

# Proceedings of the World Small Animal Veterinary Association Sydney, Australia – 2007

Hosted by:



Australian Small Animal  
Veterinary Association  
(ASAVA)



Australian Small Animal  
Veterinary Association  
(ASAVA)



Australian Small Animal  
Veterinary Association  
(ASAVA)

## Next WSAVA Congress

33rd Annual  
World Small Animal  
Veterinary Association  
14th FECAVA  
Congress

**DUBLIN, IRELAND**  
**20th - 24th August 2008**



## DIAGNOSIS AND MANAGEMENT OF PROTEIN-LOSING ENTEROPATHIES

Stanley L. Marks, BVSc, PhD, DACVIM (Internal Medicine, Oncology),  
DACVN  
University  
of California, Davis, School of Veterinary Medicine, Davis, CA, USA

Protein-losing enteropathy (PLE) is a syndrome caused by a variety of gastrointestinal diseases causing the enteric loss of albumin and globulin.<sup>1,2</sup> Intestinal inflammation, infiltration, ulceration, blood loss, and primary or secondary lymphangiectasia are well documented causes of PLE (Table 1). If left untreated, the final outcome of PLE is panhypoproteinemia with decreased intravascular oncotic pressure and the development of abdominal and pleural effusion, peripheral oedema, and death. An important sequel to PLE includes thromboembolic disease secondary to the loss of antithrombin. Protein-losing enteropathy is uncommon in cats, and most cats with PLE are diagnosed with intestinal lymphoma or severe IBD.

### Diagnostic Approach

In some animals, weight loss is the only initial symptom of PLE because the syndrome can also occur in dogs without clinical signs of gastrointestinal disease.<sup>1</sup> The signalment of the animal is important as certain breeds such as the Yorkshire Terrier, Soft-Coated Wheaten Terrier, Norwegian Lundehund, and Basenji are predisposed to PLE. Standard laboratory investigations include a *complete blood count (CBC), serum biochemistry profile, and urinalysis*. Lymphopenia is often associated with PLE secondary to lymphangiectasia. Serum albumin and total protein should be carefully evaluated in all patients with a history of weight loss, anorexia, vomiting or diarrhoea. Although PLE is typically associated with panhypoproteinemia, the absence of hypoglobulinemia does not preclude a diagnosis of PLE because there are numerous reasons for increased production of globulin in dogs (e.g., intestinal histoplasmosis or pythiosis). Additional abnormalities found on the serum biochemistry profile in association with PLE include hypocholesterolemia (secondary to malabsorption) and hypocalcemia. The causes for the hypocalcemia are multifactorial and include hypoalbuminemia (affects total calcium), decreased absorption of vitamin D, and malabsorption of magnesium. Magnesium has been shown to be pivotal for the activation of PTH in the parathyroid gland, increasing the renal and skeletal tissue responsiveness to PTH, and activation of vitamin D.<sup>3</sup> Yorkshire terriers with PLE are apparently 9.2 X more likely to develop hypomagnasemia and hypovitaminosis D compared to other canine breeds.<sup>3</sup> Measurement of *total and ionized serum magnesium* is recommended in animals with gastrointestinal disease and hypocalcemia. A faecal flotation should be routinely performed in all diarrheic animals to help rule out intestinal parasites (e.g., Hookworms) which may contribute to the loss of protein.

Once hypoalbuminemia has been documented, the cause must be identified. Important considerations for hypoalbuminemia include protein-losing enteropathy, hepatic insufficiency, protein-losing nephropathy (PLN), vasculitis, exudative skin lesions, exocrine pancreatic insufficiency (EPI), and

Addison's disease. Dogs with concurrent liver disease and intestinal disease can prove challenging, in that disorders of both organs can be associated with hypoalbuminemia. Protein-losing nephropathy can be easily eliminated from the differential list by performing a urinalysis and determining the *urine protein:creatinine ratio* if the animal is proteinuric. Caution should be heeded in the interpretation of mild increases in the UPC ratio, as animals with active urine sediment can also have a mild increase in the UPC ratio in the absence of glomerular disease. In addition, most patients with proteinuria tend to exhibit hypoalbuminemia in the presence of normo- or mild hyperglobulinemia. Dogs with Cushing's disease or dogs receiving exogenous steroids can also have abnormal UPC ratios. Once PLN has been ruled out based on the urinalysis, further evaluation of hepatic function should be determined to help rule out hepatic insufficiency as the cause for the hypoalbuminemia. Careful evaluation of hepatocellular function parameters (BUN, cholesterol, glucose, albumin, and bilirubin) on the chemistry panel should be performed before measurement of *serum bile acids*. Interpretation of liver enzyme values (ALT, AST, GGT, and ALP) should be done with caution as many dogs with severe liver disease do not have marked elevations in hepatocellular enzymes. Elevations in serum bile acid concentrations are not pathognomonic for hepatic insufficiency, as nonhepatic diseases are well documented at increasing serum bile acids (intestinal disease, pancreatitis, anemia, diabetes mellitus, etc). Occasionally, biopsy of the liver and intestinal tract is required to differentiate primary liver disease from reactive hepatopathies. Laboratory assessment of EPI can be performed by measuring concentrations of canine *trypsinogen-like immunoreactivity (cTLI)*, and evaluation of the small intestinal absorptive function can be evaluated by measuring concentrations of *serum cobalamin and folate*. Dogs that are severely hypocalcemic should be further evaluated to determine the cause for the low calcium.

