

Canine chronic enteropathy

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Categories : [Companion animal](#), [Vets](#)

Date : March 20, 2017

ABSTRACT

Chronic enteropathy is a common presenting complaint in practice and can be subdivided based on the response to treatment. The aetiology is complex, but the loss of immunologic tolerance to luminal antigens is likely to be a key component that results from altered immunity, abnormal mucosal barrier and the impact of the intestinal environment (such as food or bacteria).

A logical approach to investigation and treatment, prioritised based on clinical severity, allows good control of clinical signs in most cases. However, this disease can be challenging and a small percentage of cases will be unresponsive to treatment. Dietary manipulation, and modulation of the intestinal microbiota and the immune system are all key components of therapy and different approaches exist to each of these areas.

A number of new options for therapy are under investigation and it is hoped these will offer treatments that can improve quality of life for patients and reduce the adverse effects that can be experienced with existing approaches.

Chronic gastrointestinal disease (defined as greater than three weeks' duration) is a common presenting complaint in practice, with typical signs including diarrhoea, vomiting, weight loss and change of appetite.

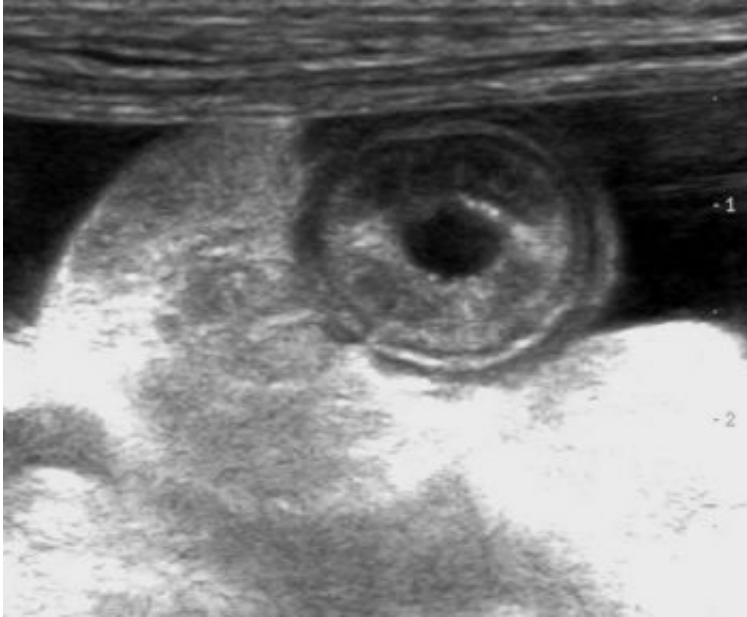


Figure 1. An ultrasonographic image of the canine small intestine showing hyperechoic mucosal striations. This finding may be associated with lacteal dilation.

A logical approach to investigations allows an accurate diagnosis in most cases; however, some confusion exists over the most appropriate terms to use for this spectrum of diseases.

The term chronic enteropathy (CE) is preferred to inflammatory bowel disease as it recognises the difference between these diseases in our patients compared to humans – namely that most dogs with this disease will not require immunosuppressant therapy (Dandrieux, 2016). Chronic enteropathy can then be subdivided, based on response to treatment, into the following categories:

- food-responsive enteropathy
- antibiotic-responsive enteropathy, or small intestinal dysbiosis
- immunosuppressant-responsive enteropathy

A further group, known as protein-losing enteropathy (PLE), exists to describe dogs with enteric protein loss. This is typically seen in dogs with more severe inflammatory disease, gastrointestinal lymphoma or lymphangiectasia.

Aetiology

The specific steps that lead to inflammation of the gastrointestinal tract – and, consequently, chronic enteropathy – are not known. However, the breakdown of immunologic tolerance to luminal antigens (including bacterial and dietary components) is likely to be critical – this may result from disruption of the mucosal barrier, immune dysregulation (Burgener et al, 2008) or disturbance in the intestinal microbiota (Xenoulis et al, 2008).

