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ACVIM Endorsed Statement | Small Animal Internal Medicine Gastroenterology

ACVIM–endorsed statement: consensus statement and systematic review on guidelines for the diagnosis and treatment of chronic inflammatory enteropathy in dogs

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Abstract

The past decade has witnessed the performance of well-designed studies that enable diagnosing canine chronic inflammatory enteropathy and trials that assess treatment options. In these guidelines, we evaluate diagnostic approaches including endoscopy, biopsy, and histopathology, disease classification, and biomarkers used in the management of this condition. Dietary treatment options were assessed, along with the additional impact of several treatments used in conjunction with first-line dietary management.

Keywords canine, diagnostic algorithm, idiopathic, meta-analysis, therapeutic trial

Abbreviations ACTH, adrenocorticotropic hormone; ACVIM, American College of Veterinary Internal Medicine; AES, ACVIM-endorsed statement; AIEC, adherent and invasive *Escherichia coli*; AMT, antimicrobial treatment; α_1PI, alpha$_1$-proteinase inhibitor; AST, luminal carbon adsorbent AST-120; BCS, body condition score; BUN, blood urea nitrogen; CABI, Centre for Agriculture and Bioscience International; CBC, complete blood count; Cbl, cobalamin (vitamin B_{12}); CCECAI, canine chronic enteropathy clinical activity index; CD, cluster of differentiation; CE, chronic enteropathy; CES, canine endoscopy score; CEUS, contrast-enhanced ultrasonography; CI, confidence interval; CIBDAI, canine inflammatory bowel disease activity index; CIE, chronic inflammatory enteropathy; cPL, canine pancreatic lipase; CR, complete remission; CRP, C-reactive protein; CSES, canine short endoscopy score; CT, computed tomography; DTA, diagnostic test accuracy; EF, *Enterococcus faecium*; Enrol, number of dogs that were enrolled to receive the intervention; FISH, fluorescence in-situ hybridization; FMT, fecal microbiota transplantation; Foxp3, Forkhead box p3; Tregs, regulatory T cells; FR, food-responsive; GC, granulomatous colitis; GI, gastrointestinal; GIC, granulomatous ileocolitis; H&E, hematoxylin/eosin stain; HCY, homocysteine; hyd, hydrolyzed; IBD, inflammatory bowel disease; IMD, immunomodulator; IgG, immunoglobulin G; IgY, immunoglobulin Y, IHC, immunohistochemistry; IL, intestinal lymphangiectasia; IL-1, interleukin-1; IR, immunosuppressant-responsive; lim, limited-ingredient; LR, low-residue; LT, long-term (>3 months); MCS, muscle condition score; miR, micro ribonucleic acid; MMA, methylmalonic acid; MTZ, metronidazole; NF-κB, nuclear factor "kappa-light-chain-enhancer" of activated B-cells; NOD2, nucleotide-binding oligomerization domain 2; NR, non-response; PARR, polymerase chain reaction for antigen receptor rearrangements; PAS, periodic acid-Schiff; PICO, population–intervention–comparison–outcome; PIT, population–index–test; PLE, protein-losing enteropathy; POCUS, point-of-care ultrasonography; PR, partial response; QOE, quality of evidence; qPCR, quantitative polymerase chain reaction; RCT, randomized controlled trial; Resp, number of dogs that responded to the intervention; RFX, rifaximin; RMBD, raw meat-based diet; RoB, risk of bias; RR, risk ratio; SD, standard diet; SI, small intestine; SOR, strength of recommendation; ST, short-term (≤3 months); TD, therapeutic diet; Th, T helper lymphocyte; TLI, trypsin-like immunoreactivity; TLR, Toll-like receptor; tx, treatment; TYL, tylosin; UPC, urine protein-to-creatinine ratio; var, varied; VCE, video capsule endoscopy; WSAVA, World Small Animal Veterinary Association

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contradictory. A draft is prepared by the panel, followed by solicitation of input by the ACVIM membership which may be incorporated into the statement. It is then submitted to the Journal of Veterinary Internal Medicine, where it is edited prior to publication. The authors are solely responsible for the content of the statements.

Authorship note: Romy M. Heilmann and Albert E. Jergens are co-chairs on the ACVIM-endorsed statement (AES) and contributed equally as first authors. Annette M. O'Connor is the methodologist for the AES. Aarti Kathrani, Karin Allenspach, Silke Salavati Schmitz, Simon L. Priestnall, and Julien R.S. Dandrieux are panel members on the AES.

Introduction

Chronic gastrointestinal (GI) signs are a common reason for dogs to be presented in primary care and referral settings, and up to 20–30% of veterinary visits in companion animals are related to vomiting or diarrhea or both.[1] Over the past decade, basic and clinical research has focused on advancing diagnostic and treatment strategies for chronic intestinal inflammation in dogs.[2]

The pathogenesis of chronic intestinal inflammation in dogs is complex and, based on current knowledge, driven by genetics, immunology, environmental factors, and GI luminal components, including diet and the microbiome. These aspects are summarized and reviewed elsewhere.[2]

The 2010 ACVIM Consensus Statement was a milestone in achieving a more standardized approach to companion animals suspected to have chronic intestinal inflammation.[3] Important advances have been made in classifying, diagnosing, and treating chronic intestinal inflammation in dogs, which warrant an update of the Consensus Statement published 15 years ago.[2,3]

A novel classification scheme and approach to ACVIM-endorsed statements (AES) was recently introduced.[4] This guideline development started before adoption by ACVIM, but elements of the new AES were incorporated. Hence, the development of this statement followed much of the newly developed AES standard operating procedure and specific AES protocol (Supplementary File S1) involving an intensive review of the relevant veterinary literature or systematic review (evidence levels I-III) and consensus building through reiterations of panel (Supplementary File S2) discussions followed by anonymous voting of the panel (Delphi method[5,6]) until a complete consensus was reached.

Materials and methods

Consensus for the terminology was developed in a 2-step process, searching for disease-characterizing terms followed by their concatenation using the Delphi method (Supplementary File S3). Information on the signalment was derived from cohort studies and case–control studies. For the diagnosis of the disease, the reference standard determined by the panel for chronic inflammatory enteropathy (CIE) was the response to treatment trials or endoscopy with histopathology or both.

Establishment of a recommended diagnostic strategy was based on a comprehensive, systematic survey of the literature conducted by using the population–index–test (PIT) format and the PubMed and Centre for Agriculture and Bioscience International (CABI) databases (accessed Jun 19, 2024; Supplementary File S4-1). After the search (search terms pertaining to species, disease, diagnostic criteria, and diagnostic tests)[7] was conducted, it was uploaded to DistillerSR (https://www.distillersr.com; Ottawa, ON, Canada), deduplication performed (no restrictions on publication date), and verified for inclusion of key references (Supplementary File S4-2). Screening titles and abstracts (level 1) using the DistillerSR AI tool (Supplementary File S4-3) was followed by full-text (level 2) assessment of the relevant titles (Supplementary File S4-4). The study design classification scheme for comparative diagnostic test accuracy (DTA) studies was used[8] with identification of the study design[9,10] and bias assessment based only on spectrum bias (Supplementary File S5).[11,12] Parameters of test accuracy (Supplementary File S6) were used to evaluate patient-important outcomes.[13–16] Panel discussions served to resolve disagreements, and consensus was built using the Delphi methodology. Recommendations for diagnostic strategy were developed (Figure 1), with consideration of the quality of the evidence overall (QOE) (rated as either very low, low, moderate, or high) and the resulting strength of the recommendation (SOR; rated as either strong, weak, or conditional).[15]

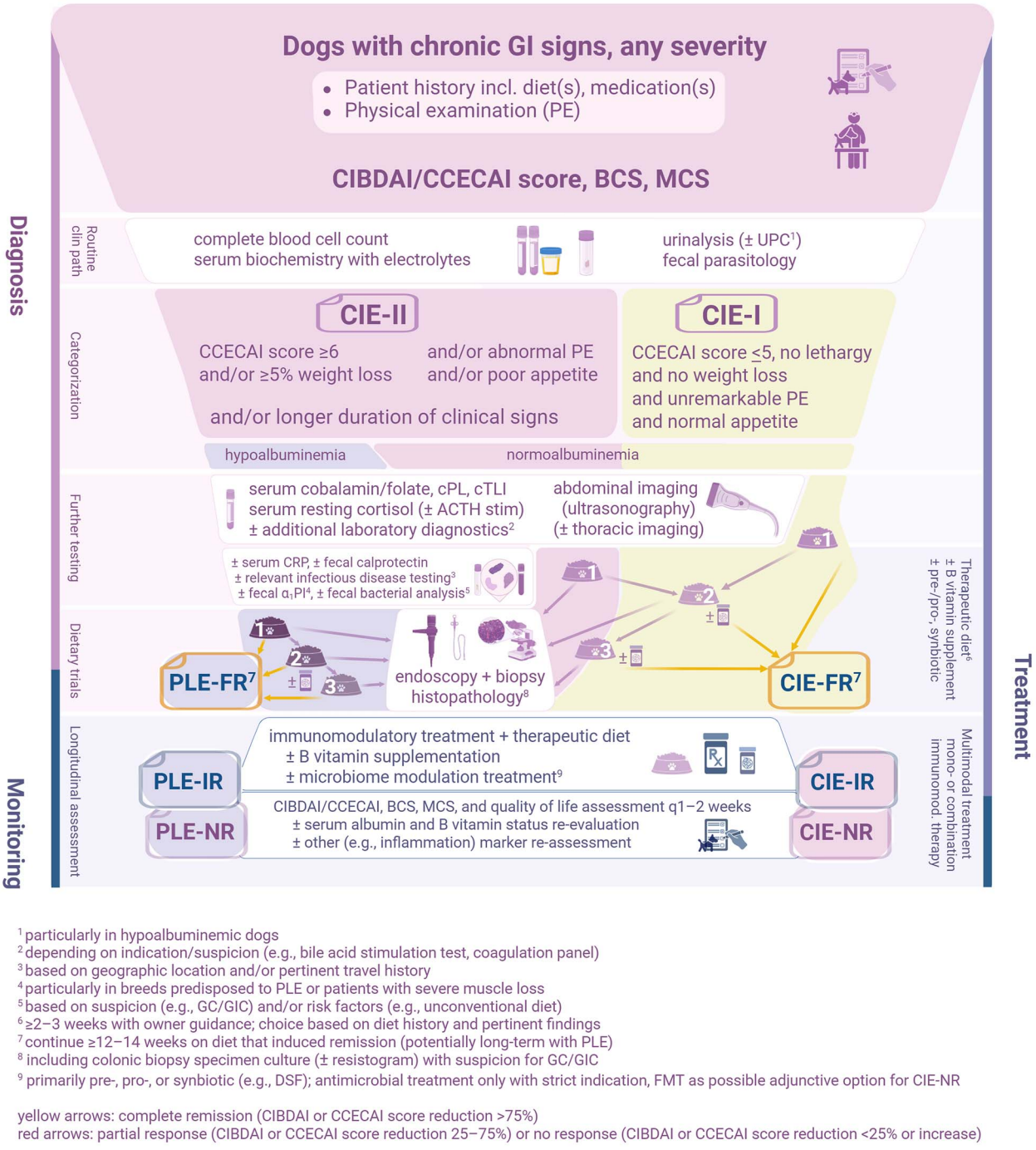
For the treatment approach, a systematic review of the literature was conducted by using the population–intervention–comparison–outcome (PICO) format and the PubMed and CABI databases (accessed Jan 12, 2025; Supplementary File S7-1). The search (search terms pertaining to species, disease, and therapeutic interventions) was entered and uploaded to DistillerSR, references were deduplicated and verified for capturing key references (Supplementary File S7-2), and screening at level 1 was pursued by 2 panelists each (Supplementary File S7-3). Relevant references were subjected to level 2 review (Supplementary File S7-3), extracting information about the PICO, study design, and risk of bias for randomized controlled trial (RCT) designs.[17] Treatment and test of treatment (diagnostic intervention as part of the diagnostic approach) recommendations were developed based on the overall evidence rating (Supplementary File S7-3).

The panel aimed to develop a guideline applicable to a broad range of settings (eg, general and referral practice, resource-rich and resource-limited environments) and provide exemplary image panels as well as practically useful scoring sheet templates (as Supplementary files).

Recommendations and justification

Terminology and target population (signalment)

Consensus for using the term CIE was reached (Supplementary File S3). The panel suggests avoiding the term inflammatory bowel disease (IBD) to delineate a similar but not identical condition in human gastroenterology.[18–20]



[1] particularly in hypoalbuminemic dogs
[2] depending on indication/suspicion (e.g., bile acid stimulation test, coagulation panel)
[3] based on geographic location and/or pertinent travel history
[4] particularly in breeds predisposed to PLE or patients with severe muscle loss
[5] based on suspicion (e.g., GC/GIC) and/or risk factors (e.g., unconventional diet)
[6] ≥2–3 weeks with owner guidance; choice based on diet history and pertinent findings
[7] continue ≥12–14 weeks on diet that induced remission (potentially long-term with PLE)
[8] including colonic biopsy specimen culture (± resistogram) with suspicion for GC/GIC
[9] primarily pre-, pro-, or synbiotic (e.g., DSF); antimicrobial treatment only with strict indication, FMT as possible adjunctive option for CIE-NR

yellow arrows: complete remission (CIBDAI or CCECAI score reduction >75%)
red arrows: partial response (CIBDAI or CCECAI score reduction 25–75%) or no response (CIBDAI or CCECAI score reduction <25% or increase)

Figure 1 Recommended sequence of diagnostic tests for approaching a CIE diagnosis in dogs. Based on patient signalment, disease severity, and chronicity, a 2-tier approach (CIE-I vs. CIE-II based on clinical assessment) is recommended (created using biorender.com).

Canine CIE describes a group of GI disorders with persistent or recurrent GI signs and variable mucosal inflammation.[2,21–23] Given the current lack of evidence that protein-losing enteropathy (PLE) and granulomatous colitis (GC) are entirely separate disease entities from CIE in dogs, both PLE and GC were considered distinct phenotypes within the spectrum of CIE phenotypes. Clinical signs of diarrhea, vomiting, alterations in appetite, or weight loss vary depending on the segment of the GI tract involved and the extent of mucosal inflammation.[2,21] Chronic inflammatory enteropathy is a multifactorial disease likely involving host immunity, genetic susceptibility, intestinal microbiota, and environmental factors.[2,24,25] The varied interplay among these factors results in increased disease heterogeneity.[2] Dysbiosis, characterized by decreased microbial diversity and increased abundance of Enterobacteriaceae,[24,26–29] and bile acid dysmetabolism[30–35] have been extensively documented. Although the mucosal cytokine profile is altered in dogs with CIE, studies have not definitively determined a T helper lymphocyte subtype 1 (Th1), Th2, or Th17 predominance.[24,36] Altered microbial metabolism (eg, decreased short-chain fatty acid production), decreased host protective factors (eg, GI mucus layer), and a disrupted intestinal epithelial barrier also contribute

to the aberrant immune responses causing chronic intestinal inflammation.[2,24,27,29,37]

Affected dogs are typically middle-aged, but the disease can occur in young dogs, particularly with food-responsive CIE.[21,23,38] A sex predisposition has not been reported.[22] Although any breed can be affected, some predispositions are recognized, including German shepherd dogs, Soft-coated wheaten terriers, and Chinese shar peis.[24,39,40] Chronic inflammatory enteropathy is prevalent worldwide; 2 studies suggest that 20–30% of companion animal visits to veterinarians are for vomiting or diarrhea or both.[1,23]

Diagnostic approach and prognosis

Chronic inflammatory enteropathy remains a diagnosis of exclusion, with several characteristics defining this spectrum of disease phenotypes, and the diagnostic evaluation integrates variables that contribute diagnostic or prognostic information or both. Although diagnostic characteristics such as sensitivity and specificity usually are based on comparative studies of detection, the panel decided that factors reported as being prognostic often also are considered to have diagnostic value. The panel identified limited evidence for the diagnostic approach because a number of studies reported in the primary literature are statistically underpowered or lack appropriate cohorts (eg, spectrum bias with comparison to healthy controls), providing poor evidence, or present case series that are not comparative (Supplementary File S5).

CLINICAL evaluation
Physical examination

Recommendation: A thorough physical examination should be performed as with any patient presented to veterinary practice. In all dogs suspected of having CIE, evidence of malnutrition, including body condition score (BCS) and muscle condition score (MCS), and indications of hypoalbuminemia (eg, ascites, peripheral edema) should be included in the diagnostic evaluation (*SOR = strong*).

Justification: Dogs with CIE, especially PLE, are susceptible to malnutrition because of GI disease. Dogs with CIE involving the small intestine (SI) have decreased BCS,[41–45] with 1 prospective cohort multicenter study documenting lower BCS at diagnosis as a negative prognostic factor for response, mortality, and long-term disease remission in dogs with immunosuppressant-responsive CIE (CIE-IR).[46] Approximately 2/3 of dogs with PLE are underconditioned and have muscle atrophy at diagnosis.[47] Severity of epaxial muscle loss and coat condition are associated with not achieving clinical remission within 6 months of diagnosis in dogs with PLE caused by inflammatory enteritis, intestinal lymphangiectasia, or both.[47] The presence of ascites or edema may indicate impaired nutrient absorption or PLE and is commonly associated with worse clinical disease and worse prognosis.[21] Because BCS, MCS, ascites, and peripheral edema are indicators of clinical disease severity and outcome, they are also useful for diagnosis (*QOE = moderate*).

Clinical disease severity grading

Recommendation: In all dogs suspected of having CIE, clinical disease severity (assessed by the disease activity scores *Canine Inflammatory Bowel Disease Activity Index* (CIBDAI) or *Canine Chronic Enteropathy Clinical Activity Index* (CCECAI) if serum albumin concentration is measured, Supplementary File S8) should be graded as part of the clinical evaluation (*SOR = strong*).

Justification: The CIBDAI and CCECAI scoring systems, including criteria that are not specific for a diagnosis of CIE, are effective in distinguishing dogs suspected of CIE from healthy dogs.[45,48–51] Both scoring tools assess clinical disease severity, with CIBDAI correlating with clinical[52] and histopathologic findings.[53–58] The CCECAI enhances prognostication by adding 3 variables (serum cobalamin, serum albumin, and pruritus) to the CIBDAI.[41,59] Data on CCECAI association with duodenal and colonic histologic lesions are inconsistent.[58,60]

Because cumulative scores obtained using both scoring systems, CIBDAI[27,31,51,53,57,61–65] and CCECAI,[46,65–67] decrease with treatment, it is inferred that they can be used for diagnosis. The CIBDAI[21,34,63,68] and CCECAI[21,38,50,69,70] are associated with CIE differentiation by response to treatment. Dogs with food-responsive CIE (CIE-FR) have the lowest scores, and those with CIE-IR the highest, although not all studies confirm the ability of CIBDAI and CCECAI to differentiate CIE-FR and CIE-IR.[67,71] The CCECAI scores are higher in dogs with PLE, because hypoalbuminemia presence and severity is a CCECAI criterion, but also reflect more severe disease.[37,68,72–75] Score decreases from baseline indicate clinical improvement (<25%: no response, 25%-75%: partial response, >75%: complete response or remission),[44,62] and both high CIBDAI[41,76] and CCECAI[21,46,50,77,78] scores correlate with worse outcomes or "nonsurvivor" status. Baseline CCECAI is variably associated with outcome in PLE, but some studies report no difference,[79–82] whereas a larger study found CCECAI to be associated with an increased risk of death.[74] Improvement in CCECAI aligns with longer survival.[73,79]

The CIBDAI[48,83] and CCECAI[48] do not differ between CIE and overall GI lymphoma phenotypes but were higher in high-grade GI lymphoma[84] and other GI cancers[85] compared with CIE.

Combining scores with additional diagnostic markers may further improve diagnostic accuracy and prediction of treatment response in CIE. Fecal calprotectin[57,69,86] and serum C-reactive protein (CRP)[51,53] aid in further defining disease severity and the distinction of CIE-IR. For serum cobalamin, studies are contradictory[87,88] (*QOE = moderate*).

Clinical pathology

Routine clinical pathology

Recommendation: In all dogs suspected of having CIE, hematology, serum biochemistry profile including electrolytes, fecal parasitology, and urinalysis (with urine protein-to-creatinine ratio [UPC] if hypoalbuminemic) should be performed concurrently or in a clinically relevant sequence to exclude conditions affecting other organs that might mimic the GI signs common with CIE and to assess overall patient status (eg, for complications of CIE) (*SOR = strong*).

