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Topic Overview

Most cases of chronic diarrhea fall under the umbrella term "chronic inflammatory enteropathy," a wide spectrum of heterogenous and ill-defined gastrointestinal disorders diagnosed according to persistent gastrointestinal signs and clinical response to therapy. Most cases are food-responsive, and diet trials usually lead to clinical improvement and/or remission. Yet when clinical signs persist, a multimodal treatment approach combining diet modifications and microbiota modulation therapies (e.g., fiber supplementation, probiotic supplementation, fecal microbiota transplantation) may be necessary to achieve complete clinical remission.

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GASTROENTEROLOGY

Multimodal Treatment Approach to Dogs With Chronic Diarrhea and the Role of the Microbiome

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Chronic diarrhea (duration of more than 3 weeks) affects dogs of all ages and can be caused by a variety of factors. Infectious causes (e.g., parasites, enteropathogens) are frequently suspected, yet recently reported rates (2.5% to 6%) show that infectious causes are relatively rare.[1,2] In most cases of chronic diarrhea, a specific cause cannot be identified; these cases are classified as chronic inflammatory enteropathy (CIE), which represents a group of gastrointestinal (GI) disorders that are heterogenous, ill-defined, and classified by clinical signs and response to treatment trials.

The major subtypes of CIE are food-responsive enteropathy (FRE) and steroid-responsive enteropathy (SRE), with FRE being the most common.[3] A previously reported subgroup, termed "antibiotic-responsive enteropathy," has fallen out of favor because it represents a very small subset of disorders with poor long-term responses. Antibiotics may improve or resolve diarrhea, but they cause severe dysbiosis and do not support GI function. Furthermore, these disorders would most likely respond to therapies other than antibiotics. For example, in a recent study that included 60 dogs with CIE, almost all dogs had either FRE or SRE and none required antibiotics.[4] Furthermore, antibiotics such as

Learning Objectives

- A thorough diet history, inclusive of treats, is pivotal for assessing and managing chronic inflammatory enteropathy in dogs.
- Multiple diet trials are the cornerstones of therapy for most cases of chronic inflammatory enteropathy.
- Antibiotics may improve or resolve diarrhea, but they cause severe dysbiosis and do not support gastrointestinal function. A relapse of diarrhea often follows discontinuation of antibiotics.
- Dysbiosis reflects an abnormal gut environment, and the dysbiosis index grades the severity of microbiome shift.
- A fecal microbiota transplantation can be useful adjunct therapy for a dog with chronic inflammatory enteropathy.

metronidazole and tylosin induce severe microbiome dysbiosis that can persist for several months.[5] Because microbiome function is an integral part of GI physiology and dysbiosis is present in a large subset of dogs with CIE, the current recommendation is to avoid antibiotic administration and instead beneficially modulate the microbiome.[6]

The pathophysiology of CIE is multifactorial. Recent data suggest that CIE is a combination of intestinal dysbiosis and inflammation as well as disruption of the protective mucus layer, which leads to increased permeability.[3] The extent of the intestinal changes varies between individual dogs. For example, approximately 40% of dogs with CIE have decreased serum cobalamin concentration, which is associated with intestinal malabsorption.[7] The dysbiosis index (DI), an indicator of a negative shift of the microbiome, is increased in approximately 50% to 70% of dogs with CIE.[8] The different underlying yet overlapping pathologies explain the heterogenous responses to different treatment trials and the potential requisite for multimodal therapy.

This article reviews the interactions between diet, intestinal function, and microbiome and provides a case example of CIE that illustrates how a combination of diet modifications and repeated fecal microbiota transplantations (FMTs) can improve the outcome.

DIET, INTESTINAL FUNCTION, AND MICROBIOME

Diet

The intestinal microbiota respond to dietary substrates; the digestibility and fiber content of a diet contribute to intestinal function. Thus, most dogs with CIE clinically improve with diet modifications. Multiple studies including highly digestible diets, hydrolyzed protein diets, and fiber-enriched diets have demonstrated clinical remission in dogs with CIE.[9,10]

Overall, while not completely understood, it is assumed that highly digestible diets reduce the residual dietary substrate in the intestinal lumen. Hydrolyzed protein diets are highly digestible and have shown positive long-term outcomes when fed to dogs with FRE.[10]