The role of genetics in CE is supported by recognised breed predispositions and the identification of specific genetic variations in, for example, toll-like receptors (Kathrani et al, 2010), while the role of the microbiota and dietary antigens is supported by the observed response to antibiotics and dietary trials respectively, as well as the changes in microbiota seen in many dogs with CE.

Irrespective of the specific causative agent, the end result is gastrointestinal inflammation, which leads to the observed clinical signs.

Panel 1. A standardised approach to chronic enteropathy

1. Clinical history and examination

- Large intestinal localisation (dyschezia, tenesmus, increased frequency of defecation, small volume of faeces, mucus and blood)
- Small intestinal localisation (large volume diarrhoea, weight loss and vomiting).
- Melaena (suggesting upper gastrointestinal [GI] bleeding/ulceration)
- Abdominal pain (uncommon in chronic enteropathy, raising suspicion of pancreatic disease, structural disorders and perforation)

2. Detection of endoparasites and enteric pathogens

- Faecal analysis (including Giardia)

3. Clinicopathological testing

- Detection of non-GI disease
 - Haematology
 - Biochemistry, including canine pancreatic lipase immunoreactivity/1,2-O-dilauryl-rac-glycero-3-glutaric acid-(6-methylresorufin ester) lipase
 - Urinalysis
 - Basal cortisol/adrenocorticotrophic hormone stimulation test
- Detection and characterisation of GI disease
 - Trypsin-like immunoreactivity
 - Folate and cobalamin

4. Diagnostic imaging

- Radiographs – structural GI disease
- Abdominal ultrasound – obstruction, intussusception, focal masses, thickening, intestinal

layering and hyperechoic striations

5. Clinical staging based on disease activity index

6. Trial treatments

Diagnosis

A standardised approach to CE has been described (Simpson, 2012). This offers clinicians a logical method of investigating these cases, allowing exclusion of extra-gastrointestinal disease, characterisation of the nature and severity of disease and pathways for treatment based on this severity assessment (**Panel 1**).

Like many medical cases, this begins with a careful clinical history and examination to localise the clinical signs (large intestinal or small intestinal) and to assess for any atypical signs that might prompt consideration of other diseases. Localisation is important as it allows us to refine our differential diagnosis list and helps guide biopsy location, should this be necessary.

The next stages include faecal analysis (if considered appropriate) and clinicopathological testing. The latter of these is important to exclude extra-gastrointestinal diseases (pancreatic, hepatic, renal and so on) and to aid in the characterisation of gastrointestinal disease. Exocrine pancreatic insufficiency (EPI) is an important differential for CE and can be reliably excluded in most cases through measurement of trypsin-like immunoreactivity (TLI). Folate and cobalamin are absorbed in the proximal and distal small intestine respectively; measurement, therefore, again assists with localising disease and is also an important factor in treatment.

Some controversy exists over the role of faecal analysis in most patients, as positive results may or may not be significant and can, therefore, mislead the clinician, and false negatives are common with *Giardia*. Infectious agents are much more commonly implicated in young animals, immunosuppressed animals or with acute gastrointestinal disease. The author does not routinely perform faecal analysis in adult dogs with CE, but does routinely administer fenbendazole at 50mg/kg by mouth for seven days to cover for *Giardia*.

Diagnostic imaging – in particular, abdominal ultrasound (**Figure 1**) – is a further useful tool. This allows assessment of the gastrointestinal wall thickness (which can be compared to published reference ranges) and layering, as well as assessment of the organs intimately associated with the gastrointestinal tract (such as the pancreas, liver or biliary tract). While many CE cases can have minimal changes on ultrasound, certain findings (such as loss of wall layering or lymphadenopathy)

might raise the clinical suspicion of neoplasia.

At this point in the investigations, clinical staging is performed to categorise the severity of the disease and this dictates the order in which treatment trials or further investigation are performed (**Figure 2**). It is important to note histology has not been shown to help differentiate between the different disease categories and, therefore, in animals with low severity scores, biopsy should be reserved for patients that have failed appropriate therapeutic trials.