Justification: Non-regenerative normocytic normochromic anemia occurs in 12–19% of dogs with CIE.[41,72,89] Increased blood neutrophil-to-lymphocyte ratios are associated with more severe clinical disease (CCECAI score) and can help differentiate CIE phenotypes based on response to treatment (CIE-FR vs. CIE-IR).[89–92] Severe CIE is linked to thrombocytosis,[42,93,94] and hypercoagulability (affecting 63–100% of PLE dogs) predisposes to thromboembolic complications.[77,94]

Hypoalbuminemia and panhypoproteinemia can result from PLE, with severity having prognostic value.[21,41,46,71–74,76,79,95]

Hypocalcemia, hypomagnesemia, and hypocholesterolemia can develop with PLE,[41,51,74,76,79,80,96,97] and increased blood urea nitrogen (BUN) concentrations are a negative prognostic indicator.[73,74,79] Electrolyte changes, affecting 5–19% of dogs with CIE, can be severe.[73] Endoparasite infestations can mimic CIE,[41] but *Giardia* spp. antigen can be shed by both healthy dogs and those with CIE[98] (*QOE = moderate*).

Further clinicopathologic testing

Recommendations: In CIE-II suspect dogs (Figure 1), tests for cobalamin (vitamin B_{12}), pancreatic disease markers (pancreatic lipase, trypsin-like immunoreactivity [TLI]), and resting serum cortisol concentration should be determined to assess disease severity and exclude potential co-morbidities or conditions affecting other organs causing overlapping GI signs (*SOR = strong*).

Bile acid or adrenocorticotropic hormone (ACTH) stimulation tests, folate (vitamin B_9), vitamin D status, and coagulation testing might be performed for some dogs (*SOR = conditional based on indication/suspicion for other conditions/co-morbidities*).

Justification: Hypocobalaminemia is a negative prognostic factor, affecting 19–61% of dogs with CIE,[21,31,41,60,69,70,72,78,87,96,99–103] but normocobalaminemia does not exclude CIE.[41,70,87,104] Intracellular cobalamin deficiency can occur with low-normal serum cobalamin concentration.[104–106] Hypofolatemia is a feature of CIE and has been reported in 1–47% of affected dogs,[31,41,69,70,72,74,78,88,96,100,102] but is not specific to CIE and can be falsely normal or increased secondary to intestinal dysbiosis or hypocobalaminemia.[88,104] Hepatic disease, exocrine pancreatic insufficiency, and chronic pancreatitis may have signs that overlap with CIE.[41,88] Increased serum specific pancreatic lipase activity or concentration, suggesting concurrent pancreatitis, is a negative prognostic indicator in dogs with CIE.[101] Eunatremic–eukalemic hypoadrenocorticism (previously referred to as atypical hypoadrenocorticism) also can mimic CIE.[107] Hypovitaminosis D is detected in up to 35% of dogs with CIE (particularly PLE) and is linked to negative outcomes[76,80,97,100,108,109] (*QOE = moderate*).

Disease biomarkers

Recommendation: In dogs categorized as CIE-II that have or have not had a properly performed dietary treatment trial, clinicians might consider testing for inflammatory markers (CRP, fecal calprotectin) or markers of GI protein loss (fecal alpha$_1$-proteinase inhibitor [α_1PI]) (*SOR = conditional based on indication/suspicion for CIE/PLE*).

Justification: Serum CRP concentration can be used to assess disease progression and response to treatment in dogs with CIE,[21,51,53,57,66,69,110] but only ≥2.7-fold changes are relevant.[111] Serum CRP concentration can help detect CIE dogs that require immunomodulatory treatment,[26] but it is not invariably linked to disease severity.[21,51] Calprotectin, measured in feces,[37,57,72,86,95,99,110] is an indicator of disease severity in dogs with CIE,[57,69,86,95] and might help predict response to treatment[69] (*QOE = moderate*).

Increased fecal α_1PI concentrations in dogs ≥1 year of age can signal intestinal protein loss and histologic lesions consistent with PLE, regardless of serum albumin status.[60,72] Several other biomarkers of inflammation or immune-mediated disease[37,51,54,57,69,72,78,84,95,99,102,112–126] or intestinal function[66,127–130] and genomic markers[37,54,85,119,120,131–133] studied in dogs with CIE (Supplementary File S6) currently have no relevance in clinical practice because they lack availability or reported diagnostic accuracy data (*QOE = low*).

Localized or systemic infectious disease testing

Recommendation: In dogs suspected of having CIE, testing for relevant infectious causes (eg, *Histoplasma capsulatum*, *Heterobilharzia americana*, *Leishmania infantum*) might be considered as part of the clinical evaluation if dogs reside or have traveled from an endemic area (*QOE = conditional based on geography*).

Justification: Although the prevalence of endemic infectious diseases (eg, intestinal histoplasmosis) in dogs suspected of CIE[125] is unknown, missing an infectious cause could be detrimental, particularly with immunomodulatory treatment (*QOE = low*).

Bacterial analyses

Recommendations: In dogs with suspected CIE, mucosal or fecal culture might be considered for dogs with specific risk factors (eg, suspected GC, raw meat-based diet) (*SOR = conditional based on suspicion/identified risk factors such as GC/raw meat-based diet*). Fecal microbiome analysis might offer an individualized approach to patient management (*SOR = weak*).

Justification: Support for an infectious bacterial cause of CIE is lacking,[21,134] but feeding a raw meat-based diet is a risk factor (eg, for *Campylobacter* spp.) and zoonotic risk.[21,41] Granulomatous colitis (GC), a unique form of CIE, is characterized by mucosal adherent and invasive *Escherichia coli* (AIEC). High antimicrobial resistance rates require mucosal culture with antimicrobial susceptibility testing.[135] Fecal microbiome alterations in dogs with CIE, with some differences between CIE-IR and CIE-FR,[27,31,45,136] are linked to metabolome patterns supporting alterations at the functional level.[27,31,34,37,44,64,65,70,84,102,119,128,136–146] The fecal dysbiosis index evaluates gut microbiome changes based on total bacteria in addition to 7 bacterial groups[147] commonly altered in dogs with CIE[27,31,45,48,62,143] (*QOE = low*).

Allergen-specific immunoglobulin

Recommendation: Given the current lack of any evidence in CIE of dogs, clinicians might consider proceeding with an adequately designed elimination diet trial rather than performing serum allergy tests in dogs with suspected CIE that have not previously had a properly performed dietary treatment trial (*SOR = conditional based on unproven benefit*).

Justification: Dietary allergen-specific immunoglobulin concentrations are not confirmed as beneficial in diagnosis or management of dogs with CIE (*QOE = no evidence*).

Diagnostic imaging

Routine diagnostic imaging

Recommendations: Diagnostic abdominal ultrasonography (evaluating intestinal walls, regional lymph nodes, other organs, and the presence of abdominal effusion) should be considered in any dog with suspected CIE to rule out diseases that mimic CIE, particularly in dogs with moderate or marked clinical signs (CIBDAI or CCECAI score ≥ 6), weight loss (≥5%), hypoalbuminemia, or no response to dietary trial (refer to Section "Diagnostic treatment trials") (*SOR = strong*).

Thoracic imaging should be considered with possible thoracic involvement of CIE (eg, pleural effusion with PLE) or suspicion of other differential diagnoses or concurrent conditions (eg, cardiac

disease, neoplasia, or infectious diseases such as histoplasmosis or blastomycosis) (*SOR = conditional based on suspicion of thoracic involvement/concurrent disease*).

Justification: B-mode *ultrasonography* (Figure 2) in dogs with CIE primarily serves to exclude other underlying disorders.[21,50,66,73,77,83,99,100,107,109,117] Intestinal wall thickening (Supplementary File S9) is common with CIE[100,148] but not predictive of inflammation.[149,150] Mucosal echogenicity changes, SI corrugation, and a high cumulative ultrasound score are associated with symptomatic CIE[148,149] but not histopathologic severity.[72,151] Normal hypoechoic SI mucosa with CIE is ≥80% sensitive and specific for CIE-FR, but findings overlap across CIE subtypes.[149] Secondary findings (eg, lymphadenopathy, SI corrugation) can be highly suggestive of GI lymphoma as opposed to CIE.[148,149] Up to 93% of PLE dogs have SI ultrasonographic alterations,[72] including peritoneal free fluid (73–79%[72,82,96]), mucosal striations or speckles (47–91%[72,82,96]), lymphadenopathy (18–40%[72,82,96]), and SI dysmotility or distension (10–23%[96,150]). These are not correlated with PLE severity or treatment requirements,[72,96,150] but can be associated with outcomes.[150] Hyperechoic striations are 75% sensitive and 96% specific for intestinal lymphangiectasia causing PLE,[150] but hyperechoic speckles are non-specific findings[149] (*QOE = moderate*).

Radiographic imaging plays a secondary role in CIE evaluation, and primarily is used to rule out obstructions or macroscopic intra-abdominal abnormalities[73,150] and to assess for pleural effusion (PLE cases) or evidence of non-CIE conditions (*QOE = very low*).

Advanced diagnostic imaging

Recommendation: Review of the literature identified too little relevant information to recommend contrast-enhanced ultrasonography (CEUS), computed tomography (CT), or magnetic resonance enterography for diagnosis of dogs with CIE. However, these modalities may be elected at the clinician's discretion (*SOR = conditional based on indication*).

Justification: Contrast-enhanced ultrasonography can differentiate symptomatic CIE dogs from healthy controls and results correlate with clinical and histologic severity,[148] but it cannot differentiate lymphoma or CIE subtypes (*QOE = low*). Other advanced imaging modalities remain unexplored in dogs with CIE (*QOE = very low*).

Diagnostic treatment trials

First-choice diagnostic intervention

Recommendation: Because CIE is a diagnosis of exclusion and is subclassified based on response to treatment (ie, CIE-FR, CIE-IR), efficacy of treatment trials is also considered diagnostic. Dietary treatment trials are the preferred first-choice diagnostic recommendation in dogs suspected of having CIE before invasive diagnostic tests (refer to Section "Endoscopy with biopsy and histopathology") are performed, provided they are clinically stable and not hypo- or anorexic (*SOR = strong*).

Justification: Dietary modification as a test of treatment[152] is an adequate therapeutic (ie, diagnostic treatment) starting point because 38–89% of dogs with CIE are food-responsive,[38,41,134,153] and many dogs maintain long-term (>3 months) clinical remission on dietary treatment alone[21,38,134,153–155] (refer to Section "Dietary intervention") (*QOE = high; includes RCTs and non-RCT designs with dietary intervention as baseline treatment*).

Dietary treatment trial

Recommendations: Complete dietary treatment trials should entail exclusive feeding of a therapeutic diet (ie, highly digestible, limited-ingredient novel protein, hydrolyzed protein, elemental protein, fiber-enriched, low- to ultra-low-fat, home-prepared) exclusively for at least 2 weeks. The choice of therapeutic diet should be selected based on diet history (Supplementary File S10), GI signs, and pertinent physical examination and diagnostic findings (refer to Section "Dietary intervention"). At least 3 trials with different diets should be considered, if possible. Owner guidance should be provided for adequate implementation of a diet trial, and clinical response monitored (using CIBDAI or CCECAI) at least weekly (*SOR = strong*).

A diet that induces clinical remission should be fed for at least 12 weeks before attempting to transition away from the therapeutic diet, but PLE dogs might benefit if maintained long-term on an effective diet (*SOR = conditional based on response to dietary intervention*).

Justification: Several diet categories can be effective in dogs with CIE, depending upon their specific GI signs and diet history,[21,33,38,66,77,82,134,153–170] and optimization of dietary soluble fiber can have beneficial effects on intestinal homeostasis.[154,164] Clinical responses typically are seen within 10-14 days of initiating dietary treatment,[21,33,55,134,153,154,156,162,168,171] but effectiveness may require more time in some dogs,[153,154,172] particularly if intermittent clinical signs occur, and long-term responses are least likely (17%) with a therapeutic GI diet (refer to Section "Dietary intervention").[153] Positive responses may be related to macronutrient amount, type, or source, antigen restriction,[154] or other nutritional factors (eg, digestibility, feeding frequency). Therefore, some dogs with CIE (non-PLE and PLE) may require ≥3 adequate dietary trials before showing a response[155,167] (*QOE = high*).

Transitioning away from therapeutic diets after sustained remission for 12-14 weeks is associated with durable clinical remission in 31–79% of dogs with CIE,[21,153] but relapse rates are high with dietary non-compliance in PLE dogs[173] (*QOE = moderate*).

Additional diagnostic treatment trials

Recommendations: Response to dietary intervention (refer to Section "Monitoring") for at least 2 weeks of exclusive feeding confirms the food-responsive disease phenotype of CIE (refer to Section "Dietary intervention"). Additional treatment with pre-, pro-, or synbiotics might be considered in dogs suspected of having CIE (PLE and non-PLE) and showing an incomplete response to dietary trials alone (refer to Section "Prebiotics, probiotics, synbiotics, and fecal microbiota transplantation") (*SOR = conditional based on response to dietary intervention*).

If possible, intestinal inflammation should first be documented and characterized (ie, GI endoscopy with biopsy performed, refer to Section "Endoscopy with biopsy and histopathology") in dogs that have failed ≥3 adequately performed dietary trials before treatment escalation (ie, use of immunomodulatory or other treatment options). Empirical antimicrobial treatment is not recommended in CIE suspects (refer to Section "Antibiotic treatment"),

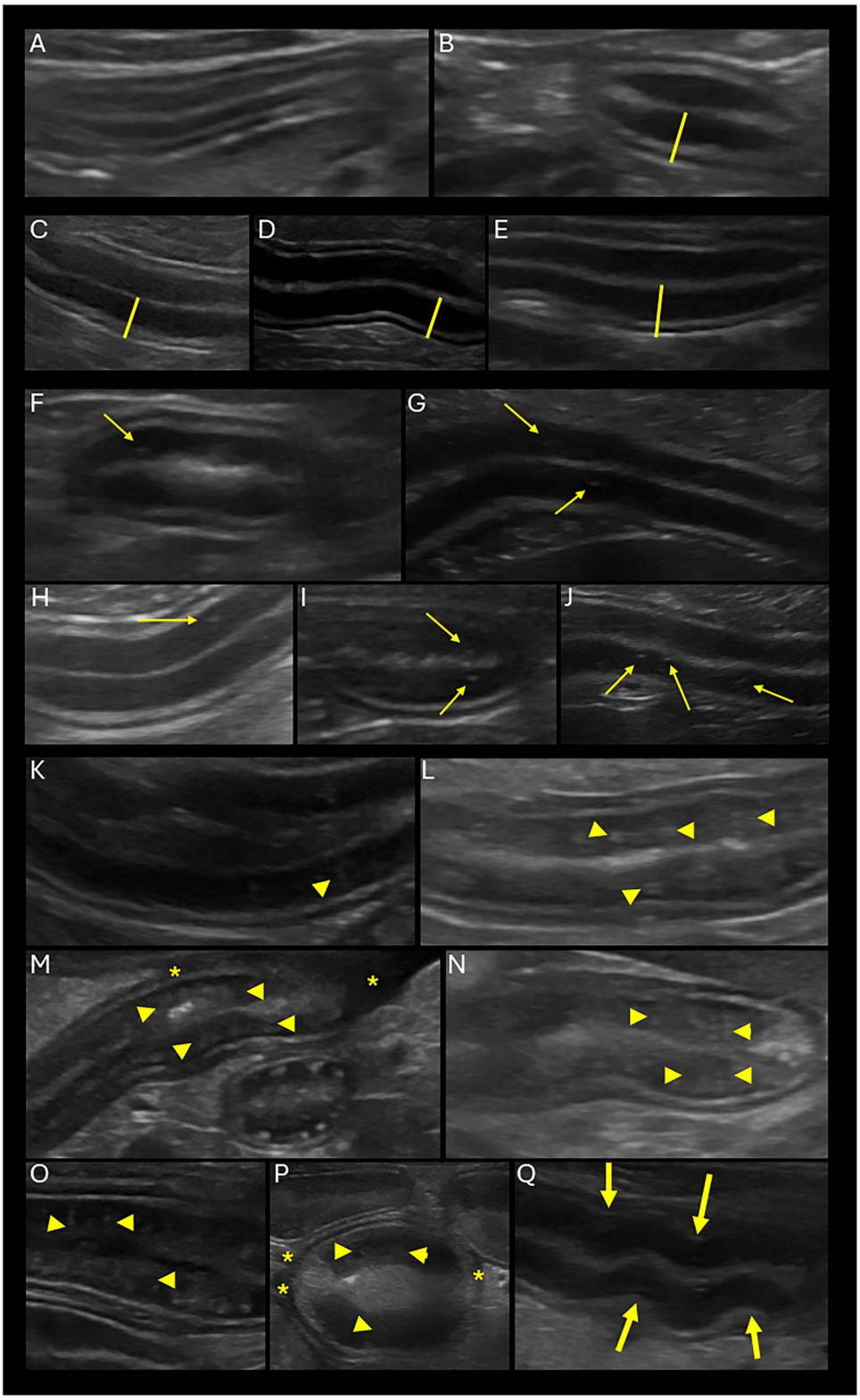


Figure 2 Image panel showing characteristic ultrasonographic findings in dogs with CIE. (A) Normal small intestinal wall, (B-E) variable degrees of intestinal wall and mucosal thickening (lines), (F-J) varying numbers of hyperechoic mucosal speckles (arrows), (K-P) increasing severity of hyperechoic mucosal striations (arrowheads), (Q) corrugated small intestinal wall (arrows), and (M, P) peritoneal fluid accumulation (asterisks).

which includes dogs suspected of having AIEC-associated GC or granulomatous ileocolitis (GIC) (*SOR = strong*).

Justification: Pre-, pro-, or synbiotics can be beneficial if given concurrently with diet or immunomodulatory treatment, but in most studies, do not significantly affect the clinical response alone.[157,174–187] One RCT showed that a specific multi (8)-strain probiotic ("De Simone Formulation"; refer to Section "Prebiotics, probiotics, synbiotics, and fecal microbiota transplantation") induced clinical remission to the same extent (albeit slightly slower) as a prednisone/metronidazole combination, with the added benefit of inducing a tolerogenic mucosal immune response[175] (*QOE = weak*).

Response to empirical antimicrobial treatment (eg, tylosin) is usually short-lived, because relapse rates after discontinuation are high and significant intestinal dysbiosis can remain long-term[38,103,188–190] (*QOE = moderate*).

Responses to immunomodulatory treatment are usually fast (median for corticosteroids, 5 days),[21,175,191] but inflammation can be secondary to other causes (diseases that mimic CIE), some of which would be adversely affected by receiving immunosuppressive treatment (eg, infectious disease such as GI histoplasmosis) or carry a worse prognosis (eg, GI neoplasia such as lymphoma; refer to Sections "Localized or systemic infectious disease testing", "Bacterial analyses", and "Additional treatment considerations"). Currently, no evidence supports combining dietary trials with a short course of anti-inflammatory treatment. A suspicion of AIEC-associated GC or GIC requires invasive diagnostic testing (ie, GI endoscopy with biopsy) to confirm the disease and perform antimicrobial sensitivity testing using mucosal tissue biopsy samples to guide the choice of antimicrobial treatment (refer to Section "Prebiotics, probiotics, synbiotics, and fecal microbiota transplantation"). Other interventions aimed at microbiome modulation (eg, fecal microbiota transplantation[192–196]) may be beneficial, but remain to be further studied before recommendations can be made (*QOE = weak*).

Endoscopy with biopsy and histopathology

Diagnostics before endoscopy

Recommendation: In dogs with suspected CIE before a properly designed dietary treatment trial or GI endoscopy, a physical examination (including assessment of CIBDAI and CCECAI scores, BCS, and MCS), routine laboratory testing (hematology, serum biochemistry profile with electrolytes, urinalysis, and fecal parasitology), further GI and pancreatic testing (including cobalamin, folate, pancreatic lipase, TLI, and resting serum cortisol concentration), and diagnostic imaging of the abdomen should be performed to rule out diseases that mimic CIE (Figure 1). Depending on baseline test results, patient characteristics, and the geographic area, additional diagnostic tests may include a bile acid stimulation test (for hepatobiliary disease), ACTH stimulation test (with low resting serum cortisol concentration), infectious disease testing (eg, *H. americana* PCR, *Histoplasma* spp. urine antigen), and advanced abdominal imaging. The results of these diagnostic tests should have been either negative (to rule out diseases that mimic CIE such as endoparasites or atypical hypoadrenocorticism) or consistent with a diagnosis of CIE (eg, hypocobalaminemia or intestinal wall thickening on ultrasonography) before proceeding with GI endoscopy (*SOR = strong*).

