

## **PROTEIN-LOSING ENTEROPATHY IN DOGS: ANY CHANCE OF A GOOD OUTCOME?**

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### **INTRODUCTION**

Protein losing enteropathy (PLE) is characterized by loss of proteins through the intestinal tract. Primary intestinal disease causing PLE mainly consists of lymphangiectasia, inflammatory bowel disease, crypt lesions and intestinal mucosal ulcerative damage. Gastrointestinal disease accompanied by hypoalbuminemia has been shown to have a guarded prognosis,<sup>1,2</sup> but there is little published information on survival or optimal treatment. Furthermore, although many studies have been published on inflammatory bowel disease including subsets of dogs suffering from PLE, there is very little literature available on large groups of dogs with PLE.

For these reasons, the most recent literature available on protein losing enteropathies in dogs will be reviewed, but recently published abstracts will also be included.

### **SURVIVAL**

Although hypoalbuminemia has been recognized as a negative prognostic factor in dogs with chronic enteropathies (CE), there are very few published studies looking specifically at survival of dogs suffering from PLE. Other parameters which have been associated with a poor outcome in dogs with CE include hypocobalaminaemia and hypovitaminosis. In dogs with PLE the presence of crypt abscesses is a negative prognostic indicator.<sup>1-4</sup>

Typically, prognosis is considered guarded in dogs with PLE and median survival times (MST) of less than 6 months or a 1-year survival of less than 50% have been reported in several publications.<sup>5-8</sup> However, two abstracts report MST over a year in some dogs.<sup>4,9</sup>

Some information is also available specifically for Yorkshire Terriers. One retrospective study reported long-term responders in Yorkshire terriers treated with prednisolone in conjunction with diet and metronidazole (12 out of 23 dogs with a MST of 44 months).<sup>10</sup> The response to diet alone has also been reported in one retrospective study (presented as an abstract).<sup>11</sup> The authors reported complete resolution of clinical signs with dietary management alone in 8 out of 11 Yorkshire terriers with a follow up period of 4 to 26 months (Dr Gilor, personal communication). Diets used included home-cooked diet, low fat diet, and hydrolysed diet.

### **DIET**

Typically, dogs with PLE undergo endoscopy at time of diagnosis because of their guarded prognosis and expected need for aggressive treatment with a combination of dietary modification and immunosuppression.

However, in the retrospective study in Yorkshire terriers mentioned earlier, some dogs responded to diet alone and the author has observed the same effect sporadically in other breeds. The central question is to determine which dogs can be trialed on diet alone knowing that the disease could progress rapidly and be fatal. The author will consider a diet trial only in dogs that are clinically well and have a good appetite. If there is no response within a week consisting of improvement in the clinical signs AND increase in the albumin, or if the animal deteriorates, more aggressive treatment is warranted. Biopsies should also be obtained (if not already performed) at this point to determine the underlying histopathological changes and rule out neoplastic disease.

If the histopathologic findings are consistent with primary lymphangiectasia alone, good success has been reported with an ultra-low fat diet.<sup>12</sup> However, lymphatic leakage can be a trigger for inflammation that can worsen the clinical signs over time. For this reason corticosteroids are often used concurrently until the clinical signs are controlled. One retrospective study analysed the outcomes in dogs with lymphangiectasia fed either a low fat diet or ultra-low fat diet.<sup>13</sup> These dogs were also treated with prednisolone and metronidazole. During the study time (2 months), no difference was seen in outcome between the two types of diet, with 79% of dogs improving. Dogs fed the ultra-low fat diet had significantly higher albumin concentrations at the end of the study. This study was not designed to look at the effect of diet alone, but supports the use of diet in the management of these cases.

## ANTIBIOTICS

Although anecdotally a few antibiotic-responsive PLE dogs have been reported,<sup>14</sup> there is no information available on the use of antibiotics alone for PLE treatment. In one abstract, there was no evidence of bacterial association with crypt pathology in Yorkshire terriers.<sup>15</sup> In rare cases with predominance of granulomatous or neutrophilic inflammation, antibiotic coverage should be considered. Ideally, tissue culture or fluorescence in situ hybridisation (FISH) should be used to confirm a bacterial component to the disease. FISH is a very sensitive method to identify bacteria in tissue, which can be used on formalin-fixed samples. Presence of invasive bacteria in the intestinal wall would be an indication for antibiotic treatment.