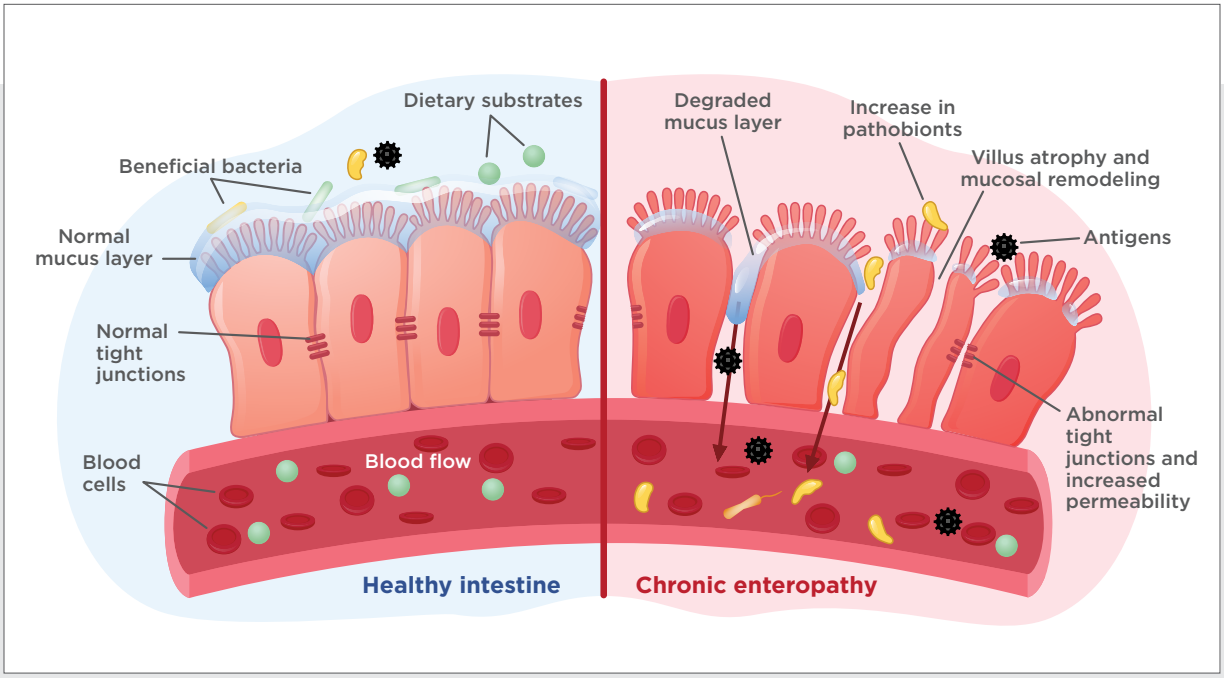

FIGURE 1. A healthy intestine **(left)** features a diverse microbiome, an established mucus layer that separates luminal bacteria from epithelial cells, a functioning epithelial barrier, and a regulated immune system. In cases of chronic inflammatory enteropathy **(right)**, several changes can occur, each potentially contributing to clinical signs. The loss of mucus allows luminal bacteria to adhere to epithelial cells, triggering proinflammatory signals. Damage to the epithelial barrier facilitates translocation of luminal antigens. A reduction of brush border transporters leads to malabsorption of nutrients, which provides a substrate for bacterial growth. Inflammation and nutrient malabsorption contribute to intestinal dysbiosis.

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Fiber-enriched diets are also typically highly digestible; fiber supplements such as psyllium husk bind water, encourage fecal bulk, and modulate the microbiota.[11] A recently published article in this journal discusses the various diets and their indications for dogs with CIE.[11] Nevertheless, there are not clear indicators of the best diet for each dog. Therefore, current recommendations include multiple diet trials for dogs with no other signs of systemic disease.[9,12]

Intestinal Function

In a healthy GI tract, dietary nutrients are broken down into smaller compounds that are subsequently absorbed by the brush border of the small intestine (**FIGURE 1**). Intestinal bacteria then metabolize some of these dietary substrates (e.g., fiber, protein, fat); the metabolites serve as an energy source and provide immunomodulatory benefits in addition to regulating motility and improving the gut barrier. Because the intestinal microbiota are in contact with intestinal epithelium and dietary substrates in the intestinal lumen, intestinal environment changes affect the microbiota composition.