Justification: Because CIE is a diagnosis of exclusion, several diagnostic tests can help rule out diseases that mimic CIE and narrow down a possible diagnosis of CIE before GI endoscopy. The goal is to exclude extra-GI diseases (eg, pancreatitis, hepatobiliary conditions, chronic kidney disease, systemic infections) as well as GI infections and neoplasia[21,43,117,145,197,198] and to confirm evidence of malabsorption or nutrient loss in PLE cases.[72,96] Considering possible differential diagnoses,[41,107] these tests commonly include a CBC, serum biochemistry profile, urinalysis, TLI, pancreatic specific lipase, resting serum cortisol concentration, fecal parasitology (including *Giardia* spp. antigen testing), serum cobalamin and folate concentrations, and abdominal ultrasonography. Less commonly, an ACTH stimulation test may be performed to rule out hypoadrenocorticism.[107] Other markers, such as CRP[21,53] fecal calprotectin, and tests for systemic infectious diseases (eg, leishmaniasis, ehrlichiosis, histoplasmosis[87]) may be recommended based on clinician preference, test availability, and geographical prevalence. Certain tests become more important with suspicion of PLE, namely serum albumin concentration,[21,72,74,79] UPC, serum total and ionized calcium and magnesium concentrations, and thoracic imaging or point-of-care ultrasonography (POCUS),[72,96] as well as abdominal CT (eg, lipogranulomatous lymphangitis).

Some diagnostic imaging findings (lymphadenopathy, abdominal free fluid, masses, evidence of extra-GI organ changes) will trigger further investigations to differentiate CIE from intestinal or multicentric neoplasia (often lymphoma), including percutaneous fine-needle aspiration of abnormal structures, tissues, or fluids for cytology. In most cases, lack of response to an appropriate dietary trial should be ascertained before performing GI endoscopy.[46,145,197,198] In instances where hyporexia or inappetence preclude dietary trials from being performed, GI endoscopy is indicated for the diagnosis of intestinal inflammation of CIE (*QOE = high*).

Timing and decision for endoscopy

Recommendation: In dogs with suspected CIE where diseases that mimic CIE have been excluded (by physical examination, clinical pathology, and diagnostic imaging) and that have not had resolution of clinical signs after (ideally) at least 3 properly designed dietary treatment trials (refer to Section "Dietary treatment trial"), endoscopy for visualization of the mucosa with endoscopic biopsy sample collection and histopathology should be performed (defined as esophagogastroduodenoscopy or ileocolonoscopy) as part of the clinical evaluation. Pursuing GI endoscopy should be decided individually and based on patient history, signalment, chronicity, and severity of clinical signs and results of routine laboratory diagnostic testing (eg, marked hypoalbuminemia) (*SOR = strong*).

Justification: Endoscopy of the GI tract is generally a safe procedure (GI perforation is extremely rare and has a good prognosis[199,200]) but requires general anesthesia and fasting of the patient, as well as large bowel preparation (repeated enemas, colonic lavage, laxative administration, or some combination of these) before ileocolonoscopy. Endoscopy allows visualization of the GI mucosa for indicating disease changes[21,43,87,117,197,198,201] and for grading individual lesions (Supplementary File S11),[201] which may provide prognostic information.[21,46,96] Saved images or video sequences also can be used for later reassessment. There

are no absolute contraindications to GI endoscopy, but patients with marked hypoalbuminemia or severe clinical signs and systemic complications might not be ideal candidates for anesthesia or pre-procedural fasting.[21,72] Surgical biopsy samples are rarely needed but are an option if GI endoscopy is not definitive (eg, questionable GI lymphoma) or if lesions are beyond the reach of the endoscope (eg, based on abdominal ultrasonography).

Although endoscopy is valuable for obtaining targeted biopsy samples, histological findings do not differentiate dogs that will respond to dietary intervention versus other treatment modalities,[21] and many dogs do respond to a dietary treatment trial.[21,38,41] However, in clinically stable dogs with hypoalbuminemia or severe clinical signs, biopsy sample collection might be considered concurrently with a dietary treatment trial. Dogs with hypoalbuminemia can experience rapid progression of clinical signs, and histology findings can guide specific treatment[21,72,96] (*QOE = moderate*).

Endoscopic procedure

Recommendation: In dogs suspected of having CIE that are undergoing endoscopy for visualization of the GI mucosa with endoscopic biopsy sample collection and histopathology, both upper and lower GI endoscopy, defined as the evaluation of the esophagus, stomach, duodenum and proximal jejunum (esophagogastroduodenoscopy) with endoscopic examination of the ileum, cecum, and colon (ileocolonoscopy) should be performed (Supplementary File S11, Figure 3). Biopsy samples collected from each segment (ideally at least 10-15 per intestinal site) should be of adequate size, quality, and quantity to allow for thorough histopathologic evaluation (*SOR = strong*). Current information is too limited to recommend video capsule endoscopy (VCE) in dogs with CIE.

Justification: The presence and severity of GI signs help localize which segments should be examined endoscopically.[202] Esophagogastroduodenoscopy allows for direct visualization and targeted mucosal biopsy of the stomach, duodenum, and proximal jejunum (small dogs).[21,72,87,96,197] In animals with PLE, mucosal biopsy of the SI can determine the cause of enteric plasma protein loss.[96,197] Abdominal ultrasonography may identify SI hyperechoic mucosal striations suggestive of lymphatic dilatation in dogs with intestinal lymphangiectasia.[149] Hypocobalaminemia or marked hypofolatemia are other indications for GI endoscopy and suggest a focal or diffuse mucosal disorder affecting absorption in the proximal (duodenum) or distal (ileum) SI.[21,31,41,60,69,70,72,74,78,87,88,96,99–102,154]

Ileoscopy necessitates colonoscopy and is performed along with upper GI endoscopy when a diffuse enteropathy (CIE, intestinal lymphoma, lymphangiectasia) is suspected or colonic disease is complicated by systemic signs (eg, anorexia, weight loss). Ileal biopsy samples can provide a diagnosis that is unavailable with duodenal biopsy and samples may contain histopathologic lesions that differ from duodenal biopsy samples.[151] Blind biopsy of the ileum should be carefully considered if passage of the endoscope through the ileocolonic valve is not possible.[151]

Colonoscopy is indicated in animals with chronic or recurrent large bowel diarrhea that does not respond to routine therapeutic trials. The recommended number of adequate endoscopic biopsy samples obtained from each organ includes: stomach (*n* = 6), duodenum (*n* = 10-15), ileum (*n* = 3-5), and colon (*n* = 9-12).[202,203] Mucosal friability, granularity, ulcers or erosions, white speckles or spots (Figure 3), and masses often are associated with histopathologic abnormalities.[197,202] Abnormal mucosal appearances should be graded using published scoring indices,[3,201] recorded in the patient's medical record using standard endoscopic reporting forms (Supplementary File S11),[3] and provided to the pathologist to assist with interpretation of the histological findings. A single study has evaluated VCE of the GI tract in dogs with CIE, documenting no significant differences in mucosal lesions compared with healthy controls[204] (*QOE = high*).

Histopathologic evaluation

Recommendation: In dogs suspected of having CIE that undergo endoscopic collection of GI biopsy samples, routine histopathological evaluation of biopsy samples from each segment should include evaluation of hematoxylin/eosin (H&E)-stained sections using the World Small Animal Veterinary Association (WSAVA) or modified WSAVA criteria (Supplementary File S12) to assess inflammatory and morphologic lesion severity (Figure 4). Immunohistochemistry (IHC) to identify inflammatory markers and leukocyte populations, special stains (eg, periodic acid-Schiff [PAS]) to identify infectious agents, and molecular diagnostic tests to characterize dysbiosis (eg, fluorescence in situ hybridization [FISH]) or differentiate severe CIE from intestinal lymphoma (eg, PCR for antigen receptor rearrangements [PARR]) and other GI cancers should be considered, depending on clinical suspicion and findings on routine histopathology (*SOR = strong*).

Justification: Histopathologic evaluation of endoscopic GI biopsy specimens has largely followed guidelines published by the WSAVA[205] or a modified (simplified) version.[206] These guidelines provide numerical severity scores for morphological and architectural findings and inflammatory changes in the stomach (antrum and fundus), duodenum, and colon. Although not included in the original guidelines,[205] scores for the ileum also are reported using guidelines for the duodenum.[206] Optimal orientation of SI samples is essential for accurate assessment and ideally should include the full villous length and mucosa extending to the muscularis. Although the WSAVA guidelines represent the first comprehensive and standardized approach to histopathologic assessment, another study determined that for some variables, interobserver agreement among pathologists was poor and proposed a simplified version, which was repeatable among pathologists and showed significant correlation with clinical disease activity in dogs with CIE.[207]

For the stomach (antrum and fundus), fibrosis is the only morphological and architectural variable that should be assessed and quantified (0-3: normal to severe alteration). Fibrosis effectively reflects glandular loss as replacement is by collagen. For duodenum and ileum, villous stunting (atrophy), crypt dilatation, lacteal dilatation, and surface epithelial injury are the morphological variables that are assessed and quantified. In the colon, surface epithelial injury, crypt dilatation and distension, fibrosis, and goblet cell numbers (formally introduced in 2014[206]) are the morphological variables assessed and quantified. In all tissues, inflammatory variables to be assessed and quantified include lamina propria infiltrates of lymphocytes, plasma cells, eosinophils, and neutrophils (scored 0-3: normal/expected to

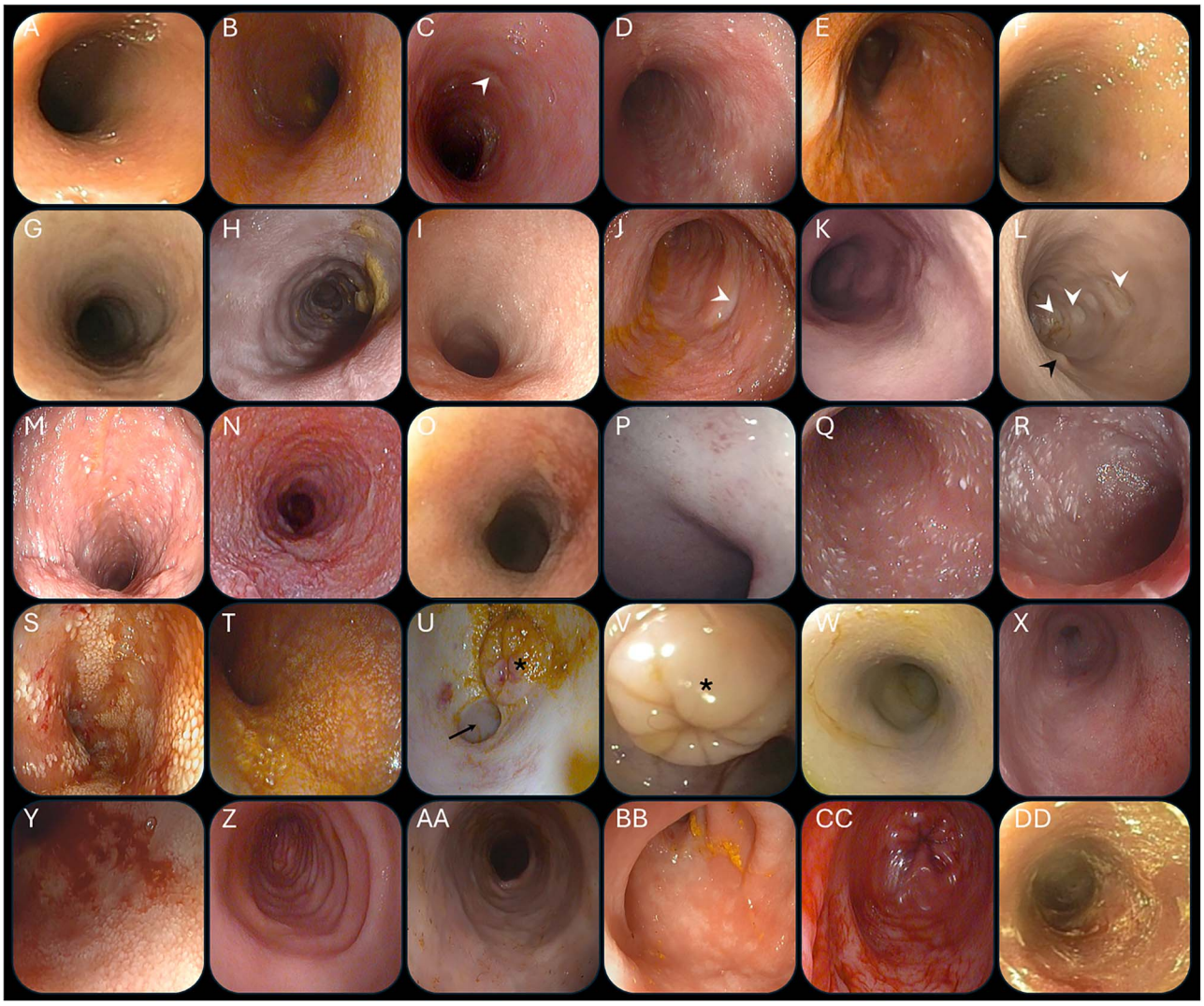


Figure 3 Image panel showing characteristic endoscopic findings in dogs with CIE. Normal small intestinal (A, W) or colon mucosa (Z), and various degrees of mucosal changes (B-U, X-Y, AA-DD), including erythema (B-E, AA, BB), edema (D-I, BB), increased granularity (D, J, K-M), friability (N, X, Y, CC), erosions/ulcerations (O, P, DD), and lymphangiectasia (Q-T). Black arrowhead: duodenal papilla (L); white arrowheads: discrete indentations associated with Peyer's patches (C, J, L); asterisk: ileo-colic valve (U, V); arrow: ileocecal junction (U).

markedly increased numbers). Additionally, in the stomach only, intraepithelial lymphocytes are assessed and quantified.

Determining lack of concordance between histopathologic diagnosis in the duodenum, compared with the ileum, for inflammation (eg, only 17% concordance for eosinophilic enteritis),[151] requires histopathologic evaluation, ideally to include both sites. Hematoxylin and eosin is the routine histochemical stain for all histopathologic assessments. Other stains, such as PAS for infectious agents and Masson's trichrome for fibrosis, currently have limited evidence to support their use in addition to what can be routinely assessed and scored based on H&E staining alone.

Although intestinal biopsy with histopathology remains the standard of reference for confirming mucosal inflammation and structural lesions of CIE, molecular tests can be used to characterize dysbiosis and differentiate severe CIE from intestinal lymphoma and other GI cancers. Molecular evidence of immunological dysregulation in affected dogs includes increased mucosal expression of nuclear factor "kappa-light-chain-enhancer" of activated B-cells (NF-κB), Ki-67 protein, and Toll-like receptor 2 (TLR2) mRNA; decreased intestinal interleukin-1 (IL-1) receptor antagonist (IL-1Ra): IL-1β ratio of mRNA and protein; and increased nucleotide-binding oligomerization domain 2 (NOD2) mRNA and NF-κB activity in inflamed tissues.[55,132,208,209] Increased numbers of innate (macrophages, dendritic cells [cluster of differentiation (CD)11c$^+$]) and adaptive (CD3$^+$ T, immunoglobulin G [IgG]) immune cells in the lamina contribute to the inflammatory process.[121–123,210–212] Although informative for defining disease pathogenesis, most tests are only used in research settings and are not available as commercial tests.

Dysbiosis is irrefutably associated with intestinal inflammation in dogs with CIE. Different molecular techniques (Illumina sequencing, FISH, and the qPCR-based fecal dysbiosis index) have confirmed general patterns of dysbiosis, including decreased biodiversity with increased numbers of Proteobacteria and decreased numbers of Fusobacteria, Clostridia, and Bacteroidaceae in biological samples.[83,147,180] Using FISH, AIEC are found within inflamed colonic mucosa of dogs with GC or GIC.[83,135,213]

Molecular testing (Supplementary File S6) may be useful in differentiating intestinal lymphoma (small cell) from severe CIE

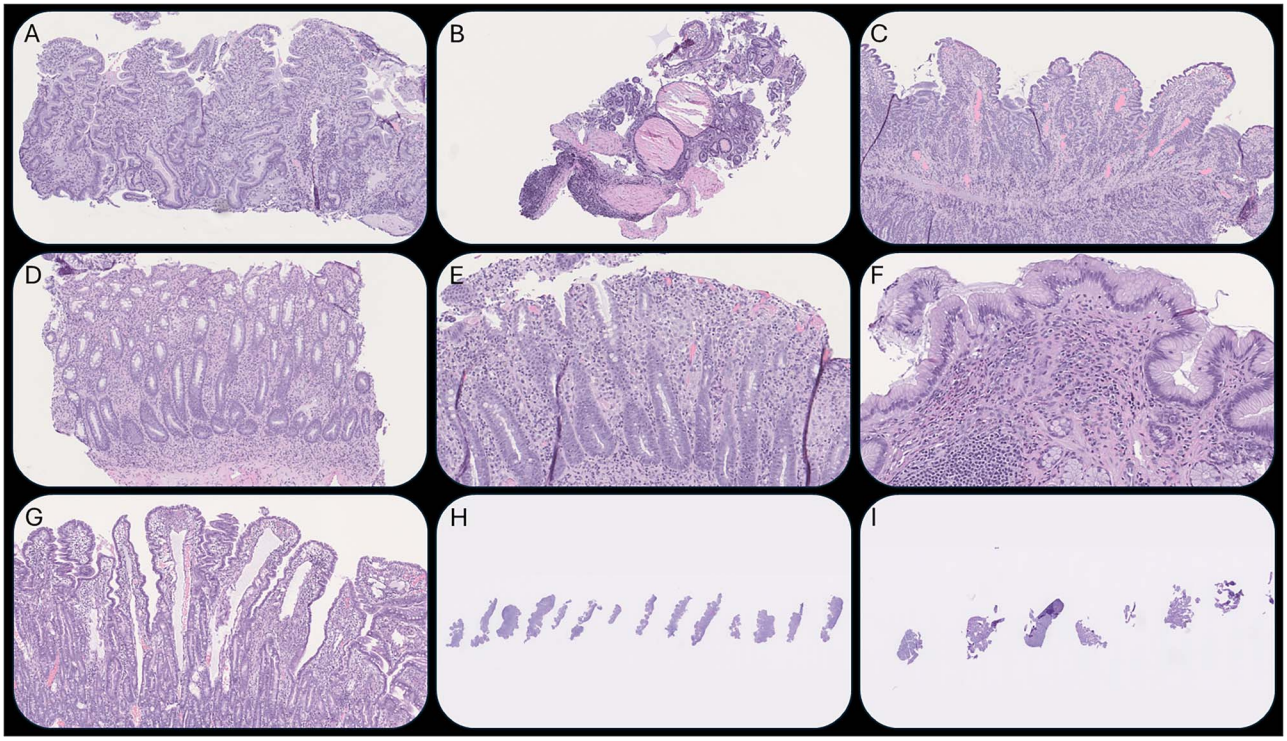


Figure 4 Image panel showing characteristic histopathologic findings in dogs with CIE. (A) Duodenum: diffuse villous atrophy (score: 2) with moderate lymphoplasmacytic inflammation (score: 2); good sample orientation. (B) Duodenum: large crypt abscesses (score: 3) but poor sample quality (small and incomplete). (C) Duodenum: diffuse, marked lymphoplasmacytic inflammation (score: 3) with moderate villous atrophy (score: 2); good sample orientation. (D) Colon: diffuse, moderate to marked (score: 2-3) histiocytic and neutrophilic (score: 1) colitis; goblet cell loss (score: Dec2). (E) Colon: as (D) surface ulceration (score: 2); dark lines = artefactual tissue folds. (F) Stomach, antrum: multifocal, moderate to marked eosinophilic (score: 2-3) gastritis. (G) Ileum: diffuse, marked lymphangiectasia (score: 3). (H) Duodenum: good number (n = 14) and well-oriented samples. (I) Duodenum: low number of poorly oriented samples (n = 6) and fragments; many only villous tips, thus inadequate for assessment.

by performing sequential analysis of H&E histology, immunophenotyping, Ki-67, and PARR or by confirming increased numbers of Forkhead box p3-positive (Foxp3$^+$) cells (regulatory T cells [Tregs]) in neoplastic tissues.[214,215] The expression of selected microRNAs (miR) in feces (miR-451, miR-223, and miR-27a) and serum (miR-20b, miR-148a-3p, miR-652) may serve as non-invasive markers to differentiate GI cancer from CIE in dogs[85] (*QOE* = *moderate*).

Follow-up endoscopy and histopathology

Recommendation: In dogs diagnosed with CIE based on histopathology that have not experienced resolution or that show worsening of clinical signs after the induction phase of treatment (ie, a properly designed treatment trial), clinicians might consider endoscopic re-evaluation of the GI mucosa (or, if full-thickness biopsy or sampling of other abdominal organs is indicated, an exploratory laparotomy or laparoscopy) and re-biopsy for histopathology as part of the clinical re-evaluation to exclude GI lymphoma missed on the first evaluation (*SOR* = *conditional*).

Justification: Few reports have shown the benefit (eg, improvement in histological inflammation) of repeat GI endoscopy with histopathology to evaluate mucosal healing and deep remission in dogs with CIE.[66,180,216] The primary value of repeat endoscopy with mucosal biopsy is to exclude GI lymphoma or other GI cancers missed on the first diagnostic evaluation (*QOE* = *low*).

Treatment approach

As for any patient, symptomatic treatment (eg, antiemetics) should be tailored to the individual clinical presentation.