Clinical staging is best achieved through use of validated scoring systems (**Table 1**) – for example, the Canine Chronic Enteropathy Activity Index (CCEAI; Allenspach et al, 2007). This gives a score from 0 to 3 on a range of clinical signs or biochemical markers to give an overall severity score out of 27. A score of:

- 0 to 3 would be classed as insignificant disease
- 4 to 5 as mild disease
- 6 to 8 as moderate disease
- 9 to 11 as severe disease
- greater than 12 as very severe disease

A classification of very severe disease has been shown to be a predictor of a negative outcome. Other reported negative prognostic factors include hypocobalaminaemia, hypoalbuminaemia, hypovitaminosis D and elevated c-reactive protein.

Should gastrointestinal biopsy be necessary, these can be obtained by endoscopy (**Figure 3**) or laparotomy, with the former preferred if significant hypoalbuminaemia is present. Whichever method is chosen, biopsies should ideally be obtained from as many locations as possible within the gastrointestinal tract to ensure changes are representative of the disease (the author routinely biopsies the stomach, duodenum, ileum and colon, unless imaging/clinicopathological testing suggests a more focal disease). Biopsy samples are assessed for the severity of inflammation and any structural changes. In addition, this step is crucial in excluding other diseases with a similar clinical presentation to CE – for example, gastrointestinal lymphoma and histiocytic ulcerative colitis.

Treatment

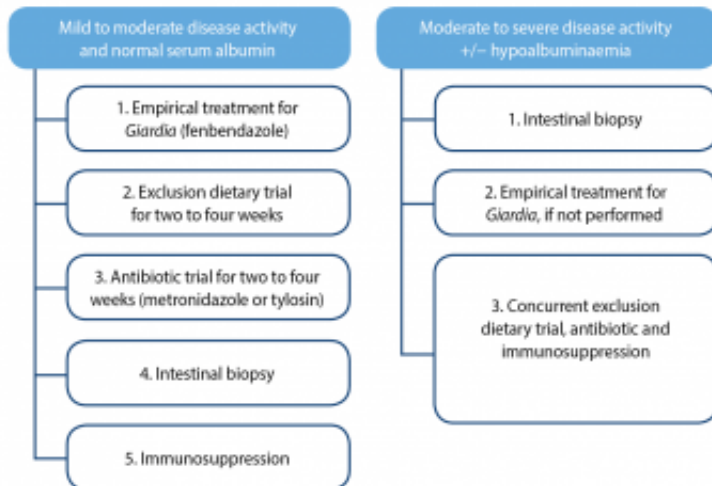


Figure 2. Treatment of chronic enteropathy based on clinical severity.

The choice of exclusion diet trial is largely a matter of clinician preference, with the main options being a commercial hydrolysed diet, commercial novel protein diet or home-cooked novel protein diet. The latter of these should be formulated by a nutritionist unless only fed for a short period of time. While hydrolysed diets have proved popular for this purpose, it should be noted some patients still react to proteins even after hydrolysatation and the author therefore favours hydrolysed diets based on novel protein sources – for example, soya protein.

Some controversy also exists about the use of antibiotics (especially long term) in CE cases as this may be at odds with responsible antibiotic guidance. This decision is ultimately up to the individual clinician's preference; however, for some patients, antibiotics offer the only effective treatment for their clinical signs. Metronidazole (10mg/kg by mouth every 12 hours) or tylosin (25mg/kg by mouth every 12 hours) are the most commonly used antibiotics for this purpose.

A number of options exist for immunosuppression in dogs, and each have their benefits and potential adverse effects. Glucocorticoids – usually prednisolone – are typically used in most cases as a first line treatment at 1mg/kg/day to 2mg/kg/day. While this drug is often effective, the catabolic effects can lead to unwanted clinical signs in already cachexic patients. This can be reduced by using budesonide – a glucocorticoid with extensive first pass metabolism and, therefore, reduced systemic side effects; however, the response can be variable and severity of adverse effects similar in some patients.