Microbiome

In physiologic amounts and appropriate ratios, intestinal microbes act as immunomodulatory signaling molecules that regulate and suppress potential pathobionts such as *Clostridium perfringens* and *Escherichia coli*.[13,14] Some bacteria species widely recognized as key are typically present in higher numbers in healthy dogs.[15] For example, *Faecalibacterium* are beneficial bacteria that ferment dietary carbohydrates into immunomodulatory short-chain fatty acids.[16] Another physiologic function of bacteria is conversion of intestinal bile acids.[13] Primary bile acids are made by the liver and released into the small intestine; in the large intestine, microbes convert a small percentage of primary bile acids to secondary bile acids. *Peptacetobacter*, also known as *Clostridium, hiranonis* is the major bile acid converter for dogs. A decrease in this beneficial species indicates irregular bile acid conversion, contributes to an abnormal intestinal microbiome, and serves as a marker of intestinal dysbiosis.[14,17] Dysbiosis is a biomarker of an abnormal gut environment, indicating alterations of microbial metabolites associated with intestinal health (e.g., short-chain fatty acids, bile acids). An altered microbiota can further exacerbate the clinical signs of CIE in some dogs.

In dogs, a DI score from 0 through 2 indicates a mild to moderate microbiome shift and a DI score above 2 indicates significant dysbiosis.

Chronic intestinal inflammation may lead to structural changes of the intestinal epithelium, ultimately leading to altered expression of transporters responsible for nutrient absorption.[18] For instance, dogs with CIE often have decreased bile acid transporters in the ileum, which corresponds to altered fecal bile acid metabolism (i.e., increased fecal primary bile acids), decreased *P hiranonis*, and ultimately dysbiosis.[19] Fecal bile acid dysmetabolism with a loss of *P hiranonis* is a common feature of dogs with intestinal dysbiosis and CIE.[8,14] Additionally, other dietary compounds (e.g., long-chain fatty acids, amino acids, carbohydrates) are increased in the fecal samples of some dogs with CIE, indicating that malabsorption is a major component of CIE. Thus, diet modifications with highly digestible ingredients are a crucial part of treatment.[9,20]

The DI is an analytically validated, commercially available, quantitative PCR assay used to assess microbiome shifts. The assay quantifies abundance of core bacterial groups that are present in feces of all healthy dogs, including *Faecalibacterium* (short-chain fatty acid producer) and *P hiranonis* (bile acid converter), which are often decreased in dogs with CIE.[8] The assay also detects pathobionts such as *E coli*, which are often increased in dogs with CIE. The DI not only provides reference intervals for bacteria species but also summarizes the data as a single number to express the overall extent of the microbiome shift from healthy. The greater the decrease of beneficial bacteria and increase of pathobionts, the greater the increase of the DI. The DI is interpreted along with the abundance of individual bacteria species, especially *P hiranonis*.[17] In dogs, a DI score from 0 through 2 indicates a mild to moderate microbiome shift and a DI score above 2 indicates significant dysbiosis. (Some dogs have a DI score less than 0 with some bacteria outside the reference intervals, which suggests minor microbiome changes.) Of note, the DI uses quantitative PCR assays

and correlates well with metagenomic sequencing techniques to assess microbiome shifts. Some studies suggest that the DI is most accurate for dogs with more severe dysbiosis (i.e., some dogs with milder microbiome changes may demonstrate only minor changes or their DI may be normal).[8,21]

When the DI is used to assess intestinal dysbiosis, dogs should not be administered omeprazole or antibiotics. Omeprazole approximately increases DI values above 0 but often below 2 (normal abundance of *P hiranonis*); DI normalizes within 1 to 2 weeks after discontinuation of omeprazole.[22] Broad-spectrum antibiotics induce severe dysbiosis (DI values up to 8). In most dogs, the microbiota normalize within 2 to 4 weeks after discontinuation of antibiotics. Nonetheless, up to 30% of dogs may have persistent dysbiosis with DI values up to 3.[23] Additionally, some dogs fed homemade diets with high protein, high fat, and low fiber may have increased DI values (typically around 2) and normal abundance of *P hiranonis*.[24]

For patients with acute diarrhea, recent studies have shown that microbiome changes are relatively mild and the DI is either unchanged or mildly increased with normal *P hiranonis* abundance.[25,26] The microbiome changes, as well as decreased beneficial *Faecalibacterium* and increased pathobionts, overlap with some of the changes observed in dogs with CIE.[25-27] However, these changes are self-limiting in patients with acute diarrhea (e.g., *C perfringens* rapidly decreases within a few days without specific treatment).[25,26] Therefore, antibiotic therapy is typically not required for acute diarrhea. Conversely, for a major subset of dogs with CIE, the DI is increased and *P hiranonis* numbers are decreased, often persistently and likely resulting from chronic intestinal mucosal changes.[20,28-30]