Dietary intervention

Recommendation: Several diet categories can be effective in dogs with CIE and should be used first, whenever possible. Multiple trials using different diet categories should be performed, with a minimum of 3 therapeutic diet trials lasting at least 2 weeks of exclusive feeding each (*SOR* = *strong*). A detailed diet history (appendix) should be obtained, and the specific GI signs considered, to determine which diets should be prioritized for the affected dog. If dietary intervention alone does not induce remission, additional treatment should be pursued, and the diet that best helped decrease the clinical signs should be continued.

Justification: An RCT (Figure 5) showed that although a therapeutic GI diet could induce remission (6/8 dogs, 75%), long-term response was less likely (17%) compared with dogs managed using a soy-based hydrolyzed protein diet (67% short-term, 79% long-term; Supplementary File S7-3D).[153] Another RCT reported short-term response in 88% and remission in 31% of dogs with CIE.[157] An uncontrolled study reported that a therapeutic GI diet induced clinical remission in 12/15 dogs (80%) with mild to moderate CIE a median of 13 days after starting the trial.[162]

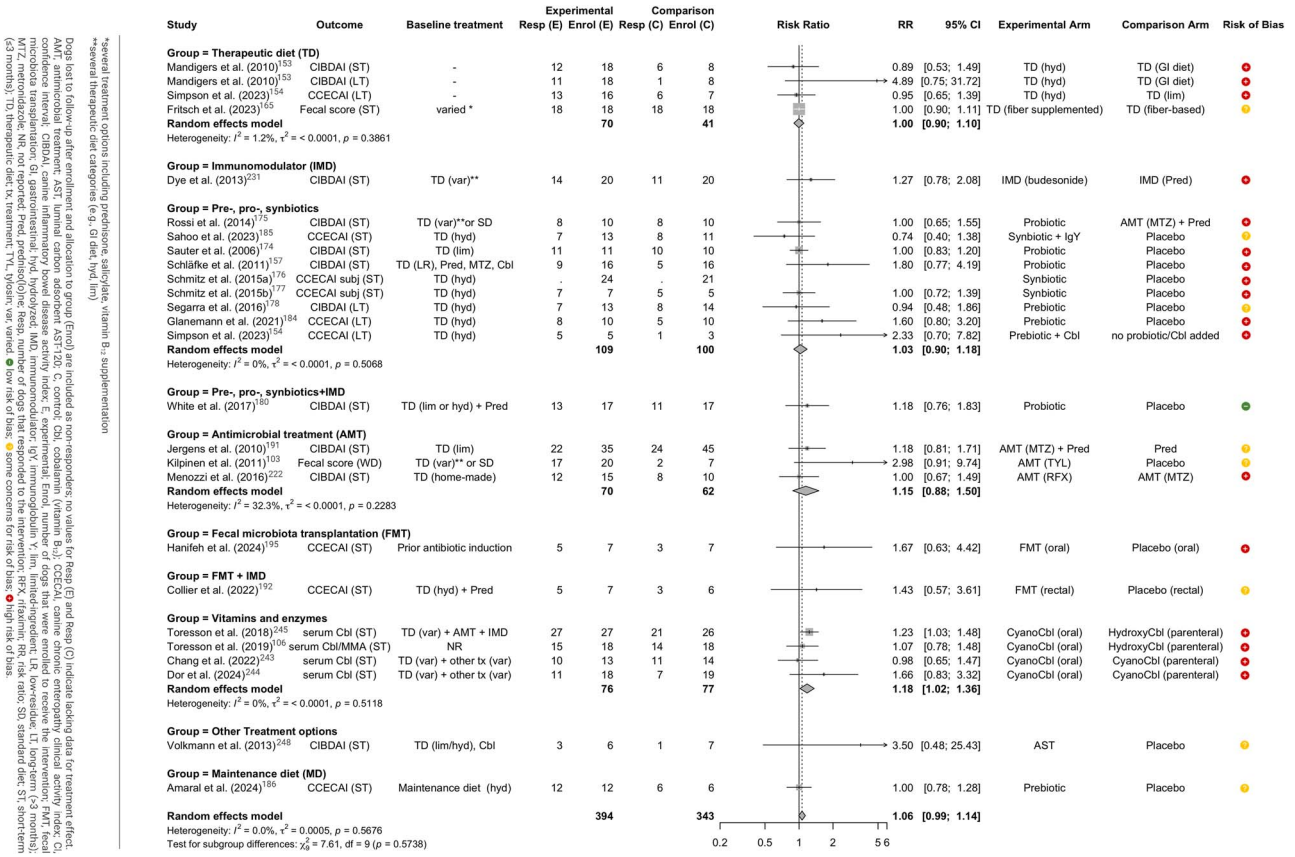


Figure 5 Forest plot summarizing the extracted data and meta-analysis of the 24 randomized-controlled trials.

Hydrolyzed protein diets are reported to have a 64–89% remission rate in referral practice, with the most significant improvement in clinical signs within 2 weeks of initiating the diet.[33,38,66,153,154,156] However, only 2 of these studies were RCTs and their risk of bias was high, mainly because of loss to follow-up after allocation to treatment (Supplementary File S7-3D and Figure 5). This diet category also improved specific intestinal histologic variables,[66,156] microbiota structure, and concentrations of fecal secondary bile acids.[33] One RCT of 23 dogs with CIE (non-PLE) showed no difference in response rates between hydrolyzed fish diet or a control diet of intact chicken and fish, with 83% of dogs responding to the allocated diet.[154] Although 1 retrospective 2-arm cohort study concluded that significant clinical improvement was seen in dogs with CIE fed with a hydrolyzed protein diet rather than a novel protein diet,[160] another retrospective study showed no difference between these 2 categories of diet.[38] However, the potential for bias in these retrospective cohort studies was high because the allocated treatment was confounded by indication and the risk of selection bias was high.

Exclusive feeding of a therapeutic elemental protein diet improved clinical signs in 16/23 (70%) dogs with inadequately controlled CIE.[168]

In a prospective 2-arm cohort study of 70 dogs with CIE, 56% responded favorably to a novel protein (salmon and rice-based) diet, with 31 dogs (79%) having no recurrence for up to 3 years when switched back to their original diet after 14 weeks of the elimination diet.[21] Two separate one-arm cohort studies assessing a salmon and rice-based diet in dogs with CIE showed responses of 10/26 (38%) and 39/65 (60%) after 10 days of feeding, respectively.[55,171] Two non-randomized controlled studies showed no improvement in histologic grade of intestinal mucosal lesions after dietary change to a salmon- and rice-based diet.[216,217] Limited data is available on insect-based or animal protein-free diets.[218]

Low-fat diets (<2 g of fat/100 kCal) are effective for intestinal lymphangiectasia (IL) causing PLE.[158,159,161,169,219] No RCTs are available to evaluate the impact of a low-fat diet. A one-arm cohort non-blinded retrospective study in 11 Yorkshire terriers with presumptive PLE and another prospective one-arm cohort study of 14 dogs with presumptive PLE and ultrasonographic evidence of IL showed that some dogs (55% in the second study) responded to a low-fat diet alone.[161,169] A one-arm unblinded trial showed that dietary fat restriction also can be effective in dogs with IL that were unresponsive to prednisolone or experienced a relapse with tapering of prednisolone (19/24 dogs, 79%).[158]

A very good to excellent response to a therapeutic, highly digestible diet supplemented with a median initial dose of 2 tablespoons of psyllium per day (fiber-enriched diet) was shown in an unblinded one-arm cohort study of 37 dogs with chronic idiopathic large bowel diarrhea, which fits the definition of CIE,[163] and a higher dose (4 tablespoons/day) led to a significant improvement in an unblinded one-arm cohort of 15 affected working dogs.[220] An RCT including 18 dogs fed a therapeutic food containing selected dietary plant fibers with antioxidant and polyphenol compounds improved signs of chronic large bowel diarrhea significantly within 1 day of initiating the diet, with 68% of dogs having complete remission by day 56.[164] A polyphenol-rich fiber supplement maintained 100% remission

in an unblinded retrospective one-arm cohort of 39 dogs with well-managed chronic gastroenteritis.[165]

All 18 dogs with CIE fed a home-cooked diet supplemented with coconut oil responded well to the diet change, demonstrating improvement in their clinical signs.[170] Home-cooked low-fat diets also have been shown to be effective for PLE and IL.[158,219] However, the increased cost of a home-cooked diet versus therapeutic dry foods and time commitment should be considered.[166] Diet decreases clinical severity scores more and generally attains better outcomes compared with glucocorticosteroids.[21,38,82,221]

Some dogs with CIE may need up to 3 therapeutic diet trials before a response is seen.[167] Although a response within 2 weeks of initiating the diet can be seen,[21,33,66,134,154,156,168] for dogs with concurrent dermatologic or intermittent GI signs, a longer period may be needed to determine effectiveness.[172] Transitioning to the original diet after 14 weeks of a novel protein (salmon and rice) diet resulted in 80% (31/39) of dogs remaining in remission,[21] and after a median of 90 days (range, 43-223 days), 11/16 (69%) dogs on a soy-based hydrolyzed protein diet and 4/6 (67%) dogs on the GI diet relapsed within a week of rechallenge.[153] Therefore, some dogs can transition successfully away from the diet, but the optimal time is unknown. Dogs with PLE caused by CIE or IL should remain on dietary management long-term to prevent relapse.[173] Pursuing additional treatment if diet alone does not induce remission benefits from utilizing the diet that helped decrease the clinical signs the most, and may help decrease the dose of medication needed or allow future discontinuation of medication.[155,158]

Microbiome modulation treatment

Antibiotic treatment

Two RCTs with moderate to high risk of bias (Supplementary File S7-3C-D) evaluated antimicrobial treatments in dogs without a response to dietary treatment trials.[103,222] Twelve studies are either 2-arm cohort or retrospective one-arm cohort studies, and they have limitations regarding outcomes, non-blinding, loss-to-follow-up, and confounding by indication.[135,188–190,213,223–229]

Evidence & recommendation I: In dogs with CIE that have failed dietary trials, antibiotics such as tylosin (25 mg/kg q24h for 7 days), metronidazole (10-15 mg/kg q12h for 21 days), or rifaximin (25 mg/kg q12h for 21 days) *might* be effective in achieving short-term partial or complete response in dogs with chronic diarrhea (85–100%) (*QOE = moderate*[103,188,222,225]). However, few high-quality trials have assessed these interventions (data on clinical outcomes are represented in S07-3C-D and Figure 5). Some of these studies had substantial loss to follow-up, which conservatively evaluated is assumed to represent failure to respond. For dogs with CIE responsive to tylosin, lower dosages (5-16 mg/kg q24h) *might* achieve similar treatment responses (*QOE = moderate*[189]). Oxytetracycline (10 mg/kg q8h for 4 weeks) *might* be effective (*QOE = low*[225]).

However, because several studies report that dogs relapse shortly after discontinuation of antibiotic administration and antibiotics can induce substantial long-lasting intestinal dysbiosis, antimicrobial stewardship *strongly dictates* that *antibiotics* should *be reserved* for cases that have failed any other treatment attempts (*QOE = moderate*[38,103,188–190]).

Evidence & recommendation II: In dogs with histologically confirmed GC or GIC due to AIEC, treatment with enrofloxacin (4.8-12.8 mg/kg q24h for 4-19 weeks) *should* be initiated (*QOE = moderate*[135,213,224,227,228]). Other fluoroquinolones *might* be considered and likely are similarly effective (*QOE = low*[213,228]). Given the frequency of antimicrobial resistance in AIEC-associated GC, antimicrobial sensitivity testing determined from colonic biopsy samples *should* be performed before starting antibiotic treatment and adjustments should be based on those results (*QOE = moderate to strong*[135,213,227–229]). Antibiotic choices *should* be made noting that in vitro efficacy against AIEC in GC does not always result in in vivo efficacy (*QOE = moderate*[135,229]).

Empirically, amikacin, cefazolin, doxycycline, and chloramphenicol *could* serve as alternatives to enrofloxacin (*QOE = low*[135,223,226,229]) when resistance is suspected or confirmed. Whether fecal microbiota transplantation (FMT) could present another alternative treatment option[194] requires further study.

Prebiotics, probiotics, synbiotics, and fecal microbiota transplantation

Recommendation: Pre-, pro-, and synbiotics have a limited role in the treatment of CIE but seem well tolerated (*SOR = conditional*). One specific multi (8)-strain probiotic ("De Simone formulation" [DSF] at 112—225 $\times$ 10^8 lyophilized bacteria/kg PO q24h) might be considered in dogs with CIE that have failed dietary treatment trials (*SOR = conditional based on response to dietary intervention*). Combination of probiotics (eg, *Saccharomyces boulardii*) with immunosuppressant treatment might be considered to aid with clinical improvement of dogs with CIE with and without PLE (*SOR = weak*). Fecal microbiota transplantation might be considered as adjunctive treatment in dogs with CIE that have not achieved or maintained clinical remission with other treatments (*SOR = conditional based on treatment response*).

Justification: Several products have been studied in dogs with CIE. Benefits are variable and often not repeatable due in part to different products used, different populations studied, measured outcomes, and underpowered studies.[157,174–187] Separate RCTs have investigated the efficacy of prebiotics[178,184,186] and probiotics[174,175,180] in dogs with CIE-FR (Supplementary File S7-3D, Figure 5). All studies reported no improvement in clinical response compared to feeding an elimination diet without prebiotic, probiotic, or placebo administration,[174,178,184,186] although improved histology scores were observed in dogs fed chondroitin sulfate and prebiotics.[178] Two other trials have evaluated the effect of an 8-strain probiotic (DSF containing 4 strains of *Lactobacillus* [*Lactobacillus paracasei* DSM 24733, *L. plantarum* DSM 24730, *Lactobacillus acidophilus* DSM 24735, and *Lactobacillus delbrueckii* subsp. *bulgaricus* DSM 24734], 3 strains of *Bifidobacterium* [*Bifidobacterium longum* DSM 24736, *B. breve* DSM 24732, and *B. infantis* DSM 24737], and 1 strain of *Streptococcus salivarius* subsp. *thermophilus* DSM 24731) in dogs with CIE-IR.[175,180] One randomized open-label trial compared an elimination diet with prednisone and metronidazole to probiotic treatment for 60 days.[175] Although CIBDAI normalized in both treatment arms, it decreased more rapidly in dogs treated with prednisone and metronidazole. However, dogs treated with DSF probiotic showed a tolerogenic mucosal immune response characterized by decreased numbers of lymphocytes and increased numbers of beneficial regulatory T-cells in the intestinal mucosa.[175] The second RCT investigated CIE dogs treated with an elimination diet and prednisone compared to a combination of

diet, prednisolone, and DSF probiotic administered for 8 weeks.[180] Both treatments resulted in rapid clinical remission. Although no improvement occurred in histologic inflammation, probiotic treatment was associated with upregulated tight junction protein expression.[180] (*QOE* = moderate) An RCT evaluating probiotic *Bifidobacterium animalis* NCIMB 41199 compared to placebo in dogs with CIE reported no group differences in clinical endpoints.[157] Another controlled trial evaluated *Saccharomyces boulardii* as a probiotic in 20 dogs with CIE, 8 of these also with PLE, receiving either *S. boulardii* or placebo with anti-inflammatory drugs for 60 days.[181] Clinical activity, fecal consistency, and BCS improved in dogs receiving adjunctive *S. boulardii* compared to placebo[181] (*QOE* = *moderate*).

Two RCTs have investigated a synbiotic containing *Enterococcus faecium* (EF) strain NCIMB 10415 E1707, fructooligosaccharides, and gum Arabic (synbiotic EF).[176,177] In 1 study, dogs with CIE-FR that received a hydrolyzed protein diet with either synbiotic EF ($n = 7$) or placebo ($n = 5$) for 6 weeks showed no difference in clinical scores, histology, and mucosal inflammatory and cytokine gene expression.[176] The second study, investigating the effects of synbiotic EF on the inflammasome, found no effect on gene expression after 6 weeks of ex vivo treatment with synbiotic EF and hydrolyzed protein diet, whereas IL-1β protein expression decreased in dogs fed an elimination diet.[177] Another RCT of 20 dogs with CIE showed no difference in clinical and endoscopic scores between dogs that received a hydrolyzed protein diet with either synbiotic-immunoglobulin Y (synbiotic-IgY; multi-strain probiotic, mannooligosaccharides, and IgY, $n = 11$) or placebo ($n = 9$) for 6 weeks.[185] Only synbiotic-treated dogs showed decreased fecal calprotectin and serum CRP concentrations, as well as favorable changes in mucosal bacteria at trial completion.[185] One case series, including 12 dogs with CIE-FR fed a hydrolyzed protein diet and synbiotic EF compared to placebo for 6 weeks, found no differences in fecal microbial composition compared to healthy dogs fed a hydrolyzed diet[182] (*QOE* = *moderate*).

Two RCTs investigated the efficacy of FMT in dogs with CIE.[192,195] One trial that randomized tylosin-responsive dogs to receive either PO FMT ($n = 7$) or placebo ($n = 7$) for 4 weeks showed no difference in treatment efficacy between groups but increased α-diversity in dogs treated with FMT.[195] A second RCT investigating 13 dogs with CIE fed a hydrolyzed or novel protein diet and treated with corticosteroids, and then randomized to receive either FMT ($n = 7$, rectal enema) or placebo ($n = 6$) for 30 days, also documented no difference in clinical (CCECAI) scores between treatment groups.[192] Separate retrospective case series using PO FMT capsules in 5 dogs and multiple rectal FMT enemas in 41 dogs in combination with medical and dietary treatment suggest that FMT may be a useful adjunctive treatment in some poorly responsive dogs with CIE.[194] Others report that CCECAI scores improved in 6/7 (86%) and 20/27 (74%) dogs that received a single rectal FMT[196] or PO freeze-dried FMT,[193] respectively (*QOE* = *weak*).

Immunomodulatory treatment

Recommendations: Induction treatment of CIE in dogs with or without PLE that have either responded partially or not responded to adequate dietary treatment (with or without the addition of probiotics) should be treated with either prednisolone or prednisone (induction of 1-2 mg/kg PO q24h or 20-40 mg/m^2 PO q24h for dogs $>$ 25 kg[230] for 2-3 weeks, and then tapered according to clinical response) or budesonide (3 mg/m^2; 3-7 kg: 0.5-1 mg PO q24h, 7-15 kg: 1-2 mg PO q24h, 15-30 kg: 2-3 mg PO q24h, $>$ 30 kg: 3-5 mg PO q24h for at least 3-4 weeks,[231] and then tapered based on clinical response[155]), or prednisolone or prednisone with cyclosporine (3-5 mg/kg PO q12-24 hours for at least 6 weeks) with the prednisolone or prednisone tapered first. If a diet can be identified that previously has induced partial remission, it should be given concurrently and should be continued beyond cessation of immunosuppressive treatment (*SOR* = *strong*).

Dogs with PLE that have failed dietary intervention might benefit from immunomodulatory treatment with glucocorticoids (dosages as above), with possible muscle atrophy and risk of thromboembolism to be considered (*SOR* = *strong*). In PLE dogs that have failed corticosteroid treatment, cyclosporine as monotherapy (5 mg/kg PO q24h for 6-10 weeks) or combined with prednisolone or prednisone, or chlorambucil (2-4 mg/m^2 PO q24h) combined with prednisolone should be considered (*SOR* = *strong*). Chlorambucil administration requires monitoring for hepatic enzyme induction and bone marrow suppression.

Justification: When comparing CIE induction treatment with either prednisone (1 mg/kg PO q12h for 3 weeks, then halved for 3 weeks) or budesonide (1-5 mg/dog PO q24h, based on size) in one RCT[231] or prednisone (1 mg/kg PO q12h for 3 weeks) versus a combination of prednisone and metronidazole (10 mg/kg PO q12h for 3 weeks) in another RCT,[191] $\geq$69% of dogs reached remission within 2-3 weeks, regardless of the type of treatment. No differences in corticosteroid-related adverse effects were noted between budesonide and prednisone treatment,[231] which can include muscle atrophy caused by protein catabolism[232] and thromboembolic risk as a consequence of hypercoagulability[233] (*QOE* = *moderate*).

Uncontrolled (1 arm) prospective and retrospective treatment trials of dogs with CIE that have failed dietary treatment as sole intervention reported good efficacy of prednisone in combination with diet,[62] prednisone in combination with metronidazole and diet,[234] or prednisolone, prednisone, or budesonide in combination with metronidazole or cyclosporine,[27] with remission achieved in all dogs within 3-4 weeks (*QOE* = *moderate*). Because there is no direct comparison, effects cannot be definitively attributed to the immunomodulatory intervention because additional time on the therapeutic diet also may be a factor that contributed to improvement in these dogs. However, dietary trials were conducted before the addition of the immunomodulator.