Currently, the role of antibiotic therapy is very poorly understood in dogs with PLE and there are concerns that their use can trigger chronic dysbiosis. Future studies looking at bacterial association with PLE and antibiotic treatment response are needed to assess the role of antibiotics in PLE treatment.

## IMMUNOSUPPRESSANTS

Prednisolone is typically used as first line treatment in dogs with PLE and is often combined with other immunosuppressive drugs because of the guarded prognosis and desire for a steroid-sparing effect. The most commonly used immunosuppressive drugs for dogs with PLE are listed in table 1.

One retrospective study compared PLE dogs treated with either azathioprine or chlorambucil.<sup>16</sup> Biopsies were obtained from all dogs and were consistent with CE. None of these dogs were diagnosed with a neoplastic process, more specifically small cell lymphoma (SCL), although no specific testing such as clonality or immunohistochemistry was performed. Dogs diagnosed in the first part of the study were treated with a combination of prednisolone and azathioprine (group A) and dogs diagnosed in the second part of the study were treated with prednisolone and chlorambucil (group C). Dogs in group C remained on their first treatment (253 days (d) [5 to 494]) longer than dogs in Group A (median: 30d [range 2 to 599]). When all censored dogs (dogs still alive at the end of the study) were taken into account as treatment failures (worst case scenario), 6-month survival rate was 15% in group A and 79% in group C. Although this study had several limitations (retrospective nature, historical case controls, absence of diet standardisation), the difference in outcome between both groups was striking. A prospective study is necessary to confirm these findings.

Another interesting retrospective study assessed prognostic factors in dogs with PLE.<sup>17</sup> Final diagnosis (using a combination of histology, immunohistochemistry and clonality testing) was CE or lymphangiectasia in 62 dogs and SCL in 19 dogs. PLE dogs with a diagnosis of SCL had a significantly worse prognosis than dogs with CE or IL (MST<500d versus >1,000d). Clonality, suggestive of SCL, was also found to be a significant negative prognostic factor (regardless of the group) with a MST of less than 200d compared to over 1,000d in the absence of clonality. Although SCL has been recognised in cats, it is not as well defined in dogs. Overall, the findings of these two studies are suggestive that a subset of dogs develops PLE secondary to SCL, which could explain the guarded prognosis reported in some studies and the favourable response to chlorambucil compared with azathioprine. The challenge remains in diagnosing these dogs, which is likely to require additional techniques to histology such as immunohistochemistry and clonality testing. The latter can be done using polymerase chain reaction (PCR) for antigen receptor rearrangements on biopsy samples.

Other treatments reported in non-responders include cyclosporine. This treatment has been used in PLE dogs refractory to steroid treatment with long-term (3 years) improvement in 7 out of 10 dogs in one study.<sup>1</sup> Another study also reports the use of cyclosporine in refractory cases, but only 1 out of 4 dogs responded.<sup>16</sup>

## CONCLUSION

There is currently a lack of studies comparing different therapies for PLE and more research is needed to determine the best treatment modality. Some dogs might respond to dietary modification alone, but the challenge is to identify which dogs will do so.

Various immunosuppressant drugs have been used in dogs with PLE. Cyclosporine holds some promise as a rescue agent in dogs that fail prednisolone therapy and chlorambucil seems more effective than azathioprine. Chlorambucil might also have a role to play as more evidence is accumulating that a subset of PLE dogs are likely to have SCL. The first challenge here is to reach a definitive diagnosis of this condition.

**Table 1.** List of immunosuppressive drugs used to treat dogs with chronic enteropathy.

Drug	Type	Dosage
<b>Prednisolone</b> <sup>1</sup>	Corticosteroid	2mg/kg or <b>30mg/m<sup>2</sup></b> , total dose, orally
<b>Cyclosporine</b>	Cyclophilin binder	5mg/kg, every 24 hours, orally
<b>Chlorambucil</b> <sup>2,3</sup>	Alkylating agent	<b>4mg/m<sup>2</sup></b> , every 24 hours, orally
<b>Azathioprine</b> <sup>2,3</sup>	Purine antagonist	2mg/kg, every 24 hours, orally for 2 weeks, then 2mg/kg, every 48 hours, orally
<b>Mycophenolate</b>	Guanosine nucleotide synthesis inhibitor	10mg/kg, every 12 hours, orally

Dose per square metres is bolded. (1) A dosage in square metres (30mg/m<sup>2</sup>) rather than kilograms is recommended in dogs over 20 kg as they are very sensitive to side effects. (2) Tablets should not be split. (3) Administer with gloves.

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