CASE EXAMPLE

Signalment and History

Chloe, a 5-year-old spayed female Maltese dog, was referred for a second opinion with regard to persistent large bowel diarrhea and vomiting for more than 2 months. Chloe's bowel movements were frequent (4 to 5 times daily) with tenesmus, and her feces were liquid with significant mucus and fresh blood (**FIGURE 2A**). She vomited daily, the vomit consisting of mostly bile and occasionally undigested food (**FIGURE 2B**). Chloe's appetite had been declining over the past 2 weeks. Chloe was appropriately vaccinated and received preventive ectoparasite and endoparasite medications. Her previous medical history was unremarkable.

Before the referral, Chloe completed sequential diet trials with a hydrolyzed soy-based extruded diet and a limited-ingredient (single protein), highly digestible (low residue) diet. The client reported that Chloe had daily access to treats and table scraps. Chloe's clinical signs failed to resolve after both diet trials, after which she was prescribed a single-strain probiotic (*Enterococcus faecium* SF68) and metronidazole (10 mg/kg PO q24h for 14 days). Her clinical signs did not resolve, and her appetite declined. The client pursued a second opinion.

Physical Examination

Chloe was bright, alert, and responsive. Her body weight (7.5 kg [16.5 lb]) and body condition score (5/9) were within normal limits, and neither had changed recently. Physical examination was largely unremarkable.

FIGURE 2. (A) Small volume of liquid feces with significant amount of mucus and fresh blood. **(B)** Bilious vomit.

Clinical and Diagnostic Staging

Chloe's CBC and routine biochemistry profile were unremarkable. Fecal flotation result was negative for GI parasites. Serum cobalamin concentration was markedly decreased, below the lower limit of detection (< 150 pg/mL, reference interval 234 to 812 pg/mL), likely indicating acquired cobalamin deficiency. Serum trypsin-like immunoreactivity was within normal limits, excluding exocrine pancreatic insufficiency. Serum basal cortisol was within normal limits, ruling out eunatremic, eukalemic hypoadrenocorticism. Abdominal ultrasonography revealed nonspecific signs of mild, diffuse enterocolitis but was otherwise unremarkable. A fecal sample was submitted to the GI laboratory at Texas A&M University to evaluate for intestinal dysbiosis using the DI. Chloe's DI was markedly increased (6.6) with concurrently decreased *P hiranonis,* indicating a major shift of Chloe's intestinal microbiota (**FIGURE 3**).

Chloe's DI was markedly increased (6.6) with concurrently decreased *P hiranonis*, indicating a major shift of Chloe's intestinal microbiota.

Differential Diagnosis

Chloe was presumptively diagnosed with CIE with likely significant intestinal mucosal remodeling and intestinal dysbiosis.

Treatment and Management

Due to Chloe's diet history, lack of response to diet trials, and diagnostic results, a multimodal treatment approach was chosen.

The client was instructed to eliminate all commercial treats with poor digestibility and table scraps from Chloe's diet. A home-cooked, single (novel) protein, moderately low-fat diet formulated by a board-certified veterinary nutritionist was chosen. Powdered psyllium husk (0.5 g/kg PO q24h) was given to provide an additional source of insoluble fiber. Also given were cyanocobalamin (500 mg PO q24h) and a multistrain, high-dose probiotic (Visbiome Vet; ExeGi Pharma, visbiomevet.com).[31] The client was instructed to keep a daily journal of Chloe's clinical signs (e.g., appetite, number of vomiting episodes, content of vomit, number of bowel movements, fecal consistency).