There is additional weak evidence to recommend budesonide in dogs with CIE that have failed dietary treatment from 1 of 2 case series.[235,236] Clinical remission was achieved in 8/11 dogs (73%) in 1 study,[235] but none of 14 dogs in the second study.[236] A prospective one-arm cohort study on 6 dogs with CIE treated with budesonide (3 mg/m^2 PO q24h) documented significant suppression of the pituitary–adrenal axis, indicating that systemic effects similar to prednisolone can be seen in dogs treated with budesonide, although clinical adverse effects may be less severe.[237]

For dogs with PLE that have failed dietary intervention, uncontrolled prospective and retrospective studies showed response rates of $\geq$74% with prednisolone as monotherapy (induction with 1-2 mg/kg PO q24h) or combined with either cyclosporine (3-5 mg/kg PO q24h for 6-8 weeks)[96,238,239] or chlorambucil (2-4 mg/m^2 PO q24h).[240] There is weak evidence that the combination treatment of cyclosporine with prednisolone has similar efficacy as prednisolone alone.[96]

Moderate evidence showed that 7/10 dogs (70%) with PLE that failed dietary intervention and prednisolone treatment (induction with 2 mg/kg PO q24h for 10 days, then tapered over 10 weeks) responded to cyclosporine monotherapy (5 mg/kg PO q24h for 10 weeks) and remained in remission 3 years after discontinuing cyclosporine treatment.[21]

In a case series,[241] 4/6 dogs (67%) with PLE caused by lipogranulomatous lymphangitis had a partial or complete response to prednisolone plus metronidazole, and successful dietary and medical management was reported in another 4 dogs.[242]

Vitamins and enzymes

Recommendation: Suboptimal vitamin B_{12} status should be treated with either PO or parenteral cobalamin supplementation, with reevaluation of cobalamin status after treatment discontinuation (*SOR* = *strong*). Supplementation to restore vitamin B_9 or vitamin D deficiency causing hypocalcemia might be carefully considered (*SOR* = *conditional*). Currently, no evidence supports pancreatic enzyme supplementation (*SOR* = *weak*).

Justification: In 4 RCTs, 126 dogs with mild to severe CIE were randomized to receive either adjunctive PO cyanocobalamin (25 μg/kg for 84 days; n = 68) or SC vitamin B_{12} (0.25-1.2 mg/dog hydroxycobalamin [n = 14] or 25 μg/kg cyanocobalamin [n = 44] for 42 days; Supplementary File S7-3D, Figure 5).[106,243–245] Outcome measures included normalization of serum cobalamin concentration in all dogs and improvement or normalization of indicators of intracellular cobalamin deficiency (homocysteine [HCY] and/or methylmalonic acid [MMA]) in 3 studies.[106,243,244] Adverse effects were not reported in any dogs.[106,243–245] Adherence and owner satisfaction were 100% with PO supplementation versus 97% with parenteral administration.[244] A RCT investigating the response of 16 dogs with CIE (non-PLE) and 8 with PLE to a 12-week intervention using a hydrolyzed fish-based diet showed that vitamin B_{12} supplementation is achievable through diet fortification (10 mg/kg versus 0.06 mg/kg) but that serum vitamin B_9 (folate) concentrations might concurrently decrease.[245] An uncontrolled study of 51 dogs also showed normalization of serum cobalamin concentrations through daily PO supplementation (0.25-1.0 mg/dog for 20-202 days; Supplementary File S7-3E).[246]

Two retrospective cohort studies detected hypovitaminosis D in dogs with PLE[247] and as a prognostic differentiator based on treatment response and outcome,[80] but vitamin D supplementation has not yet been reported in dogs with CIE. No published studies have evaluated vitamin E or K supplementation or possible benefits of pancreatic enzyme replacement therapy.

Additional treatment considerations

Recommendations: Limited information currently is available to recommend alternative or other adjunctive treatment options for CIE, such as luminally active substances (carbon adsorbents, bile acid sequestrants), mesenchymal stem cells, or implementation of an exercise program (*SOR* = *conditional*).

Additional treatment considerations for dogs with PLE might include the use of anticoagulants, but insufficient evidence currently is available to recommend an ideal thromboprophylaxis protocol. Other treatment options (eg, octreotide) require more studies in dogs with PLE (*SOR* = *conditional*).

Justification: One RCT, including 10 dogs with mild to moderate CIE, showed that administration of a luminal carbon adsorbent (AST-120 at 0.1 g/kg PO q12h for 3 weeks) was not associated with a higher rate of remission (3/5 dogs responded) versus placebo (1/5 dogs responded).[248] Short- and long-term treatment responses (81–100% remission) have been documented in uncontrolled studies, including 31 dogs with mild to moderate CIE after allogeneic adipose tissue-derived mesenchymal stem cell injection.[249–252] A structured exercise program, including aerobic and resistance training for 6 weeks, significantly improved clinical signs in sedentary dogs with CIE receiving standard treatment.[253] Use of adjunctive bile acid sequestrant (cholestyramine 40-60 mg/kg PO q12-24 hours) treatment for 5-11 months was successful in treating 2 dogs with refractory CIE without causing adverse effects in 1 case series.[254]

Although a standard anticoagulant protocol remains to be established, the increased risk of thromboembolism in cases of PLE[77,94,255] warrants consideration in the therapeutic plan for these cases (eg, rivaroxaban or clopidogrel). However, future research should determine the preferred medication choice and dosage, duration of treatment and clinical endpoint, and monitoring plan. Adjunctive human serum albumin (25%) administration had an 81% response rate in 21 dogs with treatment-refractory PLE but caused acute reactions in 10% and delayed reactions in 11% of the dogs.[256] Octreotide at 4-39 μg/kg SQ q24h was associated with improvement in 6/12 (50%) dogs with refractory PLE on dietary and immunomodulatory treatment in 1 retrospective study.[257]

Monitoring

With CIE presenting as a diagnosis of exclusion, several patient characteristics are recommended for monitoring regardless of the stage of the sequential diagnostic evaluation or current form of treatment. These should include longitudinal assessment of BCS and MCS, body weight, severity of clinical disease (CIBDAI or CCECAI score), fecal score, any potential medication adverse effects, and overall quality of life every 1-2 weeks. Markers of intestinal function (including serum cobalamin concentration), inflammation, and protein loss might be monitored during treatment if baseline results at diagnosis were established. In patients with PLE, serum albumin concentrations should at least initially be reevaluated more frequently (every 1-2 weeks) and then at longer intervals (every 2-3 months) once the dog is normoalbuminemic and remains clinically stable. Mucosal reassessment (ie, repeat endoscopy and re-biopsy for histopathology) might be considered to exclude other differential diagnoses (eg, GI lymphoma) potentially missed on the first evaluation.

The panel recommends defining clinical responsiveness preferably stratified based on the quality of the response as CIBDAI or CCECAI reduction $>$ 75% (remission), 25%-75% (partial response), or $<$ 25% (no response),[180,191,222] but at least a dichotomous assessment by CIBDAI or CCECAI reduction of $>$ 50% (response) versus $\leq$ 50% (no response).[168,176,177,248]

Research and perspective

Many novel diagnostic tests have been evaluated and shown to be promising in dogs with CIE within the past decade, most of which require further study of clinical utility as either stand-alone

diagnostic tests or integral components of diagnostic algorithms (eg, biomarker panels). As an extension of the current clinical scores and objective laboratory markers, such algorithms also may include other prognostic criteria (eg, predictors for relapse), markers for deep remission, quality-of-life indices, and behavioral biomarkers (eg, detection of discomfort based on behavioral cues). Digital health options and artificial intelligence models also can be expected to play an increasingly important role in managing dogs with CIE in the future and aid in revisiting the consensus definition for remission of CIE.

Recent progress in further understanding crosstalk within the mucosal immune system, microbiome-host interactions, and associated metabolic pathways is expected to result in novel treatment strategies tailored to the individual patient (eg, intestinal microbiome modulation, bile acid sequestration, pathway-specific monoclonal antibody treatments). Knowledge gaps to be filled also include GI endocrine pathways and the role of intestinal dysmotility in CIE in dogs. Given the small number of RCTs currently available to evaluate various treatment options for dogs with CIE, continuing efforts to pursue well-designed multicenter clinical studies are critical to further advance canine gastroenterology and optimize strategies and resources for this important research in the future.

Conclusion

Diagnosing CIE requires an integrated stepwise approach, including patient history, clinical signs, physical examination findings, sequential diagnostic tests (ie, clinicopathologic variables), and diagnostic imaging to establish a minimum database and rule out relevant diseases that mimic CIE. The individual diagnostic and patient monitoring strategy should be determined based on the dog's signalment (age, breed) and history (chronicity and severity of clinical signs, medications, and dietary history), and disease- or organ-specific non-invasive tests might be integrated into the clinical decision-making algorithm. In a stable dog, a sequence of different diagnostic interventions (treatment trials) then is recommended before more invasive diagnostic tests (eg, GI endoscopy with biopsy for histopathology; Figure 1). Documentation of CIE is a prerequisite for immunomodulatory treatment, which requires more invasive diagnostic tests, and established endoscopic and histologic scoring systems to aid in the standardized assessment of dogs suspected to have CIE. Clinical response to treatment remains the primary prognostic indicator.

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Supplementary material

Supplementary material is available at *Journal of Veterinary Internal Medicine* online.

Conflicts of interest

These are relevant to the ACVIM-endorsed statement.

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Authors declare no off-label use of antimicrobials.

Institutional animal care and use committee or other approval declaration

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References

1. O Neill DG, Church DB, PD MG, Thomson PC, Brodbelt DC. Prevalence of disorders recorded in dogs attending primary-care veterinary practices in England. *PloS One*. 2014;9:e90501. https://doi.org/10.1371/journal.pone.0090501
2. Jergens AE, Heilmann RM. Canine chronic enteropathy–current state-of-the-art and emerging concepts. *Front Vet Sci*. 2022;9:923013. https://doi.org/10.3389/fvets.2022.923013
3. Washabau RJ, Day MJ, Willard MD, et al. Endoscopic, biopsy, and histopathologic guidelines for the evaluation of gastrointestinal inflammation in companion animals. *J Vet Intern Med*. 2010;24:10-26. https://doi.org/10.1111/j.1939-1676.2009.0443.x
4. Hinchcliff KW, Morley PS, DiBartola SP, Taylor SD, Harrell KA. ACVIM-endorsed statements: consensus statements, evidence-based practice guidelines and systematic reviews. *J Vet Intern Med*. 2023;37:1957-1965. https://doi.org/10.1111/jvim.16869
5. Hsu C-C, Sandford BA. The Delphi technique: making sense of consensus. *Pract Assess Res Eval*. 2007;12:1-8. https://doi.org/10.7275/pdz9-th90
6. Thangaratinam S, Walker P, Freeman-Wang T, Luesley D, Cruickshank M, Redman CEW. Identifying the performance criteria for appraisal of colposcopists: benchmarking Delphi. *BJOG*. 2007;114:1288-1291. https://doi.org/10.1111/j.1471-0528.2007.01442.x
7. Devillé WL, Buntinx F, Bouter LM, et al. Conducting systematic reviews of diagnostic studies: didactic guidelines. *BMC Med Res Methodol*. 2002;2:9. https://doi.org/10.1186/1471-2288-2-9
8. Yang B, Olsen M, Vali Y, et al. Study designs for comparative diagnostic test accuracy: a methodological review and classification scheme. *J Clin Epidemiol*. 2021;138:128-138. https://doi.org/10.1016/j.jclinepi.2021.04.013
9. Olsen M, Zhelev Z, Hunt H, Peters JL, Bossuyt P, Hyde C. Use of test accuracy study design labels in NICE's diagnostic guidance. *Diagn Progn Res*. 2019;3:17. https://doi.org/10.1186/s41512-019-0062-9
10. Rutjes AWS, Reitsma JB, Vandenbroucke JP, Glas AS, Bossuyt PMM. Case–control and two-gate designs in diagnostic accuracy studies. *Clin Chem*. 2005;51:1335-1341. https://doi.org/10.1373/clinchem.2005.048595
11. Hall MK, Kea B, Wang R. Recognising bias in studies of diagnostic tests part 1: patient selection. *Emerg Med J*. 2019;36:431-434. https://doi.org/10.1136/emermed-2019-208446
12. Kea B, Hall MK, Wang R. Recognising bias in studies of diagnostic tests part 2: interpreting and verifying the index test. *Emerg Med J*. 2019;36:501-505. https://doi.org/10.1136/emermed-2019-208447
13. Lijmer JG, Mol BW, Heisterkamp S, et al. Empirical evidence of design-related bias in studies of diagnostic tests. *JAMA*. 1999;282:1061-1066. https://doi.org/10.1001/jama.282.11.1061
14. Rutjes AWS, Reitsma JB, Di Nisio M, Smidt N, van Rijn JC, Bossuyt PMM. Evidence of bias and variation in diagnostic accuracy studies. *CMAJ*. 2006;174:469-476. https://doi.org/10.1503/cmaj.050090
15. Schünemann HJ, Oxman AD, Brozek J, et al. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. *BMJ*. 2008;336:1106-1110. https://doi.org/10.1136/bmj.39500.677199.AE
16. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336:924-926. https://doi.org/10.1136/bmj.39489.470347.AD
17. Sargeant JM, Brennan ML, O'Connor AM. Levels of evidence, quality assessment, and risk of bias: evaluating the internal validity of primary research. *Front Vet Sci*. 2022;9:960957. https://doi.org/10.3389/fvets.2022.960957
18. Jergens AE, Simpson KW. Inflammatory bowel disease in veterinary medicine. *Front Biosci*. 2012;4:1404-1419. https://doi.org/10.2741/e470
19. Yuan Y, Sedano R, Solitano V, Nardone OM, Crowley E, Jairath V. Heterogeneity of definition of upper gastrointestinal tract in different guidelines of Crohn's disease: a scoping review. *United European Gastroenterol J*. 2024;12:1481-1488. https://doi.org/10.1002/ueg2.12697
20. Magro F, Gionchetti P, Eliakim R, et al. Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 1: definitions, diagnosis, extra-intestinal manifestations, pregnancy, cancer surveillance, surgery, and ileo-anal pouch disorders. *J Crohns Colitis*. 2017;11:649-670. https://doi.org/10.1093/ecco-jcc/jjx008
21. Allenspach K, Wieland B, Gröne A, Gaschen F. Chronic enteropathies in dogs: evaluation of risk factors for negative outcome. *J Vet Intern Med*. 2007;21:700-708. https://doi.org/10.1111/j.1939-1676.2007.tb03011.x
22. Cerquetella M, Spaterna A, Laus F, et al. Inflammatory bowel disease in the dog: differences and similarities with humans. *World J Gastroenterol*. 2010;16:1050-1056. https://doi.org/10.3748/wjg.v16.i9.1050
23. Dandrieux JRS, Mansfield CS. Chronic enteropathy in canines: prevalence, impact and management strategies. *Vet Med (Auckl)*. 2019;10:203-214. https://doi.org/10.2147/VMRR.S162774
24. Allenspach K. Clinical immunology and immunopathology of the canine and feline intestine. *Vet Clin North Am Small Anim Pract*. 2011;41:345-360. https://doi.org/10.1016/j.cvsm.2011.01.004

25. Siel D, Beltrán CJ, Martínez E, et al. Elucidating the role of innate and adaptive immune responses in the pathogenesis of canine chronic inflammatory enteropathy—a search for potential biomarkers. *Animals*. 2022;12:1645. https://doi.org/10.3390/ani12131645
26. Eissa N, Kittana H, Gomes-Neto JC, Hussein H. Mucosal immunity and gut microbiota in dogs with chronic enteropathy. *Res Vet Sci*. 2019;122:156-164. https://doi.org/10.1016/j.rvsc.2018.11.019
27. Minamoto Y, Otoni CC, Steelman SM, et al. Alteration of the fecal microbiota and serum metabolite profiles in dogs with idiopathic inflammatory bowel disease. *Gut Microbes*. 2015;6:33-47. https://doi.org/10.1080/19490976.2014.997612
28. Schmitz S, Suchodolski J. Understanding the canine intestinal microbiota and its modification by pro-, pre- and synbiotics—what is the evidence? *Vet Med Sci*. 2016;2:71-94. https://doi.org/10.1002/vms3.17
29. Ziese AL, Suchodolski JS. Impact of changes in gastrointestinal microbiota in canine and feline digestive diseases. *Vet Clin North Am Small Anim Pract*. 2021;51:155-169. https://doi.org/10.1016/j.cvsm.2020.09.004
30. Giaretta PR, Rech RR, Guard BC, et al. Comparison of intestinal expression of the apical sodium-dependent bile acid transporter between dogs with and without chronic inflammatory enteropathy. *J Vet Intern Med*. 2018;32:1918-1926. https://doi.org/10.1111/jvim15332
31. Guard BC, Honneffer JB, Jergens AE, et al. Longitudinal assessment of microbial dysbiosis, fecal unconjugated bile acid concentrations, and disease activity in dogs with steroid-responsive chronic inflammatory enteropathy. *J Vet Intern Med*. 2019;33:1295-1305. https://doi.org/10.1111/jvim.15493
32. Blake AB, Guard BC, Honneffer JB, Lidbury JA, Steiner JM, Suchodolski JS. Altered microbiota, fecal lactate, and fecal bile acids in dogs with gastrointestinal disease. *PloS One*. 2019;14:e0224454. https://doi.org/10.1371/journal.pone.0224454
33. Wang S, Martins R, Sullivan MC, et al. Diet-induced remission in chronic enteropathy is associated with altered microbial community structure and synthesis of secondary bile acids. *Microbiome*. 2019;7:126. https://doi.org/10.1186/s40168-019-0740-4
34. O'Reilly EL, Horvatić A, Kuleš J, et al. Faecal proteomics in the identification of biomarkers to differentiate canine chronic enteropathies. *J Proteomics*. 2022;254:104452. https://doi.org/10.1016/j.jprot.2021.104452
35. Comito R, Porru E, Interino N, et al. Metabolic bile acid profile impairments in dogs affected by chronic inflammatory enteropathy. *Metabolites*. 2023;13:980. https://doi.org/10.3390/metabo13090980
36. Heilmann RM, Suchodolski JS. Is inflammatory bowel disease in dogs and cats associated with a Th1 or Th2 polarization? *Vet Immunol Immunopathol*. 2015;168:131-134. https://doi.org/10.1016/j.vetimm.2015.10.008
37. Wilke VL, Nettleton D, Wymore MJ, et al. Gene expression in intestinal mucosal biopsy specimens obtained from dogs with chronic enteropathy. *Am J Vet Res*. 2012;73:1219-1229. https://doi.org/10.2460/ajvr.73.8.1219
38. Allenspach K, Culverwell C, Chan D. Long-term outcome in dogs with chronic enteropathies: 203 cases. *Vet Rec*. 2016;178:368. https://doi.org/10.1136/vr.103557
39. Kathrani A, Werling D, Allenspach K. Canine breeds at high risk of developing inflammatory bowel disease in the southeastern UK. *Vet Rec*. 2011;169:635. https://doi.org/10.1136/vr.d5380
40. Kathrani A, Lee H, White C, et al. Association between nucleotide oligomerisation domain two (Nod2) gene polymorphisms and canine inflammatory bowel disease. *Vet Immunol Immunopathol*. 2014;161:32-41. https://doi.org/10.1016/j.vetimm.2014.06.003
41. Volkmann M, Steiner JM, Fosgate GT, Zentek J, Hartmann S, Kohn B. Chronic diarrhea in dogs—retrospective study in 136 cases. *J Vet Intern Med*. 2017;31:1043-1055. https://doi.org/10.1111/jvim.14739
42. Mehain SO, Haines JM, Lee PM. Platelet indices as biomarkers for characterization and determination of severity in canine chronic enteropathy. *Vet J*. 2019;248:37-41. https://doi.org/10.1016/j.tvjl.2019.04.003
43. Soontararak S, Chow L, Johnson V, et al. Humoral immune responses against gut bacteria in dogs with inflammatory bowel disease. *PloS One*. 2019;14:e0220522. https://doi.org/10.1371/journal.pone.0220522
44. Benvenuti E, Pierini A, Gori E, et al. Serum amino acid profile in 51 dogs with immunosuppressant-responsive enteropathy (IRE): a pilot study on clinical aspects and outcomes. *BMC Vet Res*. 2020;16:117. https://doi.org/10.1186/s12917-020-02334-2
45. Díaz-Regañón D, García-Sancho M, Villaescusa A, et al. Characterization of the fecal and mucosa-associated microbiota in dogs with chronic inflammatory enteropathy. *Animals*. 2023;13:326. https://doi.org/10.3390/ani13030326
46. Benvenuti E, Pierini A, Bottero E, et al. Immunosuppressant-responsive enteropathy and non-responsive enteropathy in dogs: prognostic factors, short- and long-term follow up. *Animals*. 2021;11:2637. https://doi.org/10.3390/ani11092637
47. Wootton FE, Hoey CSFK, Woods G, et al. An undernutrition screening score for dogs with protein-losing enteropathy: a prospective multicenter study. *J Vet Intern Med*. 2023;37:1821-1829. https://doi.org/10.1111/jvim.16794
48. Omori M, Maeda S, Igarashi H, et al. Fecal microbiome in dogs with inflammatory bowel disease and intestinal lymphoma. *J Vet Med Sci*. 2017;79:1840-1847. https://doi.org/10.1292/jvms.17-0045
49. Karlovits S, Manz A, Allenspach K, et al. Ki-67/CD3 ratio in the diagnosis of chronic inflammatory enteropathy in dogs. *J Vet Intern Med*. 2020;34:92-97. https://doi.org/10.1111/jvim.15680
50. Manz A, Allenspach K, Kummer S, et al. Upregulation of signal transducer and activator of transcription 3 in dogs with chronic inflammatory enteropathies. *J Vet Intern Med*. 2021;35:1288-1296. https://doi.org/10.1111/jvim.16141
51. Lee J-H, Kim H-S, Lee D, et al. Clinical signs, duodenal histopathological grades, and serum high-mobility group box 1 concentrations in dogs with inflammatory bowel disease. *J Vet Intern Med*. 2021;35:2205-2214. https://doi.org/10.1111/jvim.16258