Alternatively, other immunosuppressant medications can be used in addition to glucocorticoids, allowing a more rapid dose reduction. The author uses either ciclosporin (at 5mg/kg every 12 to 24 hours) or chlorambucil (at 4mg/m²/day to 6mg/m²/day initially) most commonly for this purpose – both of which can then be tapered over a period of months. However, choice of adjunctive medication is largely a matter of personal preference as published comparative studies are lacking. Azathioprine can also be useful when finances are limited, but has become less popular after some

evidence suggesting worse outcomes with the use of this drug (Dandrieux et al, 2013).

As previously mentioned, cobalamin supplementation is also a vital component of treatment if identified as hypcobalaminaemia, as it reduces the effectiveness of other treatments. Traditionally, this has been with injectable therapy; however, evidence suggests oral supplementation is effective in many cases (Toresson et al, 2016). The use of antithrombotics – for example, ultra low dose aspirin – should also be considered in PLE due to the risk of thromboembolic disease. The use of probiotics is an area of some controversy and is discussed later in this article.

Short-term supportive treatments can also be useful in some cases, including antacids, antiemetics, prokinetics and mucosal protectants. Some clinicians elect to use gastroprotectants routinely during administration of glucocorticoids; however, no evidence exists to suggest they reduce the risk of adverse effects.

Monitoring and prognosis

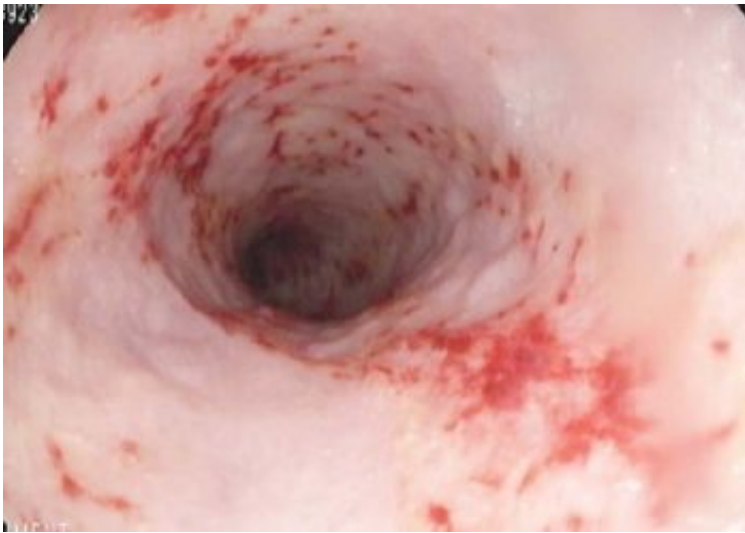


Figure 3. An endoscopic view of the canine duodenum showing multiple areas of ulceration. Biopsy showed a moderate eosinophilic enteritis.

Close monitoring is important over the first few months of treatment to make decisions regarding treatment escalation or de-escalation. These decisions can be guided by a number of factors – the most important of which is clinical response (such as control of clinical signs or weight gain).

Repeat clinical severity scoring, using the CCEAI, gives a more objective measure of response and aids client compliance by highlighting areas of improvement. These results are supported by monitoring of serum proteins – especially in PLE cases. It is possible other more objective markers – for example, the acute phase protein or c-reactive protein – may also be useful in this context, but

this is still under investigation.

Should there be a poor clinical response then treatment is typically escalated by the addition of immunosuppression (or an adjunctive immunosuppressant if glucocorticoids are already being used). Clinicians should also consider reassessment to ensure poor response is not due to an unidentified complication (such as malignancy or hypocobalaminemia).

If a positive response to treatment is seen then treatment is typically tapered over a period of months whilst monitoring clinical signs. The requirement for long-term therapy can be very variable between different patients with most cases requiring some degree of life-long intervention.

