World Small Animal Veterinary Association World Congress Proceedings, 2013

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Protein losing enteropathy (PLE) is the loss of proteins, most commonly albumin, via the gastrointestinal tract. Hypoalbuminaemia most commonly combined with hypoglobulinaemia in an animal with diarrhoea and or vomiting suggests PLE. A lack of GI signs does not eliminate PLE as a differential for low plasma protein concentration. Panhypoproteinaemia is highly suggestive of gastrointestinal loss of both albumin and globulin, but the concentration of globulins can vary with PLE.

Pathophysiology

In the normal dog, protein is normally lost into the GI tract, digested into amino acids, and then re-absorbed again. In the patient with PLE, this normal loss of plasma proteins can be enhanced by the damaged mucosa or even more by increased leakage of lymph into the GI lumen. Many GI diseases, either acute or chronic, can result in PLE if it is severe enough. The following mechanisms may explain the protein loss:

- Cardiac failure or lymphatic obstruction interfere with the reabsorbing mechanisms.
- Mucosal damage can lead to protein loss into the intestinal lumen quicker than the normal reabsorption.
- Dilated intestinal crypts can be associated with PLE even without major lesions in the intestinal mucosa.

GI protein loss is commonly both albumin and globulins. When albumin is lost into the gut, the liver can increase its synthesis of albumin remarkably. However, albumin loss greater than the degree of albumin synthesis results in hypoalbuminemia. Globulin will most commonly also be lost, but plasma globulin concentration can vary from low to normal to elevated depending on the underlying disease. With an antigenic stimulation, the synthesis of globulins may be equal or even exceed the loss of globulins into the GI tract.

Hypoalbuminaemia, and more so hypoproteinaemia, results in decreased oncotic pressure that may lead to loss of fluid into a body cavity effusion. Subsequent ascites, pleural effusion, and/or peripheral oedema may result. Another potential complicating factor is the loss of antithrombin III (AT-III), which can result in a hypercoagulable state. Marked loss of AT-III is uncommon in PLE compared to patients with protein losing nephropathy.

Causes of PLE

Any GI disease can cause PLE if it is severe enough. Chronic GI diseases that may

cause PLE include inflammatory bowel disease (IBD), neoplasia (particularly lymphoma), lymphangiectasia, histoplasmosis, GI parasites, and pythiosis. Other causes include alimentary tract ulceration/erosion, severe disease of intestinal crypts, and antibiotic-responsive enteropathy. The major causes of PLE in juvenile dogs tend to be parasites and chronic intussusception. All of these cause primarily small-bowel diarrhoea, but may sometimes also cause vomiting or large-bowel diarrhoea. Not uncommonly, GI signs may be absent or anorexia and abdominal pain can be found. Acute GI diseases (e.g., parvovirosis) can also cause PLE. These are generally easier to treat than chronic GI diseases and are potentially reversible. Congestive heart failure may interfere with the reabsorbing mechanisms of the lymphatic system, which can lead to lymphatic hypertension and eventually to PLE.

Diagnostic Approach to PLE Patient

A CBC usually shows nonspecific changes with the exception of lymphopaenia that is often seen with lymphangiectasia. A regenerative anaemia may be seen with gastrointestinal blood loss; however, as the PLE progresses, the anaemia may become non-regenerative and even hypochromic/microcytic due to iron deficiency.

The serum biochemistry profile shows a low albumin concentration. Globulin concentrations are commonly decreased, but may be normal or even increased depending on the cause and severity of the PLE. Furthermore, hypocholesterolaemia, hypomagnesaemia, hypocalcaemia (pseudo or true), and variable elevations in liver enzyme concentrations may be present. To rule out PLE, a urinalysis should always be performed with the measurement of a protein-creatinine ratio. If it is unclear whether the clinical signs and the hypoalbuminaemia could be due to a hepatopathy, liver function tests (e.g., pre and postprandial bile acids or an ammonia tolerance test) are sometimes indicated.

Faecal alpha-1 protease inhibitor (alpha-1 PI) concentration may be elevated. This test detects loss of alpha-1 PI in faeces. Alpha-1 PI is a plasma protein with a molecular weight similar to that of albumin. Unlike albumin, it is not degraded by enzymes in the GI tract and is excreted in the feces essentially intact. Species-specific assays are necessary and one has been developed for use in dogs (Texas A&M University, GI lab).

Serum cobalamin concentrations may be abnormal. If present, this needs to be addressed therapeutically.