52. Furukawa R, Takahashi K, Hara Y, et al. Clinical characteristics of dogs presenting with vomiting as a gastrointestinal sign of chronic enteropathy. *Vet Anim Sci*. 2022;17:100255. https://doi.org/10.1016/j.vas.2022.100255
53. Jergens AE, Schreiner CA, Frank DE, et al. A scoring index for disease activity in canine inflammatory bowel disease. *J Vet Intern Med*. 2003;17:291-297. https://doi.org/10.1111/j.1939-1676.2003.tb02450.x
54. Dandrieux JR, Bornand VF, Doherr MG, Kano R, Zurbriggen A, Burgener IA. Evaluation of lymphocyte apoptosis in dogs with inflammatory bowel disease. *Am J Vet Res*. 2008;69:1279-1285. https://doi.org/10.2460/ajvr.69.10.1279
55. Luckschander N, Hall JA, Gaschen F, et al. Activation of nuclear factor-kappaB in dogs with chronic enteropathies. *Vet Immunol Immunopathol*. 2010;133:228-236. https://doi.org/10.1016/j.vetimm.2009.08.014
56. Wagner A, Junginger J, Lemensieck F, Hewicker-Trautwein M. Immunohistochemical characterization of gastrointestinal macrophages/phagocytes in dogs with inflammatory bowel disease (IBD) and non-IBD dogs. *Vet Immunol Immunopathol*. 2018;197:49-57. https://doi.org/10.1016/j.vetimm.2018.01.011
57. Otoni CC, Heilmann RM, García-Sancho M, et al. Serologic and fecal markers to predict response to induction therapy in dogs with idiopathic inflammatory bowel disease. *J Vet Intern Med*. 2018;32:999-1008. https://doi.org/10.1111/jvim.15123
58. Allenspach KA, Mochel JP, Du Y, et al. Correlating gastrointestinal histopathologic changes to clinical disease activity in dogs with idiopathic inflammatory bowel disease. *Vet Pathol*. 2019;56:435-443. https://doi.org/10.1177/0300985818813090
59. Münster M, Hörauf A, Bilzer T. Assessment of disease severity and outcome of dietary, antibiotic, and immunosuppressive interventions by use of the canine IBD activity index in 21 dogs with chronic inflammatory bowel disease. *Berl Munch Tierarztl Wochenschr*. 2006;119:493-505.
60. Heilmann RM, Parnell NK, Grützner N, et al. Serum and fecal canine α_1-proteinase inhibitor concentrations reflect the severity of intestinal crypt abscesses and/or lacteal dilation in dogs. *Vet J*. 2016;207:131-139. https://doi.org/10.1016/j.tvjl.2015.10.042
61. Dumusc SD, Ontsouka EC, Schnyder M, et al. Cyclooxygenase-2 and 5-lipoxygenase in dogs with chronic enteropathies. *J Vet Intern Med*. 2014;28:1684-1691. https://doi.org/10.1111/jvim.12463
62. Atherly T, Rossi G, White R, et al. Glucocorticoid and dietary effects on mucosal microbiota in canine inflammatory bowel disease. *PloS One*. 2019;14:e0226780. https://doi.org/10.1371/journal.pone.0226780
63. Sauter SN, Allenspach K, Blum JW. Cytokine mRNA abundance in intestinal biopsies from dogs with chronic diarrhea. *Vet Med*. 2007;52:353-364. https://doi.org/10.17221/1876-VETMED
64. Spichiger AC, Allenspach K, Zbinden Y, et al. Plasma insulin-like growth factor-1 concentration in dogs with chronic enteropathies. *Vet Med*. 2006;51:35-43. https://doi.org/10.17221/5515-VETMED
65. Riehm MD, Mayhue EJ, Jugan MC. Plasma glucagon-like peptide-2 concentrations are lower in dogs with chronic enteropathies than in healthy dogs. *Am J Vet Res*. 2023;84:1-8. https://doi.org/10.2460/ajvr.23.06.0149
66. Walker D, Knuchel-Takano A, McCutchan A, et al. A comprehensive pathological survey of duodenal biopsies from dogs with diet-responsive chronic enteropathy. *J Vet Intern Med*. 2013;27:862-874. https://doi.org/10.1111/jvim.12093
67. Martínez-López LM, Perez-Gonzalez A, Washington EA, et al. Hierarchical modelling of immunoglobulin coated bacteria in dogs with chronic enteropathy shows reduction in coating with disease remission but marked inter-individual and treatment-response variability. *PloS One*. 2021;16:e0255012. https://doi.org/10.1371/journal.pone.0255012
68. Luckschander-Zeller N, Hammer SE, Ruetgen BC, et al. Clonality testing as complementary tool in the assessment of different patient groups with canine chronic enteropathy. *Vet Immunol Immunopathol*. 2019;214:109893. https://doi.org/10.1016/j.vetimm.2019.109893
69. Heilmann RM, Berghoff N, Mansell J, et al. Association of fecal calprotectin concentrations with disease severity, response to treatment, and other biomarkers in dogs with chronic inflammatory enteropathies. *J Vet Intern Med*. 2018;32:679-692. https://doi.org/10.1111/jvim.15065
70. Crisi PE, Luciani A, Di Tommaso M, et al. The fatty acid-based erythrocyte membrane lipidome in dogs with chronic enteropathy. *Animals*. 2021;11:2604. https://doi.org/10.3390/ani11092604
71. Pietra M, Galiazzo G, Bresciani F, et al. Evaluation of prognostic factors, including duodenal p-glycoprotein expression, in canine chronic enteropathy. *Animals*. 2021;11:2315. https://doi.org/10.3390/ani11082315
72. Equilino M, Théodoloz V, Gorgas D, et al. Evaluation of serum biochemical marker concentrations and survival time in dogs with protein-losing enteropathy. *J Am Vet Med Assoc*. 2015;246:91-99. https://doi.org/10.2460/javma.246.1.91
73. Nakashima K, Hiyoshi S, Ohno K, et al. Prognostic factors in dogs with protein-losing enteropathy. *Vet J*. 2015;205:28-32. https://doi.org/10.1016/j.tvjl.2015.05.001
74. Kathrani A, Sánchez-Vizcaíno F, Hall EJ. Association of chronic enteropathy activity index, blood urea concentration, and risk of death in dogs with protein-losing enteropathy. *J Vet Intern Med*. 2019;33:536-543. https://doi.org/10.1111/jvim.15448
75. Wennogle SA, Priestnall SL, Suárez-Bonnet A, Soontararak S, Webb CB. Lymphatic endothelial cell immunohistochemical markers for evaluation of the intestinal lymphatic vasculature in dogs with chronic inflammatory enteropathy. *J Vet Intern Med*. 2019;33:1669-1676. https://doi.org/10.1111/jvim.15545
76. Titmarsh H, Gow AG, Kilpatrick S, et al. Association of vitamin D status and clinical outcome in dogs with a chronic enteropathy. *J Vet Intern Med*. 2015;29:1473-1478. https://doi.org/10.1111/jvim.13603
77. Wennogle SA, Olver CS, Shropshire SB. Coagulation status, fibrinolysis, and platelet dynamics in dogs with chronic inflammatory enteropathy. *J Vet Intern Med*. 2021;35:892-901. https://doi.org/10.1111/jvim.16092
78. Cabrera-García AI, Protschka M, Alber G, et al. Dysregulation of gastrointestinal RAGE (receptor for advanced glycation end products) expression in dogs with chronic inflammatory

enteropathy. *Vet Immunol Immunopathol*. 2021;234:110216. https://doi.org/10.1016/j.vetimm.2021.110216
79. Gianella P, Lotti U, Bellino C, et al. Clinicopathologic and prognostic factors in short- and long-term surviving dogs with protein-losing enteropathy. *Schweiz Arch Tierheilkd*. 2017;159:163-169. https://doi.org/10.17236/sat00108
80. Allenspach K, Rizzo J, Jergens AE, Chang YM. Hypovitaminosis D is associated with negative outcome in dogs with protein losing enteropathy: a retrospective study of 43 cases. *BMC Vet Res*. 2017;13:96. https://doi.org/10.1186/s12917-017-1022-7
81. Kathrani A, Lezcano V, Hall EJ, et al. Indoleamine-pyrrole 2,3-dioxygenase-1 (IDO-1) mRNA is over-expressed in the duodenal mucosa and is negatively correlated with serum tryptophan concentrations in dogs with protein-losing enteropathy. *PloS One*. 2019;14:e0218218. https://doi.org/10.1371/journal.pone.0218218
82. Nagata N, Ohta H, Yokoyama N, et al. Clinical characteristics of dogs with food-responsive protein-losing enteropathy. *J Vet Intern Med*. 2020;34:659-668. https://doi.org/10.1111/jvim.15720
83. Cassmann E, White R, Atherly T, et al. Alterations of the ileal and colonic mucosal microbiota in canine chronic enteropathies. *PloS One*. 2016;11:e0147321. https://doi.org/10.1371/journal.pone.0147321
84. Nakazawa M, Maeda S, Omori M, et al. Duodenal expression of antimicrobial peptides in dogs with idiopathic inflammatory bowel disease and intestinal lymphoma. *Vet J*. 2019;249:47-52. https://doi.org/10.1016/j.tvjl.2019.05.006
85. Lyngby JG, Gòdia M, Brogaard L, et al. Association of fecal and serum microRNA profiles with gastrointestinal cancer and chronic inflammatory enteropathy in dogs. *J Vet Intern Med*. 2022;36:1989-2001. https://doi.org/10.1111/jvim.16530
86. Grellet A, Heilmann RM, Lecoindre P, et al. Fecal calprotectin concentrations in adult dogs with chronic diarrhea. *Am J Vet Res*. 2013;74:706-711. https://doi.org/10.2460/ajvr.74.5.706
87. Pérez-Merino EM, Cristóbal-Verdejo I, Duque-Carrasco FJ, Espadas-González L, Pastor-Sirvent N, Usón-Casaús FJ. Relationship between serum cobalamin concentration and endoscopic ileal appearance and histology in dogs with chronic inflammatory enteropathy. *J Vet Intern Med*. 2022;36:957-965. https://doi.org/10.1111/jvim.16436
88. Ullal TV, Marks SL, Huebner SN, Taylor SL, Shelley CD. Association of folate concentrations with clinical signs and laboratory markers of chronic enteropathy in dogs. *J Vet Intern Med*. 2023;37:455-464. https://doi.org/10.1111/jvim.16681
89. Marchesi MC, Maggi G, Cremonini V, et al. Monocytes count, NLR, MLR and PLR in canine inflammatory bowel disease. *Animals*. 2024;14:837. https://doi.org/10.3390/ani14060837
90. Becher A, Suchodolski JS, Steiner JM, Heilmann RM. Blood neutrophil-to-lymphocyte ratio (NLR) as a diagnostic marker in dogs with chronic enteropathy. *J Vet Diagn Invest*. 2021;33:516-527. https://doi.org/10.1177/1040638721992057
91. Benvenuti E, Pierini A, Gori E, Lucarelli C, Lubas G, Marchetti V. Neutrophil-to-lymphocyte ratio (NLR) in canine inflammatory bowel disease (IBD). *Vet Sci*. 2020;7:141. https://doi.org/10.3390/vetsci7030141
92. Cagnasso F, Borrelli A, Bottero E, et al. Comparative evaluation of peripheral blood neutrophil to lymphocyte ratio, serum albumin to globulin ratio and serum C-reactive protein to albumin ratio in dogs with inflammatory protein-losing enteropathy and healthy dogs. *Animals*. 2023;13:484. https://doi.org/10.3390/ani13030484
93. Pierini A, Esposito G, Gori E, et al. Platelet abnormalities and platelet-to-lymphocyte ratios in canine immunosuppressant-responsive and non-responsive enteropathy: a retrospective study in 41 dogs. *J Vet Med Sci*. 2021;83:248-253. https://doi.org/10.1292/jvms.20-0291
94. Nagahara T, Ohno K, Nagao I, et al. Changes in the coagulation parameters in dogs with protein-losing enteropathy between before and after treatment. *J Vet Med Sci*. 2021;83:1295-1302. https://doi.org/10.1292/jvms.21-0137
95. Nestler J, Syrjä P, Kilpinen S, et al. Duodenal and colonic mucosal S100A8/A9 (calprotectin) expression is increased and correlates with the severity of select histologic lesions in dogs with chronic inflammatory enteropathy. *BMC Vet Res*. 2024;20:393. https://doi.org/10.1186/s12917-024-04256-9
96. Salavati Schmitz S, Gow A, Bommer N, Morrison L, Mellanby R. Diagnostic features, treatment, and outcome of dogs with inflammatory protein-losing enteropathy. *J Vet Intern Med*. 2019;33:2005-2013. https://doi.org/10.1111/jvim.15571
97. Gow AG, Else R, Evans H, Berry JL, Herrtage ME, Mellanby RJ. Hypovitaminosis D in dogs with inflammatory bowel disease and hypoalbuminaemia. *J Small Anim Pract*. 2011;52:411-418. https://doi.org/10.1111/j.1748-5827.2011.01082.x
98. Perrucci S, Berrilli F, Procopio C, Di Filippo MM, Pierini A, Marchetti V. *Giardia duodenalis* infection in dogs affected by primary chronic enteropathy. *Open Vet J*. 2020;10:74-79. https://doi.org/10.4314/ovj.v10i1.12
99. Heilmann RM, Volkmann M, Otoni CC, et al. Fecal S100A12 concentration predicts a lack of response to treatment in dogs affected with chronic enteropathy. *Vet J*. 2016;215:96-100. https://doi.org/10.1016/j.tvjl.2016.03.001
100. Serafini F, Maxwell KM, Zhu X, Lennon EM. Dysregulated serum concentrations of fat-soluble vitamins in dogs with chronic enteropathy. *J Vet Intern Med*. 2024;38:2612-2619. https://doi.org/10.1111/jvim.17107
101. Kathrani A, Steiner JM, Suchodolski J, et al. Elevated canine pancreatic lipase immunoreactivity concentration in dogs with inflammatory bowel disease is associated with a negative outcome. *J Small Anim Pract*. 2009;50:126-132. https://doi.org/10.1111/j.1748-5827.2008.00693.x
102. Kathrani A, Allenspach K, Fascetti AJ, Larsen JA, Hall EJ. Alterations in serum amino acid concentrations in dogs with protein-losing enteropathy. *J Vet Intern Med*. 2018;32:1026-1032. https://doi.org/10.1111/jvim.15116
103. Kilpinen S, Spillmann T, Syrjä P, Skrzypczak T, Louhelainen M, Westermarck E. Effect of tylosin on dogs with suspected tylosin-responsive diarrhea: a placebo-controlled, randomized, double-blinded, prospective clinical trial. *Acta Vet Scand*. 2011;53:26. https://doi.org/10.1186/1751-0147-53-26
104. Kather S, Kacza J, Pfannkuche H, et al. Expression of the cobalamin transporters cubam and MRP1 in the canine ileum–upregulation in chronic inflammatory enteropathy. *PloS One*. 2024;19:e0296024. https://doi.org/10.1371/journal.pone.0296024

105. Berghoff N, Suchodolski JS, Steiner JM. Association between serum cobalamin and methylmalonic acid concentrations in dogs. *Vet J*. 2012;191:306-311. https://doi.org/10.1016/j.tvjl.2011.03.005
106. Toresson L, Steiner JM, Spodsberg E, et al. Effects of oral versus parenteral cobalamin supplementation on methylmalonic acid and homocysteine concentrations in dogs with chronic enteropathies and low cobalamin concentrations. *Vet J*. 2019;243:8-14. https://doi.org/10.1016/j.tvjl.2018.11.004
107. Hauck C, Schmitz SS, Burgener IA, et al. Prevalence and characterization of hypoadrenocorticism in dogs with signs of chronic gastrointestinal disease: a multicenter study. *J Vet Intern Med*. 2020;34:1399-1405. https://doi.org/10.1111/jvim.15752
108. Titmarsh HF, Gow AG, Kilpatrick S, et al. Low vitamin D status is associated with systemic and gastrointestinal inflammation in dogs with a chronic enteropathy. *PloS One*. 2015;10:e0137377. https://doi.org/10.1371/journal.pone.0137377
109. Wennogle SA, Priestnall SL, Suárez-Bonnet A, Webb CB. Comparison of clinical, clinicopathologic, and histologic variables in dogs with chronic inflammatory enteropathy and low or normal serum 25-hydroxycholecalciferol concentrations. *Vet Intern Med*. 2019;33:1995-2004. https://doi.org/10.1111/jvim.15614
110. Heilmann RM, Jergens AE, Ackermann MR, Barr JW, Suchodolski JS, Steiner JM. Serum calprotectin concentrations in dogs with idiopathic inflammatory bowel disease. *Am J Vet Res*. 2012;73:1900-1907. https://doi.org/10.2460/ajvr.73.12.1900
111. Carney PC, Ruaux CG, Suchodolski JS, Steiner JM. Biological variability of C-reactive protein and specific canine pancreatic lipase immunoreactivity in apparently healthy dogs. *J Vet Intern Med*. 2011;25:825-830. https://doi.org/10.1111/j.1939-1676.2011.0729.x
112. Sattasathuchana P, Allenspach K, Lopes R, Suchodolski JS, Steiner JM. Evaluation of serum 3-bromotyrosine concentrations in dogs with steroid-responsive diarrhea and food-responsive diarrhea. *J Vet Intern Med*. 2017;31:1056-1061. https://doi.org/10.1111/jvim.14742
113. Sattasathuchana P, Thengchaisri N, Minamoto Y, et al. Serum and fecal 3-bromotyrosine concentrations in dogs with chronic inflammatory enteropathy: clinical parameters and histopathological changes. *Animals*. 2023;13:2804. https://doi.org/10.3390/ani13172804
114. Anfinsen KP, Berghoff N, Priestnall SL, Suchodolski JS, Steiner JM, Allenspach K. Urinary and faecal N-methylhistamine concentrations do not serve as markers for mast cell activation or clinical disease activity in dogs with chronic enteropathies. *Acta Vet Scand*. 2014;56:90. https://doi.org/10.1186/s13028-014-0090-y
115. Berghoff N, Hill S, Parnell NK, Mansell J, Suchodolski JS, Steiner JM. Fecal and urinary N-methylhistamine concentrations in dogs with chronic gastrointestinal disease. *Vet J*. 2014;201:289-294. https://doi.org/10.1016/j.tvjl.2014.05.016
116. Heilmann RM, Otoni CC, Jergens AE, Grützner N, Suchodolski JS, Steiner JM. Systemic levels of the anti-inflammatory decoy receptor soluble RAGE (receptor for advanced glycation end products) are decreased in dogs with inflammatory bowel disease. *Vet Immunol Immunopathol*. 2014;161:184-192. https://doi.org/10.1016/j.vetimm.2014.08.003
117. Heilmann RM, Grellet A, Allenspach K, et al. Association between fecal S100A12 concentration and histologic, endoscopic, and clinical disease severity in dogs with idiopathic inflammatory bowel disease. *Vet Immunol Immunopathol*. 2014;158:156-166. https://doi.org/10.1016/j.vetimm.2014.01.006
118. Hanifeh M, Sankari S, Rajamäki MM, et al. S100A12 concentrations and myeloperoxidase activities are increased in the intestinal mucosa of dogs with chronic enteropathies. *BMC Vet Res*. 2018;14:125. https://doi.org/10.1186/s12917-018-1441-0
119. Manchester AC, Ammons DT, Lappin MR, Dow S. Single cell transcriptomic analysis of the canine duodenum in chronic inflammatory enteropathy and health. *Front Immunol*. 2024;15:1397590. https://doi.org/10.3389/fimmu.2024.1397590
120. Hirokawa M, Takahashi K, Miyajima M, et al. Expression of genes encoding inflammasome sensor subunits in the duodenal and colonic mucosae of dogs with chronic enteropathy. *J Vet Med Sci*. 2021;83:1161-1166. https://doi.org/10.1292/jvms.20-0519
121. Hernandez J, Rouillé E, Chocteau F, et al. Nonhypoalbuminemic inflammatory bowel disease in dogs as disease model. *Inflamm Bowel Dis*. 2021;27:1975-1985. https://doi.org/10.1093/ibd/izab064
122. Mayoral I, Peña L, Rodriguez-Franco F, Sainz A, Tesouro MA, Ynaraja E. Immunohistological study of IgA, IgG and IgM in endoscopic biopsies of dogs with plasmacytic-lymphocytic colitis. *Zentralbl Veterinarmed B*. 1996;43:613-620. https://doi.org/10.1111/j.1439-0450.1996.tb00360.x
123. Agulla B, Villaescusa A, Sainz Á, et al. Peripheral and intestinal T lymphocyte subsets in dogs with chronic inflammatory enteropathy. *J Vet Intern Med*. 2024;38:1437-1448. https://doi.org/10.1111/jvim.17036
124. Florey J, Viall A, Streu S, et al. Use of a granulocyte immunofluorescence assay designed for humans for detection of antineutrophil cytoplasmic antibodies in dogs with chronic enteropathies. *J Vet Intern Med*. 2017;31:1062-1066. https://doi.org/10.1111/jvim.14774
125. Langlois DK, Pritchard JC, Tolbert MK, et al. Clinical utility of an immunoglobulin A-based serological panel for the diagnosis of chronic enteropathy in dogs. *J Vet Intern Med*. 2023;37:446-454. https://doi.org/10.1111/jvim.16636
126. Estruch JJ, Barken D, Bennett N, et al. Evaluation of novel serological markers and autoantibodies in dogs with inflammatory bowel disease. *J Vet Intern Med*. 2020;34:1177-1186. https://doi.org/10.1111/jvim.15761
127. Kobayashi S, Ohno K, Uetsuka K, et al. Measurement of intestinal mucosal permeability in dogs with lymphocytic-plasmacytic enteritis. *J Vet Med Sci*. 2007;69:745-749. https://doi.org/10.1292/jvms.69.745
128. Dinesh N, Slovak JE, Kogan C, Kopper JJ. Preliminary evaluation of serum zonulin in canine chronic enteropathies. *J Small Anim Pract*. 2022;63:679-685. https://doi.org/10.1111/jsap.13506
129. Gerou-Ferriani M, Allen R, Noble PJM, German AJ, Caldin M, Batchelor DJ. Determining optimal therapy of dogs with chronic enteropathy by measurement of serum citrulline.