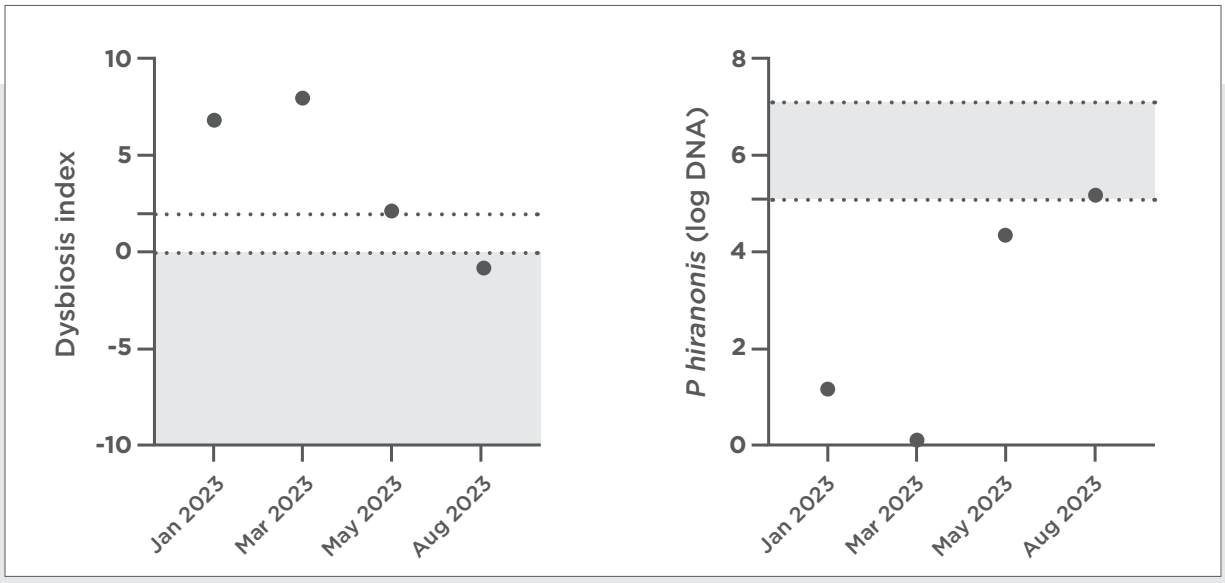

FIGURE 3. Dysbiosis index (DI) and *Peptacetobacter hiranonis* abundance before fecal microbiota transplantation (FMT) **(January and March)**, 2 months after FMT **(May)**, and 5 months after FMT **(August)** show a gradual return of eubiosis (DI < 0) and normal *P hiranonis* fecal abundance, which indicate complete clinical remission. (Gray areas indicate normal reference intervals.)

FMT should not be used as a stand-alone treatment without concurrent diet modifications and potentially fiber supplementation.

Within 1 week of beginning the new treatment regimen, the client reported a significant improvement of Chloe's appetite, vomiting frequency (decreasing from daily to twice a week), and fecal consistency (occasional episodes of hematochezia). Chloe was classified as having a partially responsive FRE. The treatment protocol remained unchanged, and the client was instructed to continue the daily journal.

At the 2-month follow-up appointment, the client reported that Chloe's clinical signs were unchanged with an overall improvement from initial presentation but noted occasional episodes of vomiting and hematochezia with poorly formed feces. Another fecal sample showed persistent, severe dysbiosis (7.7) and extremely low numbers of *P hiranonis* (**FIGURE 3**). These results are highly suggestive of chronic mucosal remodeling, and dysbiosis was suspected to be a contributing factor to her residual clinical signs.

Because multiple recently published case studies indicated that FMT as an adjunct therapy can improve the clinical signs of dogs with CIE, FMT was recommended.[32,33] FMT by retention enema was performed (**BOX 1**), involving infusion of a solution containing feces from a previously screened healthy canine donor through a soft, wide-bore rectal catheter into the ascending colon of the patient.[32] FMT was performed 2 times, 2 weeks apart, while the current diet and treatment regimen remained unchanged.

Follow-up phone conversations at 2 and 4 weeks after the FMTs revealed complete clinical resolution with no additional episodes of vomiting and normal fecal consistency (**FIGURE 4**). Chloe's complete clinical remission was associated with a gradual return of the DI to normal and normal fecal abundance of *P hiranonis* (**FIGURE 3**).

At the last follow-up appointment, 5 months after the last FMT and 8 months after initial presentation, Chloe remained in clinical remission.

FIGURE 4. Normal feces indicative of complete clinical response 2 and 4 weeks after fecal microbiota transplantation.

BOX 1 Fecal Microbiota Transplantation (FMT) Protocol for Chloe

FMT donor: 4-year-old healthy, privately owned dog with normal body weight. Donor had not been on antibiotics or received other medical treatments for previous 12 months. Donor had a complete diagnostic work-up that included dysbiosis index (DI; DI < 0) and screening for enteropathogens (negative for *Clostridioides difficile*, canine parvovirus, *Clostridium perfringens* netF toxin gene, *Campylobacter jejuni*, and *Salmonella* species).