When retrospectively reviewed, the expected response to this standardised approach is dependent on the presence or absence of PLE. In dogs with a normal serum albumin, approximately 75% will be diet-responsive, 15% antibiotic-responsive and 10% immunosuppressant-responsive. In dogs with low serum albumin, 35% were controlled with diet long-term, 35% required long-term immunosuppression and 30% died or were euthanised.

Overall, the literature suggests 10% to 20% of CE cases will die or be euthanised as a result of their condition.

New treatments

Table 1. The Canine Chronic Enteropathy Activity Index

Category	Description	Score	Total
Attitude/activity	Normal	0	
	Slightly decreased	1	
	Moderately decreased	2	
	Severely decreased	3	
Appetite	Normal	0	
	Slightly decreased	1	
	Moderately decreased	2	
	Severely decreased	3	
Vomiting	Normal	0	
	Mild (<1x/week)	1	
	Moderate (2x/week to 3x/week)	2	
	Severe (>3x/week)	3	
Stool consistency	Normal	0	
	Slightly soft faeces	1	
	Very soft faeces	2	
	Watery diarrhoea	3	
Stool frequency	Normal	0	
	Slightly increased (2 x/d to 3x/d or blood/mucal/both)	1	
	Moderately increased (4x/d to 5x/d)	2	
	Severely increased (>6x/d)	3	
Weight loss	None	0	
	Mild (<5%)	1	
	Moderate (5% to 10%)	2	
	Severe (>10%)	3	
Albumin levels	Albumin >30g/L	0	
	Albumin 15g/L to 18.9g/L	1	
	Albumin 12g/L to 14.9g/L	2	
	Albumin <12g/L	3	
Acute/peripheral oedema	None	0	
	Mild acute/peripheral oedema	1	
	Moderate acute/peripheral oedema	2	
	Severe acute/plaosal effusion/peripheral oedema	3	
Pruritus	No pruritus	0	
	Occasional itching	1	
	Regular itching, but sleeps when asleep	2	
	Regularly wakes up due to itching	3	
Total score			

Almqvist et al 2007

Table 1. The Canine Chronic Enteropathy Activity Index.

Improved understanding of the factors involved in CE has led to interest in a number of new treatment areas. The most exciting of these is probably the role of the microbiota in gastrointestinal – and, indeed, systemic – health.

Improved techniques for bacterial identification have allowed us to demonstrate dysbiosis in many dogs with CE; however, whether this is a cause or effect of the disease is not entirely clear at this time. We also presume the response of many dogs to antibiotics is due to the changes in the microbiota seen with these drugs. However, concerns about long-term antibiotic use has prompted investigation of other methods of achieving the same results. The two main treatments with this aim are the use of probiotics or the use of faecal transplantation.

A huge number of probiotic (or prebiotic/synbiotic) products are available on the market and often seem an attractive option to pet owners. Some evidence exists, based on a small number of dogs, that these could have some benefit in CE cases (Rossi et al, 2014). However, the true content of many of these preparations is questionable (Weese and Martin, 2011) and the author's clinical experience disappointing. Some cases exist that seem to have a positive response and, as our ability to better characterise dysbiosis improves, it may allow more accurate identification of such cases. At this time, not enough evidence exists to advise routine use of these treatments or guide which products are most appropriate.

Faecal transplantation has gained interest in human medicine for treatment of certain challenging gastrointestinal diseases – for example, *Clostridium difficile*. Preliminary studies in dogs suggest faecal transplantation can lead to alteration of the microbiota and improved clinical signs in some dogs; however, in the majority of cases, this benefit is short-lived (lasting weeks to months). Again, it is likely case selection is crucial to this technique and is a work in progress in several centres.

Other areas of interest in CE include the development of new immunosuppressants and the role of bile acid malabsorption in poorly responsive cases.

Conclusions

CE is a common presentation in practice, but, with a logical approach to diagnosis and treatment, a positive response can be seen in most patients.

- Some drugs mentioned in this article are used under the cascade.

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