J Vet Intern Med. 2018;32:993-998. https://doi.org/10.1111/jvim.15124
130. Sakai K, Hatoya S, Furuya M, et al. Decreased serum zinc concentration in dogs with lymphocytic-plasmacytic enteritis, and its associations with disease severity and prognosis. *J Vet Med Sci*. 2020;82:759-763. https://doi.org/10.1292/jvms.20-0109
131. Aono K, Azuma Y-T, Nabetani T, et al. Correlation between toll-like receptor 4 and nucleotide-binding oligomerization domain 2 (NOD2) and pathological severity in dogs with chronic gastrointestinal diseases. *Vet Immunol Immunopathol*. 2019;210:15-22. https://doi.org/10.1016/j.vetimm.2019.03.003
132. McMahon LA, House AK, Catchpole B, et al. Expression of toll-like receptor 2 in duodenal biopsies from dogs with inflammatory bowel disease is associated with severity of disease. *Vet Immunol Immunopathol*. 2010;135:158-163. https://doi.org/10.1016/j.vetimm.2009.11.012
133. Konstantinidis AO, Pardali D, Adamama-Moraitou KK, et al. Colonic mucosal and serum expression of microRNAs in canine large intestinal inflammatory bowel disease. *BMC Vet Res*. 2020;16:69. https://doi.org/10.1186/s12917-020-02287-6
134. Dandrieux JRS, Martinez Lopez LM, Prakash N, Mansfield CS. Treatment response and long term follow up in nineteen dogs diagnosed with chronic enteropathy in Australia. *Aust Vet J*. 2019;97:301-307. https://doi.org/10.1111/avj.12846
135. Craven M, Dogan B, Schukken A, et al. Antimicrobial resistance impacts clinical outcome of granulomatous colitis in boxer dogs. *J Vet Intern Med*. 2010;24:819-824. https://doi.org/10.1111/j.1939-1676.2010.0527.x
136. Kalenyak K, Isaiah A, Heilmann RM, Suchodolski JS, Burgener IA. Comparison of the intestinal mucosal microbiota in dogs diagnosed with idiopathic inflammatory bowel disease and dogs with food-responsive diarrhea before and after treatment. *FEMS Microbiol Ecol*. 2018;94:2. https://doi.org/10.1093/femsec/fix173
137. Giaretta PR, Suchodolski JS, Jergens AE, et al. Bacterial biogeography of the colon in dogs with chronic inflammatory enteropathy. *Vet Pathol*. 2020;57:258-265. https://doi.org/10.1177/0300985819891259
138. Higueras C, Escudero R, Rebolé A, et al. Changes in faecal and plasma amino acid profile in dogs with food-responsive enteropathy as indicators of gut homeostasis disruption: a pilot study. *Vet Sci*. 2023;10:112. https://doi.org/10.3390/vetsci10020112
139. Higueras C, Sainz Á, García-Sancho M, Rodríguez-Franco F, Rey AI. Faecal short-chain, long-chain, and branched-chain fatty acids as markers of different chronic inflammatory enteropathies in dogs. *Animals*. 2024;14:1825. https://doi.org/10.3390/ani14121825
140. Rubio CP, Martínez-Subiela S, Hernández-Ruiz J, Tvarijonaviciute A, Cerón JJ, Allenspach K. Serum biomarkers of oxidative stress in dogs with idiopathic inflammatory bowel disease. *Vet J*. 2017;221:56-61. https://doi.org/10.1016/j.tvjl.2017.02.003
141. Tamura Y, Ohta H, Kagawa Y, et al. Plasma amino acid profiles in dogs with inflammatory bowel disease. *J Vet Intern Med*. 2019;33:1602-1607. https://doi.org/10.1111/jvim.15525
142. Walker HK, Boag AM, Ottka C, et al. Serum metabolomic profiles in dogs with chronic enteropathy. *J Vet Intern Med*. 2022;36:1752-1759. https://doi.org/10.1111/jvim.16419
143. Xu J, Verbrugghe A, Lourenço M, et al. Does canine inflammatory bowel disease influence gut microbial profile and host metabolism? *BMC Vet Res*. 2016;12:114. https://doi.org/10.1186/s12917-016-0736-2
144. Furukawa R, Furuya M, Hara Y, et al. Expression profiles of TWEAK and Fn14 genes in the duodenal and colonic mucosae of dogs with chronic enteropathy. *Jap J Vet Res*. 2023;71:27-34. https://doi.org/10.57494/jjvr.71.1_27
145. Benvenuti E, Pierini A, Gori E, et al. Serum homocysteine concentration in dogs with immunosuppressant-responsive enteropathy. *J Vet Sci*. 2020;21:e47. https://doi.org/10.4142/jvs.2020.21.e47
146. Febo E, Crisi PE, Oddi S, et al. Circulating endocannabinoids as diagnostic markers of canine chronic enteropathies: a pilot study. *Front Vet Sci*. 2021;8:655311. https://doi.org/10.3389/fvets.2021.655311
147. AlShawaqfeh MK, Wajid B, Minamoto Y, et al. A dysbiosis index to assess microbial changes in fecal samples of dogs with chronic inflammatory enteropathy. *FEMS Microbiol Ecol*. 2017;93:11. https://doi.org/10.1093/femsec/fix136
148. Nisa K, Lim SY, Shinohara M, et al. Evaluation of duodenal perfusion by contrast-enhanced ultrasonography in dogs with chronic inflammatory enteropathy and intestinal lymphoma. *J Vet Intern Med*. 2019;33:559-568. https://doi.org/10.1111/jvim.15432
149. Gaschen L, Kircher P, Stüssi A, et al. Comparison of ultrasonographic findings with clinical activity index (CIBDAI) and diagnosis in dogs with chronic enteropathies. *Vet Radiol Ultrasound*. 2008;49:56-64. https://doi.org/10.1111/j.1740-8261.2007.00318.x
150. Ohta H, Nagata N, Yokoyama N, et al. Prognostic value of small intestinal dilatation in dogs with protein-losing enteropathy. *J Vet Med Sci*. 2021;83:378-384. https://doi.org/10.1292/jvms.20-0489
151. Caulfield S, Priestnall SL, Kathrani A. Concordance of the histopathologic diagnosis of concurrent duodenal and ileal biopsy specimens in dogs. *Animals*. 2021;11:2938. https://doi.org/10.3390/ani11102938
152. Glasziou P, Rose P, Heneghan C, Balla J. Diagnosis using "test of treatment". *BMJ*. 2009;338:b1312. https://doi.org/10.1136/bmj.b1312
153. Mandigers PJJ, Biourge V, van den Ingh TSGAM, Ankringa N, German AJ. A randomized, open-label, positively-controlled field trial of a hydrolyzed protein diet in dogs with chronic small bowel enteropathy. *J Vet Intern Med*. 2010;24:1350-1357. https://doi.org/10.1111/j.1939-1676.2010.0632.x
154. Simpson KW, Miller ML, Loftus JP, Rishniw M, Frederick CE, Wakshlag JJ. Randomized controlled trial of hydrolyzed fish diets in dogs with chronic enteropathy. *J Vet Intern Med*. 2023;37:2334-2343. https://doi.org/10.1111/jvim.16844
155. Hodel S, Brugger D, Kook PH. Long-term evaluation of the initial response to therapy in 60 dogs with chronic inflammatory enteropathy. *J Vet Intern Med*. 2024;38:2444-2453. https://doi.org/10.1111/jvim.17161

156. Marks SL, Laflamme DP, McAloose D. Dietary trial using a commercial hypoallergenic diet containing hydrolyzed protein for dogs with inflammatory bowel disease. *Vet Ther*. 2002;3:109-118.
157. Schläfke B. *Effects of Bifidobacterium animalis NCIMB 41199 in dogs with chronic enteropathies*Dr. med. vet. thesis,. Germany: Free University of Berlin; 2011.
158. Okanishi H, Yoshioka R, Kagawa Y, Watari T. The clinical efficacy of dietary fat restriction in treatment of dogs with intestinal lymphangiectasia. *J Vet Intern Med*. 2014;28:809-817. https://doi.org/10.1111/jvim.12327
159. Simmerson SM, Armstrong PJ, Wünschmann A, Jessen CR, Crews LJ, Washabau RJ. Clinical features, intestinal histopathology, and outcome in protein-losing enteropathy in Yorkshire terrier dogs. *J Vet Intern Med*. 2014;28:331-337. https://doi.org/10.1111/jvim.12291
160. Marchesi MC, Timpano CC, Busechian S, Pieramati C, Rueca F. The role of diet in managing inflammatory bowel disease affected dogs: a retrospective cohort study on 76 cases. *Vet Ital*. 2017;53:297-302. https://doi.org/10.12834/VetIt.566.2700.1
161. Rudinsky AJ, Howard JP, Bishop MA, Sherding RG, Parker VJ, Gilor C. Dietary management of presumptive protein-losing enteropathy in Yorkshire terriers. *J Small Anim Pract*. 2017;58:103-108. https://doi.org/10.1111/jsap.12625
162. Tørnqvist-Johnsen C, Campbell S, Gow A, Bommer NX, Salavati S, Mellanby RJ. Investigation of the efficacy of a dietetic food in the management of chronic enteropathies in dogs. *Vet Rec*. 2020;186:26. https://doi.org/10.1136/vr.105172
163. Leib MS. Treatment of chronic idiopathic large-bowel diarrhea in dogs with a highly digestible diet and soluble fiber: a retrospective review of 37 cases. *J Vet Intern Med*. 2000;14:27-32. https://doi.org/10.1892/0891-6640(2000)014
164. Fritsch DA, Wernimont SM, Jackson MI, MacLeay JM, Gross KL. A prospective multicenter study of the efficacy of a fiber-supplemented dietary intervention in dogs with chronic large bowel diarrhea. *BMC Vet Res*. 2022;18:244. https://doi.org/10.1186/s12917-022-03302-8
165. Fritsch DA, Jackson MI, Wernimont SM, et al. Adding a polyphenol-rich fiber bundle to food impacts the gastrointestinal microbiome and metabolome in dogs. *Front Vet Sci*. 2022;9:1039032. https://doi.org/10.3389/fvets.2022.1039032
166. Kratzer GR, Shepherd M, Delaney SJ, Winston JA, Rudinsky AJ, Parker VJ. Home-cooked diets cost more than commercially prepared dry kibble diets for dogs with chronic enteropathies. *J Am Vet Med Assoc*. 2022;260:S53-S60. https://doi.org/10.2460/javma.22.07.0284
167. Schramm A, Kook PH. A descriptive study on the extent of dietary information obtained during consultations at a veterinary teaching hospital. *Animals*. 2022;12:661. https://doi.org/10.3390/ani12050661
168. Manchester AC, Dow S, Chow L, Gagne J, Lappin MR. Efficacy of an elemental diet in achieving clinical remission in dogs with chronic enteropathy. *J Vet Intern Med*. 2023;37:2322-2333. https://doi.org/10.1111/jvim.16846
169. Myers M, Martinez SA, Shiroma JT, Watson AT, Hostutler RA. Prospective evaluation of low-fat diet monotherapy in dogs with presumptive protein-losing enteropathy. *J Am Anim Hosp Assoc*. 2023;59:74-84. https://doi.org/10.5326/JAAHA-MS-7248
170. Vecchiato CG, Pinna C, Sung C-H, et al. Fecal microbiota, bile acids, sterols, and fatty acids in dogs with chronic enteropathy fed a home-cooked diet supplemented with coconut oil. *Animals*. 2023;13:502. https://doi.org/10.3390/ani13030502
171. Luckschander N, Allenspach K, Hall J, et al. Perinuclear antineutrophilic cytoplasmic antibody and response to treatment in diarrheic dogs with food responsive disease or inflammatory bowel disease. *J Vet Intern Med*. 2006;20:221-227. https://doi.org/10.1111/j.1939-1676.2006.tb02849.x
172. Tiffany S, Parr JM, Templeman J, et al. Assessment of dog owners' knowledge relating to the diagnosis and treatment of canine food allergies. *Can Vet J*. 2019;60:268-274.
173. Green J, Kathrani A. Incidence of relapse of inflammatory protein-losing enteropathy in dogs and associated risk factors. *J Vet Intern Med*. 2022;36:1981-1988. https://doi.org/10.1111/jvim.16561
174. Sauter SN, Benyacoub J, Allenspach K, et al. Effects of probiotic bacteria in dogs with food responsive diarrhoea treated with an elimination diet. *J Anim Physiol Anim Nutr*. 2006;90:269-277. https://doi.org/10.1111/j.1439-0396.2005.00595.x
175. Rossi G, Pengo G, Caldin M, et al. Comparison of microbiological, histological, and immunomodulatory parameters in response to treatment with either combination therapy with prednisone and metronidazole or probiotic VSL#3 strains in dogs with idiopathic inflammatory bowel disease. *PloS One*. 2014;9:e94699. https://doi.org/10.1371/journal.pone.0094699
176. Schmitz S, Glanemann B, Garden OA, et al. A prospective, randomized, blinded, placebo-controlled pilot study on the effect of *enterococcus faecium* on clinical activity and intestinal gene expression in canine food-responsive chronic enteropathy. *J Vet Intern Med*. 2015;29:533-543. https://doi.org/10.1111/jvim.12563
177. Schmitz S, Werling D, Allenspach K. Effects of *ex-vivo* and *in-vivo* treatment with probiotics on the inflammasome in dogs with chronic enteropathy. *PloS One*. 2015;10:e0120779. https://doi.org/10.1371/journal.pone.0120779
178. Segarra S, Martínez-Subiela S, Cerdà-Cuéllar M, et al. Oral chondroitin sulfate and prebiotics for the treatment of canine inflammatory bowel disease: a randomized, controlled clinical trial. *BMC Vet Res*. 2016;12:49. https://doi.org/10.1186/s12917-016-0676-x
179. Rossi G, Cerquetella M, Scarpona S, et al. Effects of probiotic bacteria on mucosal polyamines levels in dogs with IBD and colonic polyps: a preliminary study. *Benef Microbes*. 2018;9:247-255. https://doi.org/10.3920/BM2017.0024
180. White R, Atherly T, Guard B, et al. Randomized, controlled trial evaluating the effect of multi-strain probiotic on the mucosal microbiota in canine idiopathic inflammatory bowel disease. *Gut Microbes*. 2017;8:451-466. https://doi.org/10.1080/19490976.2017.1334754
181. D'Angelo S, Fracassi F, Bresciani F, et al. Effect of *saccharomyces boulardii* in dog with chronic enteropathies: double-blinded, placebo-controlled study. *Vet Rec*. 2018;182:258. https://doi.org/10.1136/vr.104241
182. Pilla R, Guard BC, Steiner JM, et al. Administration of a synbiotic containing *enterococcus faecium* does not significantly

