical control should be used. Once remission is established, a gradual taper should be pursued to minimize adverse effects while maintaining disease control.

The author prefers to initiate therapy with close monitoring and dietary management alone, then institute immunomodulatory therapy if there is no response within 7 to 10 days of initiating dietary therapy. However, the risk–benefit profile favors starting glucocorticoids concurrently with dietary therapy for dogs with severe clinical signs and poor appetites that limit reliable intake of the recommended diet, or when close monitoring, serial biochemistry assessment, and follow-up are not feasible. In these situations, administering glucocorticoids alongside dietary therapy is a reasonable alternative. Once a clinical response has been observed, the glucocorticoid dose can be tapered by 25% every 3 to 4 weeks.

Glucocorticoids

Dogs with CIE-PLE that have either partially or not responded adequately to dietary therapy should be treated with prednisone or prednisolone. Anti-inflammatory to immunosuppressive doses (0.5 to 2 mg/kg/day, not to exceed 40 mg/m^2 in large-breed dogs) of prednisone are recommended for dogs with CIE-PLE that have failed to respond to dietary therapy. For dogs with IL and suspected secondary CIE, anti-inflammatory doses (0.5 to 1 mg/kg/day) of prednisone are likely sufficient to decrease inflammation associated with lymph leakage and granuloma formation. Dogs with lipogranulomatous lymphangitis, a PLE disease characterized by the formation of lipogranulomas secondary to chronic lipid-rich chyle leakage through dilated or ruptured vessels, may require higher doses of prednisone or prednisolone (1 to 2 mg/kg/day).[42]

Impaired intestinal absorption of glucocorticoids has been proposed as a potential cause of treatment failure of dogs with PLE, prompting some clinicians to initiate parenteral therapy or transition from oral to parenteral formulations in dogs with inadequate responses.[1] However, no current evidence supports switching from oral to parenteral glucocorticoid administration.[43]

Secondary Agents

Dogs with PLE that have failed dietary interventions alongside glucocorticoid treatment may benefit from treatment with secondary immunosuppressants. These therapies include cyclosporine USP-modified preparation (5 mg/kg PO q24h) as a monotherapy or combined with glucocorticoids, or chlorambucil (2 to 6 mg/m^2 PO q24h) as a monotherapy or combined with prednisone or prednisolone (**TABLE 4**).[19] Mycophenolate

TABLE 4 Second-Line Immunosuppressive Medications for Treatment of Protein-Losing Enteropathy

DRUG	DOSE
Cyclosporine USP-modified preparation	5 mg/kg PO q24h[10,11]
Chlorambucil	2–6 mg/m^2 q24h[12]

is generally avoided because it inhibits the purine synthesis pathway, which enterocytes rely on for rapid turnover.[44] Careful monitoring for adverse effects (e.g., myelosuppression with chlorambucil) is imperative when prescribing immunosuppressive agents.

Literature comparing treatment protocols for dogs with PLE remains limited. In the only study directly comparing combination immunosuppressive protocols, prednisone plus chlorambucil was associated with a longer median survival time than prednisone plus azathioprine.[12] To date, no studies have compared the efficacy of chlorambucil to cyclosporine.

Second-line immunosuppressive agents do not always confer additional benefit. In 1 study, the addition of cyclosporine to prednisolone did not improve response rates or survival times compared to prednisolone alone.[11]

Microbiome Modulation

Dogs with PLE can develop an altered enteric microbiota (i.e., intestinal dysbiosis).[45] Empirical antibiotic treatment (e.g., tylosin) is no longer recommended given the high relapse rates and long-term negative effects on the microbiome.[19] Instead, probiotics or fecal microbiota transplantation (FMT) are recommended.

Probiotics

No studies evaluate the use of probiotics for dogs with PLE managed under standardized treatment protocols, which limits the interpretation of clinical benefit. The effects of probiotics are strain-specific, and they may be beneficial if given concurrently with dietary management and with or without immunomodulatory treatment. To date, 2 commercial probiotic products have shown potential benefit for canine CIE. The yeast probiotic *Saccharomyces boulardii* has been shown to improve the Canine Chronic Enteropathy Clinical Activity Index (CCECAI) score, stool frequency, stool consistency, and body condition score of dogs with CIE with and without concurrent hypoproteinemia.[46] In addition, the De Simone probiotic mixture (Visbiome, ExiGI Pharma) has been shown to increase the mucosal expression of tight junction proteins in dogs with CIE, improving intestinal barrier function.[47,48]

Fecal Microbiota Transplantation

FMT can be considered an adjunctive treatment for dogs with PLE that have not achieved or maintained clinical remission with other treatments.[49,50] In 1 study of dogs with CIE, including some with and without PLE that were refractory or partially refractive to standard therapy, FMT resulted in clinical improvement in 72% of dogs and a sustained response in 51% of dogs. Furthermore, administration of FMT permitted glucocorticoid reduction in more than half of the dogs that demonstrated a clinical response.[49]

Adjunctive Therapy

Anticoagulant Therapy

Severe CIE is linked to thrombocytosis and hypercoagulability (63% to 100% of dogs with PLE), predisposing thromboembolic complications.[51,52] This hypercoagulability has been shown to improve following successful disease management.[52] Based on the 2022 CURATIVE (Consensus on the Rational Use of Antithrombotics and Thrombolytics in Veterinary Critical Care) Guidelines, dogs with PLE are classified as "high risk" for thrombosis.[53] Therefore, additional treatment considerations for dogs with PLE include the use of anticoagulants unless the risk for gastrointestinal bleeding outweighs the potential benefits. Although insufficient evidence exists to recommend an ideal thromboprophylaxis protocol, most dogs are administered clopidogrel (2 to 3 mg/kg PO q24h).[19] Clopidogrel is often discontinued once the serum albumin level is >2.5 g/dL. Given the risk for gastrointestinal bleeding, particularly in dogs concurrently receiving prednisone, and the limited options available to manage diffuse gastrointestinal hemorrhage, the author reserves clopidogrel for dogs with marked systemic inflammation and presumed increased thrombotic risk or for those with clinical suspicion or confirmed evidence of thromboembolism or infarction.