The ultrasonographic appearance of streaks in the submucosa is considered diagnostic for PLE, but not all cases of PLE have this change. Ultrasound-guided fine needle aspiration may be attempted in cases with markedly thickened bowel wall before intestinal biopsies are taken. Abdominal ultrasound is the preferred way to diagnose intussusceptions, especially if they are difficult to palpate. Abdominal radiographs or barium contrast studies are not sensitive for PLE.

When PLE has been diagnosed based on laboratory and diagnostic imaging results, intestinal biopsy is the ultimate means of establishing a diagnosis. Biopsies can be taken surgically, via laparoscopy, or via endoscopy. Feeding some cream or corn oil the night before the procedure might improve the diagnosis of lymphangiectasia. Flexible endoscopy should be performed by a skilled person who can pass the pylorus with confidence and take deep/adequate biopsies. A definitive diagnosis can often be achieved with this technique. If flexible endoscopy is done, one should biopsy both the duodenum and ileum. It is not necessary to enter the ileum with the endoscope to

obtain a good tissue sample of the ileal mucosa.

Laparotomy and laparoscopy are good means of obtaining diagnostic samples, but it is surprisingly easy to procure non-diagnostic samples with these techniques. Endoscopy does have the advantage of allowing one to visualize mucosal lesions that are "invisible" when looking at the serosa. In some cases, the diagnosis can only be obtained by biopsy of these focal lesions. If full-thickness biopsies are obtained in severely hypoalbuminaemic animals, serosal patch grafting will minimize the risk of suture line leakage. A nonabsorbable or poorly absorbable suture (such as PDS) should also be used.

Treatment/Management

- Treat the underlying disease. This might not be easily possible or delayed (wait for biopsy results). In the meantime, supportive care is necessary (see below).
- Depending on the clinical signs (ascites, oedema), it may be necessary to give colloids intravenously. Colloid solutions, in contrast to crystalloids (sodium-based or glucose- based electrolyte solutions) contain molecules large enough so they cannot leave the vasculature. Colloid solutions, therefore, have the same effect as plasma albumin that is holding water within the vascular compartment. Examples of synthetic colloid solutions include dextrans and hydroxyethyl starch (Hetastarch).
  Hetastarch: 20 ml/kg per 24 hours or give it over 4-6 hours. Hetastarch is usually preferred because it is bigger than the dextrans.
- Plasma may be necessary in emergency situations, but unfortunately in patients with PLE, transfused plasma is almost invariably completely ineffective as the donated albumin will continue to leak out of the damaged gut.
  Plasma: (10-20 ml/kg over 2-3 hours). It is very unlikely that plasma will raise albumin level significantly, if at all.
- Human albumin: while quite expensive, this is the best option in the short-term when clinical signs are severe, or shortly before a surgical procedure is planned. As this is a foreign protein, severe reactions are possible and repeated administration is contraindicated.
  - **Dose calculation (don't exceed 2g/kg/day)**:
    - Albumin deficit (grams) = 10 x (albumin desired (g/L) - current albumin (g/L)) X kg x 0.3
    - BW (kg) x volume distribution (45 ml/kg) x deficit (2.0 g/dl - patient)(1000 mg/g)(dl/100 ml) x albumin concentration (ml/mg)
    - 1.5 g/kg
    - 1-2 ml/kg of 25% solution
- If ascites or pleural fluid is interfering with respirations or causing discomfort, manual draining may be necessary. Unfortunately, unless effective specific therapy is used, the fluid tends to come back shortly after drainage. Repeated body cavity drainage might result in dehydration and hypovolaemia due to excessive fluid loss, and also carries a significant risk of causing secondary bacterial pleuritis or peritonitis. Thus, drainage should only be performed when very large volumes of body cavity fluid are present.
- Diuretics (spironolactone plus/minus furosemide) don't work well in dogs with PLE. Nonetheless, in cases with severe effusion, spironolactone can be tried,

sometimes combined with furosemide. Be aware of the potential to dehydrate the patient. Spironolactone: 2 mg/kg PO q 8-12 h. Add furosemide at 2 mg/kg PO q 8-12 h.

- Patients with PLE may also lose antithrombin III and might be at risk for hypercoagulability. A platelet aggregation inhibitor may be needed in rare instances. We often combine
  - Aspirin: 0.5 mg/kg PO q 12 h and
  - Clopidogrel bisulfate: 3-5 mg/kg PO q 24 h
- Dietary management: most patients will benefit from an ultralow fat diet. If possible, combine with a novel, protein-antigen source (e.g., white turkey). Medium-chain triglyceride supplementation is no longer advocated.

Speaker Information

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