FMT protocol: On the day of FMT, fresh feces were collected from the donor and suspended in 0.9% sodium chloride solution at an approximately 1:1 weight-to-volume ratio. The solution was mixed by a laboratory blender within 1 hour of sample collection. The fecal solution was filtered through a medical gauze pad and distributed into 60-mL sterile syringes to be administered by enema using polyvinyl chloride catheters (16-Fr to 21-Fr according to dog's size). FMT was performed with a dose of 2.5 to 5 grams of feces per kg of recipient's body weight.[32] After FMT, the patient was confined to cage rest for 2 hours to prevent premature defecation.

Discussion

Over time, chronic inflammation can cause intestinal mucosal remodeling, which may lead to loss of intestinal function, malabsorption of nutrients, and dysbiosis that may be reflected with a persistently high DI. Many dogs with CIE clinically improve after diet modifications, yet they can still have increased intestinal mucosal inflammatory infiltrates and, to some degree, decreased intestinal barrier and absorptive function.[34] The clinical remission of these dogs is associated with partial improvement of the microbiome; however, abnormal intestinal changes persist in most dogs for at least several months.[14,20,35,36] Therefore, functional markers of intestinal disease (e.g., decreased cobalamin, increased DI) can remain abnormal despite partial or complete clinical remission. Furthermore, new data suggest that mucosal dysfunction is present before the onset of clinical signs in dogs at risk for CIE.[37]

FMT is an emerging and promising adjunct treatment for the management of intestinal disorders, especially CIE with dysbiosis. Of note, FMT should not be used as a stand-alone treatment without concurrent diet modifications and potentially fiber supplementation. Initial data suggest that dogs with milder forms of dysbiosis have a more favorable long-term response to FMT, and dogs with more severe dysbiosis typically have a favorable short-term response and often require multiple FMTs.[29,32] FMT can improve the DI and increase the abundance of *P hiranonis*, as observed with Chloe after 2 FMTs (**FIGURE 3**). However, several studies have demonstrated that dogs with CIE and a persistently high DI often experience dysbiosis recurrences and/or relapses in clinical signs.[28,29,32] Repeated FMTs can help induce clinical remission; however, future studies are needed to better define the optimal number and frequency of FMTs.

Clinical guidelines for FMT in companion animals have been recently published and are available online along with video resources, information about screening donors, and various protocols.[33]

SUMMARY

Many dogs with chronic diarrhea are food-responsive and respond to 1 or more diet trials. Diet trials and fiber supplementation should be the first-line treatment approach to chronic diarrhea. However, underlying GI pathology remains for many dogs. An increased DI is a potential predictor of persistent underlying intestinal dysfunction and/or clinical relapse. FMT is a promising treatment that can be used as an adjunct therapy for dogs with refractory CIE; however, repeated transplantations will most likely be needed. TVP

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Multimodal Treatment Approach to Dogs With Chronic Diarrhea and the Role of the Microbiome

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CE QUIZ QUESTIONS

1. What is the primary diagnostic feature of chronic inflammatory enteropathy (CIE) of dogs?
   a. Presence of specific enteropathogens in feces
   b. Persistent or recurrent chronic gastrointestinal signs and nonconclusive response to therapy
   c. Decreased serum cobalamin levels
   d. Increased serum folate levels

2. What is a major contributor to nutrient malabsorption in dogs with CIE?
   a. Decreased mucus production
   b. Loss of brush border transporters
   c. Overproduction of bile acids
   d. Increased cobalamin absorption

3. A dysbiosis index score above 2 indicates:
   a. Normal microbiome composition
   b. Mild dysbiosis
   c. Significant dysbiosis
   d. Self-limiting dysbiosis

4. The most common phenotype of CIE of dogs is:
   a. Antibiotic-responsive enteropathy
   b. Food-responsive enteropathy
   c. Steroid-responsive enteropathy
   d. Nonresponsive enteropathy

5. Why should antibiotics such as metronidazole and tylosin be avoided as treatment of CIE in dogs?
   a. They are not effective against enteropathogens.
   b. They can cause severe dysbiosis, do not support gastrointestinal function, and lack long-term efficacy.
   c. They increase the absorption of bile acids.
   d. They reduce short-chain fatty acid production.