Measurement of *faecal  $\alpha$ 1-proteinase inhibitor ( $\alpha$ 1-PI)* can be used to further support a diagnosis of PLE in animals with concurrent liver disease or PLN, although this test is limited by logistical constraints in that samples must be shipped frozen, and there is currently only one laboratory that performs the ELISA at Texas A & M University.<sup>4</sup>  $\alpha$ 1-proteinase inhibitor is the same size as albumin and is lost in the intestinal tract and excreted via the feces where it can be measured as a marker for PLE. Three separate voided faecal specimens are collected into special volume-calibrated cups available from the laboratory. It is important that the faecal specimens be naturally voided as digital extraction of the faecal specimen can result in microscopic blood loss and false elevations in faecal  $\alpha$ 1-PI. The faecal specimens should be immediately frozen after collection and shipped on ice via overnight mail to the laboratory.

Abdominal imaging via *ultrasonography* can be particularly helpful to further elucidate the cause of PLE, as many dogs with intestinal lymphangiectasia show evidence of hyperechoic mucosal striations secondary to lacteal dilation.<sup>5</sup> In addition, abdominal ultrasonography can be helpful for aspirating abdominal fluid for cytological characterization.

Most dogs with PLE require *intestinal biopsies* to confirm the diagnosis, and empiric dietary and medical trials that are commonly utilized for dogs with no evidence of panhypoproteinemia are typically avoided in an effort to procure a specific diagnosis as soon as possible. Gastroduodenoscopy and biopsy can be used to diagnose lymphangiectasia in most patients if appropriate biopsy technique is utilized and biopsies of the duodenum and ileum are obtained. Gastroduodenoscopy also affords one the opportunity to evaluate the intestinal mucosa for erythema and dilated lacteals that are filled with chyle. Occasionally the dilated lymphatics are located below the mucosal layer and can be missed endoscopically despite the implementation of appropriate biopsy technique. Exploratory laparotomy and biopsy affords one the luxury of full-thickness biopsies that are usually easier for pathologists to interpret; however, the disease can be patchy or multifocal underscoring the importance of obtaining multiple full-thickness biopsies from the duodenum, jejunum, and ileum. Lipogranulomas are commonly seen on the serosal aspect of the intestine in dogs with lymphangiectasia. Caution should be heeded when performing full-thickness biopsies in animals that are hypoproteinemic with ascites. These patients are at increased risk for dehiscence, and implementation of nonabsorbable or poorly absorbable suture should limit the risk of suture line leakage.

### **Management of PLE**

The goal of therapy for intestinal lymphangiectasia is to decrease the enteric loss of plasma protein, resolve associated intestinal or lymphatic inflammation, and control effusion or oedema. The prognosis for PLE is guarded because of the variable underlying causes and severity of the disease when diagnosed.

#### Medical Management

Parenteral fluid therapy: Administration of *colloids* such as Dextran 70 or Hetastarch can be used to increase the plasma oncotic pressure in animals that are severely hypoalbuminemic. This is typically administered prior to surgery in an effort to minimize complications associated with low plasma colloidal oncotic pressure. The administration of fresh frozen plasma is an expensive and less efficient means of increasing the COP in dogs that are severely hypoalbuminemic. Parenteral fluid therapy can be discontinued when the albumin is > 1.5 g/dl and any ascites or peripheral oedema has resolved. Loop diuretics such as *furosemide* (1-2 mg/kg, SC or PO) can be used to decrease abdominal or pleural effusions, although caution should be heeded in monitoring the patient's hydration status and serum potassium concentrations. Potassium sparing diuretics such as *spironolactone* (2-4 mg/kg PO or IV) can be used together with furosemide to decrease the likelihood of hypokalemia arising.