Supportive Care

Medications such as maropitant (2 mg/kg PO q24h) may be used to reduce vomiting. Effusions in the abdomen or thorax should be drained only if they cause discomfort or respiratory compromise as doing so can worsen electrolyte disturbances. Diuretics are generally discouraged because they may exacerbate electrolyte imbalances and promote dehydration.

Fluid therapy should be administered judiciously given the risk for third-spacing in patients with severe hypoalbuminemia. Plasma transfusions or canine albumin provide transient benefits for dogs with PLE and, therefore, should be reserved for critically unwell patients such as those with hypotension or those requiring anesthesia (e.g., for feeding tube placement or endoscopy). Plasma therapy is often unpractical; large volumes (20 to 30 mL/kg) are required to raise albumin by 0.5 g/dL. Furthermore, infused proteins may leak into the diseased gastrointestinal tract, potentially exacerbating the loss of lymph and immune system components.[1] Therefore, their use should be restricted to carefully selected dogs at high risk.

Monitoring and Defining Clinical Remission

The CCECAI is a valuable tool for monitoring PLE. This scoring system integrates clinical signs (e.g., attitude/activity, appetite, vomiting, stool consistency, stool frequency, weight loss) with 3 additional factors associated with prognosis: serum albumin concentration, pruritus, and evidence of peripheral edema and/or ascites.[10] In most clinical trials, response to therapy is defined as >50% reduction in the initial score (partial response) or a final CCECAI score ≤3. This index is routinely used to assess treatment response of dogs with PLE. Although normalization of serum albumin into the laboratory reference range is often desired, this may not be achievable or necessary for all dogs. In practice, a serum albumin ≥2.5 g/dL is considered acceptable when clinical signs are well-controlled.

Refractory Cases

Some dogs with PLE have minimal response to initial management with diet, anti-inflammatory or immunosuppressive doses of glucocorticoids, and/or second-line immunosuppressive medications. For these dogs, tapering the medications and focusing on dietary management are recommended. In 1 study, 8 out of 10 dogs with PLE that failed to respond to combination therapy with diet, glucocorticoids, and/or second-line immunosuppressive agents experienced clinical remission when switched to another diet.[26] Therefore, in refractory cases, a dietary adjustment, ideally by consulting a board-certified veterinary nutritionist, is strongly recommended.

Because adverse food reactions can arise through multiple mechanisms, a single diet trial cannot exclude all possibilities. One study found that 63% of dogs with food-responsive CIE failed at least 1 diet trial despite ultimately responding to diet; some dogs may undergo 3 therapeutic diet trials before a response is noted.[54,55] Therefore, if an inadequate response occurs, another diet should be considered. For dogs in which plasma albumin levels have normalized and all clinical signs have resolved except for persistent soft stool, fiber supplementation is recommended rather than considering further immunosuppression or a different diet.

Prognosis

PLE carries a guarded prognosis with a pooled fatality rate of 54% across 445 cases.[1] In 1 study, the in-hospital mortality rate was 22%; the most common causes of death or euthanasia included financial limitations, failure to improve, and aspiration pneumonia.[56] Early treatment response appears to be an important prognostic indicator.[57] However, despite some dogs responding to initial treatment, relapse remains common. In 1 study of dogs with CIE-PLE, poor dietary compliance was associated with relapse, supporting long-term adherence to dietary management.[58] Shifting the therapeutic focus away from routine immunosuppression of dogs with PLE and toward strategic dietary management may be critical for achieving successful outcomes.

Summary

PLE is a heterogenous syndrome of dogs characterized by excessive enteric protein loss, most commonly associated with IL, CIE, or a combination of both. Diagnosis requires the exclusion of other causes of hypoalbuminemia followed by a systematic evaluation to determine the underlying etiology. Because CIE arises from a complex interplay among diet, microbiome, host factors, and immune dysregulation, no single therapy is uniformly effective. Treatment should target these interrelated factors: diet, micronutrient status, immune modulation, and microbial balance. Management of PLE should be individualized, with dietary modification forming the foundation of therapy. TVP

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CE Quiz Questions

1. **In evaluating a dog with suspected protein-losing enteropathy (PLE), which of the following tests should be performed to help exclude nongastrointestinal causes of hypoalbuminemia?**
   a. Pancreatic lipase immunoreactivity
   b. Resting cortisol with or without adrenocorticotropic hormone stimulation test
   c. Serum trypsin-like immunoreactivity
   d. Urine blastomycosis antigen

2. **Which of the following is most important for the management of intestinal lymphangiectasia?**
   a. Antibiotics
   b. Cyclosporine
   c. Dietary fat restriction
   d. Immunosuppressive doses of glucocorticoids

3. **Which ultrasonographic finding is most strongly associated with intestinal lymphangiectasia?**
   a. Hyperechoic mucosal striations
   b. Intestinal corrugation
   c. Loss of intestinal wall layering
   d. Marked intestinal wall thickening

4. **Dietary management of most dogs with PLE should initially emphasize which of the following strategies?**
   a. High-carbohydrate, calorically dense diet
   b. Highly digestible, fat-restricted diet
   c. High-protein, high-fat diet
   d. Minimally processed raw diet

5. **Dogs with PLE are considered at a high risk for which of the following complications?**
   a. Constipation
   b. Hypoglycemia
   c. Pancreatitis
   d. Thromboembolism