Most dogs with lymphangiectasia do not warrant anti-inflammatory therapy, unless the intestinal biopsies show evidence of moderate to severe intestinal inflammation with the lymphangiectasia. In these animals a tapering dose of *prednisone* or *prednisolone* can be administered starting at 1-2 mg/kg BID with a gradual taper over the ensuing 8-12 weeks. Large-breed dogs can be

started on *azathioprine* concurrent with the prednisone in an effort to reduce the amount of steroid administered and decrease adverse effects. Azathioprine is administered to dogs at a dosage of 1-2 mg/kg SID for 10-14 days, followed by 1-2 mg/kg every second day. Prednisone dosage is typically reduced by 50% if administered concurrently with azathioprine. In dogs with severe malabsorption, orally administered prednisone is unlikely to be absorbed properly, and one should administer the prednisone parenterally for the first week before switching to oral administration. A recently published study documented the therapeutic benefit of *cyclosporine* (5 mg/kg SID for dogs with IBD refractory to prednisone therapy).<sup>6</sup> *Cobalamin* (*vitamin B12*) should be administered parenterally in all dogs with subnormal serum cobalamin concentrations. The author administers cobalamin at a dose of 500 to 1000 µg per dog SC once weekly for 6 weeks. Readministration of cobalamin should be based on reevaluation of serum cobalamin concentrations and resolution of clinical signs. Patients that are severely hypocalcemic (despite attempted correction for the hypoalbuminemia) should be considered for parenteral magnesium supplementation in the form of magnesium sulphate at 1 mEq/kg/day. *Magnesium* can also be supplemented orally as magnesium hydroxide (milk of magnesia) at a dosage of 5-15 ml per dog/24 hrs. *Antibiotics* such as metronidazole (10 mg/kg BID) or tylosin (20 mg/kg BID) both for 3 weeks are often administered to dogs with IBD.

#### Dietary Management

Severe dietary fat restriction is one of the most important aspects in the management of dogs with intestinal lymphangiectasia. Diets that are highly digestible and that contain < 20% fat calories on an ME basis are recommended.<sup>7</sup> The author recommends the feeding of a premium commercial-based diet if possible; however, there are a small number of dogs with severe lymphangiectasia that will need further fat restriction than that provided in commercial diets, and home-cooked diets are warranted. These home-cooked diets should be made up by a veterinary nutritionist to ensure that the diets are complete and balanced. Dogs with concurrent IBD and lymphangiectasia are more challenging to manage from a dietary perspective, because these animals need a novel, select protein source diet that is also markedly fat restricted and virtually all commercial diets do not fit these criteria. An alternative to consider is the use of hypoallergenic diets containing hydrolyzed protein sources and moderate amounts of dietary fat. Failure to respond favorably to these diets warrants a home-cooked diet that is more fat-restricted and contains a novel, select protein source. Administration of medium chain triglycerides (MCT's) to enhance the caloric density of the diet are not recommended due to their unpleasant taste and potential for inducing diarrhoea. Recent evidence also suggests that MCT's are not transported entirely via the portal circulation to the liver, and can exacerbate the lymphangiectasia. Total *parenteral nutrition* can be administered to cachectic animals with severe hypoalbuminemia and intractable vomiting or diarrhoea.

#### **References:**

1. Petersen PB, Willard MD. Vet Clin Am Small Anim Pract 2003;33:1061-82.
2. Kull PA, et al. J Am Vet Med Assoc 2001;15;219(2):197-202.
3. Kimmel SE, Waddell LS, Michel KE. J Am Vet Med Assoc 2000;217:703-706.
4. Murphy KF, et al. Vet Clin Pathol 2003;32(2):67-72.
5. Sutherland-Smith J, et al. 2007;48(1):51-7.
6. Allenspach K, et al. J Vet Intern Med 2006;20(2):239-44.
7. Marks SL, Fascetti AJ. Nutritional management of diarrhoeal disease. In: Kirk's Current Veterinary Therapy XIII. Editors, Bonagura J.D; 2000;653-658.

**Table 1**  
**Causes of Protein-Losing-Enteropathy (PLE)**

A. Diseases affecting intestinal lymphatic drainage

Primary lymphangiectasia

- Congenital or idiopathic acquired
- Breed predisposition
  - Yorkshire Terrier
  - Maltese Terrier
  - Norwegian Lundehund
  - Soft Coated Wheaten Terrier\*
  - Poodle

Secondary lymphangiectasia

- IBD
- Neoplasia
- Congestion secondary to right-sided heart failure or portal hypertension

B. Acute or chronic inflammatory diseases that result in increased mucosal

permeability to protein

- Inflammatory bowel disease (eosinophilic or lymphoplasmacytic enteritis)
- Granulomatous enteritis (histoplasmosis, Pythiosis)
- Intestinal neoplasia, (lymphoma, carcinoma)
- Immunoproliferative enteropathy of Basenjis
- Parasitic enteritis in young animals
- Villous atrophy, gluten enteropathy, certain viral and bacterial enteritides
- Chronic obstruction or intussusception

C. Gastrointestinal Blood Loss

- Bleeding tumors
- Ulceration/erosion
- Intestinal parasites (Hookworms)

\* Soft Coated Wheaten Terriers develop PLE and PLN (protein-losing nephropathy).