alter fecal microbiota richness or diversity in dogs with and without food-responsive chronic enteropathy. *Front Vet Sci*. 2019;6:277. https://doi.org/10.3389/fvets.2019.00277
183. Isidori M, Rueca F, Massacci FR, et al. The use of *Ascophyllum nodosum* and *Bacillus subtilis* C-3102 in the management of canine chronic inflammatory enteropathy: a pilot study. *Animals*. 2021;11:3417. https://doi.org/10.3390/ani11123417
184. Glanemann B, Seo Y-J, Priestnall SL, et al. Clinical efficacy of prebiotics and glycosaminoglycans versus placebo In dogs with food responsive enteropathy receiving a hydrolyzed diet: a pilot study. *PloS One*. 2021;16:e0250681. https://doi.org/10.1371/journal.pone.0250681
185. Sahoo DK, Allenspach K, Mochel JP, et al. Synbiotic-IgY therapy modulates the mucosal microbiome and inflammatory indices in dogs with chronic inflammatory enteropathy: a randomized, double-blind, placebo-controlled study. *Vet Sci*. 2022;10:25. https://doi.org/10.3390/vetsci10010025
186. Amaral AR, Rentas MF, Rosa TCT, et al. Microbiota in mild inflammatory bowel disease (IBD) can be modulated by beta-glucans and mannanoligosaccharides: a randomized, double-blinded study in dogs. *Vet Sci*. 2024;11:349. https://doi.org/10.3390/vetsci11080349
187. Koyama K, Akiyama R, Oda H, et al. Effect of commercial prescription diets containing prebiotics on clinical signs and fecal microbiome in dogs with intestinal disease. *Pol J Vet Sci*. 2024;27:599-610. https://doi.org/10.24425/pjvs.2024.152950
188. Westermarck E, Skrzypczak T, Harmoinen J, et al. Tylosin-responsive chronic diarrhea in dogs. *J Vet Intern Med*. 2005;19:177-186. https://doi.org/10.1111/j.1939-1676.2005.tb02679.x
189. Kilpinen S, Spillmann T, Westermarck E. Efficacy of two low-dose oral tylosin regimens in controlling the relapse of diarrhea in dogs with tylosin-responsive diarrhea: a prospective, single-blinded, two-arm parallel, clinical field trial. *Acta Vet Scand*. 2014;56:43. https://doi.org/10.1186/s13028-014-0043-5
190. Kilpinen S, Rantala M, Spillmann T, Björkroth J, Westermarck E. Oral tylosin administration is associated with an increase of faecal enterococci and lactic acid bacteria in dogs with tylosin-responsive diarrhoea. *Vet J*. 2015;205:369-374. https://doi.org/10.1016/j.tvjl.2015.04.031
191. Jergens AE, Crandell J, Morrison JA, et al. Comparison of oral prednisone and prednisone combined with metronidazole for induction therapy of canine inflammatory bowel disease: a randomized-controlled trial. *J Vet Intern Med*. 2010;24:269-277. https://doi.org/10.1111/j.1939-1676.2009.0447.x
192. Collier AJ, Gomez DE, Monteith G, et al. Investigating fecal microbial transplant as a novel therapy in dogs with inflammatory bowel disease: a preliminary study. *PloS One*. 2022;17:e0276295. https://doi.org/10.1371/journal.pone.0276295
193. Innocente G, Patuzzi I, Furlanello T, et al. Machine learning and canine chronic enteropathies: a new approach to investigate FMT effects. *Vet Sci*. 2022;9:502. https://doi.org/10.3390/vetsci9090502
194. Toresson L, Spillmann T, Pilla R, et al. Clinical effects of faecal microbiota transplantation as adjunctive therapy in dogs with chronic enteropathies—a retrospective case series of 41 dogs. *Vet Sci*. 2023;10:271. https://doi.org/10.3390/vetsci10040271
195. Hanifeh M, Scarsella E, Rojas CA, et al. Oral fecal microbiota transplantation in dogs with tylosin-responsive enteropathy—a proof-of-concept study. *Vet Sci*. 2024;11:439. https://doi.org/10.3390/vetsci11090439
196. Pérez-Accino J, Salavati M, Glendinning L, Salavati SS. Effect of a single rectal fecal microbiota transplantation on clinical severity and fecal microbial communities in dogs with chronic inflammatory enteropathy. *J Vet Intern Med*. 2025;39:e17264. https://doi.org/10.1111/jvim.17264
197. García-Sancho M, Sainz A, Villaescusa A, Rodríguez A, Rodríguez-Franco F. White spots on the mucosal surface of the duodenum in dogs with lymphocytic plasmacytic enteritis. *J Vet Sci*. 2011;12:165-169. https://doi.org/10.4142/jvs.2011.12.2.165
198. Benvenuti E, Pierini A, Benali SL, et al. Evaluation of duodenal endoscopic and histologic findings, including counts of forkhead box P3-positive regulatory T cells, in dogs with immunosuppressant-responsive enteropathy. *Am J Vet Res*. 2021;82:218-224. https://doi.org/10.2460/ajvr.82.3.218
199. Irom S, Sherding R, Johnson S, Stromberg P. Gastrointestinal perforation associated with endoscopy in cats and dogs. *J Am Anim Hosp Assoc*. 2014;50:322-329. https://doi.org/10.5326/JAAHA-MS-5727
200. Woolhead VL, Whittemore JC, Stewart SA. Multicenter retrospective evaluation of ileocecocolic perforations associated with diagnostic lower gastrointestinal endoscopy in dogs and cats. *J Vet Intern Med*. 2020;34:684-690. https://doi.org/10.1111/jvim.15731
201. Slovak JE, Wang C, Sun Y, et al. Development and validation of an endoscopic activity score for canine inflammatory bowel disease. *Vet J*. 2015;203:290-295. https://doi.org/10.1016/j.tvjl.2014.12.030
202. Jergens AE, Willard MD, Allenspach K. Maximizing the diagnostic utility of endoscopic biopsy in dogs and cats with gastrointestinal disease. *Vet J*. 2016;214:50-60. https://doi.org/10.1016/j.tvjl.2016.04.008
203. Willard MD, Mansell J, Fosgate GT, et al. Effect of sample quality on the sensitivity of endoscopic biopsy for detecting gastric and duodenal lesions in dogs and cats. *J Vet Intern Med*. 2008;22:1084-1089. https://doi.org/10.1111/j.1939-1676.2008.0149.x
204. Holmberg J, Ljungvall I, Pelander L, et al. Video capsule endoscopy findings in dogs with chronic enteropathy and in healthy dogs. *J Vet Intern Med*. 2024;38:2454-2463. https://doi.org/10.1111/jvim.17168
205. Day MJ, Bilzer T, Mansell J, et al. Histopathological standards for the diagnosis of gastrointestinal inflammation in endoscopic biopsy samples from the dog and cat: a report from the world small animal veterinary association gastrointestinal standardization group. *J Comp Pathol*. 2008;138:S1-S43. https://doi.org/10.1016/j.jcpa.2008.01.001
206. Jergens AE, Evans RB, Ackermann M, et al. Design of a simplified histopathologic model for gastrointestinal inflammation in dogs. *Vet Pathol*. 2014;51:946-950. https://doi.org/10.1177/0300985813511123
207. Willard MD, Moore GE, Denton BD, et al. Effect of tissue processing on assessment of endoscopic intestinal biopsies in

dogs and cats. *J Vet Intern Med*. 2010;24:84-89. https://doi.org/10.1111/j.1939-1676.2009.0432.x
208. Maeda S, Ohno K, Nakamura K, et al. Mucosal imbalance of interleukin-1β and interleukin-1 receptor antagonist in canine inflammatory bowel disease. *Vet J*. 2012;194:66-70. https://doi.org/10.1016/j.tvjl.2012.02.026
209. Okanishi H, Hayashi K, Sakamoto Y, et al. NOD2 mRNA expression and NFkappaB activation in dogs with lymphocytic plasmacytic colitis. *J Vet Intern Med*. 2013;27:439-444. https://doi.org/10.1111/jvim.12082
210. Kathrani A, Schmitz S, Priestnall SL, et al. CD11c+ cells are significantly decreased in the duodenum, ileum and colon of dogs with inflammatory bowel disease. *J Comp Pathol*. 2011;145:359-366. https://doi.org/10.1016/j.jcpa.2011.03.010
211. Junginger J, Lemensieck F, Moore PF, Schwittlick U, Nolte I, Hewicker-Trautwein M. Canine gut dendritic cells in the steady state and in inflammatory bowel disease. *Innate Immun*. 2014;20:145-160. https://doi.org/10.1177/1753425913485475
212. Dandrieux JR, Martinez Lopez LM, Stent A, et al. Changes in duodenal CD163-positive cells in dogs with chronic enteropathy after successful treatment. *Innate Immun*. 2018;24:400-410. https://doi.org/10.1177/1753425918799865
213. Cochran L, Hill S, Lotti U, et al. Clinical characteristics and long-term outcome of *E. coli*-associated granulomatous ileocolitis in dogs: five cases (2010-2014). *J Small Anim Pract*. 2021;62:588-598. https://doi.org/10.1111/jsap.13313
214. Carrasco V, Rodríguez-Bertos A, Rodríguez-Franco F, et al. Distinguishing intestinal lymphoma from inflammatory bowel disease in canine duodenal endoscopic biopsy samples. *Vet Pathol*. 2015;52:668-675. https://doi.org/10.1177/0300985814559398
215. Maeda S, Ohno K, Fujiwara-Igarashi A, Uchida K, Tsujimoto H. Changes in Foxp3-positive regulatory T cell number in the intestine of dogs with idiopathic inflammatory bowel disease and intestinal lymphoma. *Vet Pathol*. 2016;53:102-112. https://doi.org/10.1177/0300985815591081
216. Schreiner NMS, Gaschen F, Gröne A, Sauter SN, Allenspach K. Clinical signs, histology, and CD3-positive cells before and after treatment of dogs with chronic enteropathies. *J Vet Intern Med*. 2008;22:1079-1083. https://doi.org/10.1111/j.1939-1676.2008.0153.x
217. Allenspach K, Steiner JM, Shah BN, et al. Evaluation of gastrointestinal permeability and mucosal absorptive capacity in dogs with chronic enteropathy. *Am J Vet Res*. 2006;67:479-483. https://doi.org/10.2460/ajvr.67.3.479
218. Bresciani F, Minamoto Y, Suchodolski JS, et al. Effect of an extruded animal protein-free diet on fecal microbiota of dogs with food-responsive enteropathy. *J Vet Intern Med*. 2018;32:1903-1910. https://doi.org/10.1111/jvim.15227
219. Wennogle SA, Stockman J, Webb CB. Prospective evaluation of a change in dietary therapy in dogs with steroid-resistant protein-losing enteropathy. *J Small Anim Pract*. 2021;62:756-764. https://doi.org/10.1111/jsap.13334
220. Alves JC, Jorge P, Santos A. The effect of photobiomodulation therapy on the management of chronic idiopathic large-bowel diarrhea in dogs. *Lasers Med Sci*. 2022;37:2045-2051. https://doi.org/10.1007/s10103-021-03469-w
221. Economu L, Chang Y-M, Priestnall SL, Kathrani A. The effect of assisted enteral feeding on treatment outcome in dogs with inflammatory protein-losing enteropathy. *J Vet Intern Med*. 2021;35:1297-1305. https://doi.org/10.1111/jvim.16125
222. Menozzi A, Dall'Aglio M, Quintavalla F, Dallavalle L, Meucci V, Bertini S. Rifaximin is an effective alternative to metronidazole for the treatment of chronic enteropathy in dogs: a randomised trial. *BMC Vet Res*. 2016;12:217. https://doi.org/10.1186/s12917-016-0851-0
223. Stokes JE, Kruger JM, Mullaney T, Holan K, Schall W. Histiocytic ulcerative colitis in three non-boxer dogs. *J Am Anim Hosp Assoc*. 2001;37:461-465. https://doi.org/10.5326/15473317-37-5-461
224. Hostutler RA, Luria BJ, Johnson SE, et al. Antibiotic-responsive histiocytic ulcerative colitis in 9 dogs. *J Vet Intern Med*. 2004;18:499-504. https://doi.org/10.1892/0891-6640(2004)18
225. German AJ, Day MJ, Ruaux CG, Steiner JM, Williams DA, Hall EJ. Comparison of direct and indirect tests for small intestinal bacterial overgrowth and antibiotic-responsive diarrhea in dogs. *J Vet Intern Med*. 2003;17:33-43. https://doi.org/10.1892/0891-6640(2003)017
226. Churcher RK, Watson AD. Canine histiocytic ulcerative colitis. *Aust Vet J*. 1997;75:710-713. https://doi.org/10.1111/j.1751-0813.1997.tb12250.x
227. Mansfield CS, James FE, Craven M, et al. Remission of histiocytic ulcerative colitis in boxer dogs correlates with eradication of invasive intramucosal *Escherichia coli*. *J Vet Intern Med*. 2009;23:964-969. https://doi.org/10.1111/j.1939-1676.2009.0363.x
228. Manchester AC, Hill S, Sabatino B, et al. Association between granulomatous colitis in French bulldogs and invasive *Escherichia coli* and response to fluoroquinolone antimicrobials. *J Vet Intern Med*. 2013;27:56-61. https://doi.org/10.1111/jvim.12020
229. Merino-Gutierrez V, Puig J, Feo-Bernabe L. Successful treatment of 3 dogs with fluoroquinolone-resistant *Escherichia coli* associated granulomatous colitis. *Top Companion Anim Med*. 2022;47:100621. https://doi.org/10.1016/j.tcam.2021.100621
230. Purcell BL, Woodward AP, Leeming MG, Dandrieux JRS. Influence of bodyweight on prednisolone pharmacokinetics in dogs. *PloS One*. 2025;20:e0326586. https://doi.org/10.1371/journal.pone.0326586
231. Dye TL, Diehl KJ, Wheeler SL, Westfall DS. Randomized, controlled trial of budesonide and prednisone for the treatment of idiopathic inflammatory bowel disease in dogs. *J Vet Intern Med*. 2013;27:1385-1391. https://doi.org/10.1111/jvim.12195
232. Yoshida K, Matsuoka T, Kobatake Y, Takashima S, Nishii N. Quantitative assessment of muscle mass and gene expression analysis in dogs with glucocorticoid-induced muscle atrophy. *J Vet Med Sci*. 2022;84:275-281. https://doi.org/10.1292/jvms.21-0325
233. O'Kell AL, Grant DC, Panciera DL, Troy GC, Weinstein NM. Effects of oral prednisone administration with or without ultralow-dose acetylsalicylic acid on coagulation parameters in healthy dogs. *Am J Vet Res*. 2012;73:1569-1576. https://doi.org/10.2460/ajvr.73.10.1569
234. García-Sancho M, Rodríguez-Franco F, Sainz A, Mancho C, Rodríguez A. Evaluation of clinical, macroscopic, and

histopathologic response to treatment in nonhypoproteinemic dogs with lymphocytic-plasmacytic enteritis. *J Vet Intern Med*. 2007;21:11-17. https://doi.org/10.1892/0891-6640(2007)21[11:EOCMAH]2.0.CO;2

235. Pietra M, Fracassi F, Diana A, et al. Plasma concentrations and therapeutic effects of budesonide in dogs with inflammatory bowel disease. *Am J Vet Res*. 2013;74:78-83. https://doi.org/10.2460/ajvr.74.1.78
236. Rychlik A, Kołodziejska-Sawerska A, Nowicki M, Szweda M. Clinical, endoscopic and histopathological evaluation of the efficacy of budesonide in the treatment of inflammatory bowel disease in dogs. *Pol J Vet Sci*. 2016;19:159-164. https://doi.org/10.1515/pjvs-2016-0020
237. Tumulty JW, Broussard JD, Steiner JM, Peterson ME, Williams DA. Clinical effects of short-term oral budesonide on the hypothalamic-pituitary-adrenal axis in dogs with inflammatory bowel disease. *J Am Anim Hosp Assoc*. 2004;40:120-123. https://doi.org/10.5326/0400120
238. Jablonski SA, Strohmeyer JL, Buchweitz JP, Lehner AF, Langlois DK. Prednisolone pharmacokinetics in dogs with protein-losing enteropathy. *J Vet Intern Med*. 2025;39:e17277. https://doi.org/10.1111/jvim.17277
239. Allenspach K, Rüfenacht S, Sauter S, et al. Pharmacokinetics and clinical efficacy of cyclosporine treatment of dogs with steroid-refractory inflammatory bowel disease. *J Vet Intern Med*. 2006;20:239-244. https://doi.org/10.1892/0891-6640(2006)20
240. Dandrieux JRS, Noble PJM, Scase TJ, Cripps PJ, German AJ. Comparison of a chlorambucil-prednisolone combination with an azathioprine-prednisolone combination for treatment of chronic enteropathy with concurrent protein-losing enteropathy in dogs: 27 cases (2007-2010). *J Am Vet Med Assoc*. 2013;242:1705-1714. https://doi.org/10.2460/javma.242.12.1705
241. Lecoindre A, Lecoindre P, Cadoré JL, et al. Focal intestinal lipogranulomatous lymphangitis in 10 dogs. *J Small Anim Pract*. 2016;57:465-471. https://doi.org/10.1111/jsap.12522
242. Crisonà M, Tardo AM, Pietra M, et al. Successful clinical management of canine intestinal lipogranulomatous lymphangitis through exclusive medical and nutritional treatment: four cases (2018-2023). *J Small Anim Pract*. 2025;66:52-60. https://doi.org/10.1111/jsap.13783
243. Chang C-H, Lidbury JA, Suchodolski JS, Steiner JM. Effect of oral or injectable supplementation with cobalamin in dogs with hypocobalaminemia caused by chronic enteropathy or exocrine pancreatic insufficiency. *J Vet Intern Med*. 2022;36:1607-1621. https://doi.org/10.1111/jvim.16528
244. Dor C, Nixon S, Salavati Schmitz S, et al. Efficacy and tolerance of oral versus parenteral cyanocobalamin supplement in hypocobalaminaemic dogs with chronic enteropathy: a controlled randomised open-label trial. *J Small Anim Pract*. 2024;65:317-328. https://doi.org/10.1111/jsap.13705
245. Toresson L, Steiner JM, Razdan P, et al. Comparison of efficacy of oral and parenteral cobalamin supplementation in normalising low cobalamin concentrations in dogs: a randomised controlled study. *Vet J*. 2018;232:27-32. https://doi.org/10.1016/j.tvjl.2017.12.010
246. Toresson L, Steiner JM, Suchodolski JS, Spillmann T. Oral cobalamin supplementation in dogs with chronic enteropathies and hypocobalaminemia. *J Vet Intern Med*. 2016;30:101-107. https://doi.org/10.1111/jvim.13797
247. Kimmel SE, Waddell LS, Michel KE. Hypomagnesemia and hypocalcemia associated with protein-losing enteropathy in Yorkshire terriers: five cases (1992-1998). *J Am Vet Med Assoc*. 2000;217:703-706. https://doi.org/10.2460/javma.2000.217.703
248. Volkmann M, Wirtherle NC, Beddies GF, Kohn B. Efficacy of AST-120 in dogs with chronic idiopathic enteropathies. *J Vet Intern Med*. 2013;27:1637-1641. https://doi.org/10.1111/jvim.12212
249. Pérez-Merino EM, Usón-Casaús JM, Zaragoza-Bayle C, et al. Safety and efficacy of allogeneic adipose tissue-derived mesenchymal stem cells for treatment of dogs with inflammatory bowel disease: clinical and laboratory outcomes. *Vet J*. 2015;206:385-390. https://doi.org/10.1016/j.tvjl.2015.08.003
250. Pérez-Merino EM, Usón-Casaús JM, Duque-Carrasco J, et al. Safety and efficacy of allogeneic adipose tissue-derived mesenchymal stem cells for treatment of dogs with inflammatory bowel disease: endoscopic and histological outcomes. *Vet J*. 2015;206:391-397. https://doi.org/10.1016/j.tvjl.2015.07.023
251. Cristóbal JI, Duque FJ, Usón-Casaús J, Barrera R, López E, Pérez-Merino EM. Complete blood count-derived inflammatory markers changes in dogs with chronic inflammatory enteropathy treated with adipose-derived mesenchymal stem cells. *Animals*. 2022;12:2798. https://doi.org/10.3390/ani12202798
252. Cristóbal JI, Duque FJ, Usón-Casaús J, Martínez MS, Míguez MP, Pérez-Merino EM. Oxidative stress in dogs with chronic inflammatory enteropathy treated with allogeneic mesenchymal stem cells. *Vet Res Commun*. 2024;48:901-910. https://doi.org/10.1007/s11259-023-10265-0
253. Huang H-P, Lien Y-H. Effects of a structured exercise programme in sedentary dogs with chronic diarrhoea. *Vet Rec*. 2017;180:224. https://doi.org/10.1136/vr.103902
254. Toresson L, Steiner JM, Suchodolski JS. Cholestyramine treatment in two dogs with presumptive bile acid diarrhoea: a case report. *Canine Med Genet*. 2021;8:1. https://doi.org/10.1186/s40575-021-00099-x
255. Goodwin LV, Goggs R, Chan DL, Allenspach K. Hypercoagulability in dogs with protein-losing enteropathy. *J Vet Intern Med*. 2011;25:273-277. https://doi.org/10.1111/j.1939-1676.2011.0683.x
256. Loyd KA, Cocayne CG, Cridland JM, Hause WR. Retrospective evaluation of the administration of 25% human albumin to dogs with protein-losing enteropathy: 21 cases (2003-2013). *J Vet Emerg Crit Care*. 2016;26:587-592. https://doi.org/10.1111/vec.12484
257. Jablonski SA, Mazepa ASW, Tolbert MK. Use of octreotide for the treatment of protein-losing enteropathy in dogs: retrospective study of 18 cases. *J Vet Intern Med*. 2024;38:145-151. https://doi.org/10.1111/jvim.16966
258. Allenspach K, Bergman PJ, Sauter S, Gröne A, Doherr MG, Gaschen F. P-glycoprotein expression in lamina propria lymphocytes of duodenal biopsy samples in dogs with chronic idiopathic enteropathies. *J Comp Pathol*. 2006;134:1-7. https://doi.org/10.1016/j.jcpa.2005.06.003

259. Galler A, Rütgen BC, Haas E, et al. Immunophenotype of peripheral blood lymphocytes in dogs with inflammatory bowel disease. *J Vet Intern Med*. 2017;31:1730-1739. https://doi.org/10.1111/jvim.14812
260. van der Heyden S, Vercauteren G, Daminet S, et al. Expression of P-glycoprotein in the intestinal epithelium of dogs with lymphoplasmacytic enteritis. *J Comp Pathol*. 2011;145:199-206. https://doi.org/10.1016/j.jcpa.2011.01.003
261. Furukawa R, Hara Y, Furuya K, et al. Expression of genes encoding interleukin 15 and its receptor subunits in the duodenal and colonic mucosae of dogs with chronic enteropathy. *Vet Anim Sci*. 2022;17:100256. https://doi.org/10.1016/j.vas.2022.100256
262. Maeda S, Ohno K, Nakamura K, et al. Quantification of chemokine and chemokine receptor gene expression in duodenal mucosa of dogs with inflammatory bowel disease. *Vet Immunol Immunopathol*. 2011;144:290-298. https://doi.org/10.1016/j.vetimm.2011.08.020
263. Jergens A, Young J, Moore D, et al. Bcl-2/caspase 3 mucosal imbalance favors T cell resistance to apoptosis in dogs with inflammatory bowel disease. *Vet Immunol Immunopathol*. 2014;158:167-174. https://doi.org/10.1016/j.vetimm.2014.01.004
264. Hiyoshi S, Ohno K, Uchida K, et al. Association between lymphocyte antigen receptor gene rearrangements and histopathological evaluation in canine chronic enteropathy. *Vet Immunol Immunopathol*. 2015;165:138-144. https://doi.org/10.1016/j.vetimm.2015.03.009
265. Konstantinidis AO, Adamama-Moraitou KK, Pardali D, et al. Colonic mucosal and cytobrush sample cytokine mRNA expression in canine inflammatory bowel disease and their correlation with disease activity, endoscopic and histopathologic score. *PloS One*. 2021;16:e0245713. https://doi.org/10.1371/journal.pone.0245713
266. Delaney F, O'Brien RT, Waller K. Ultrasound evaluation of small bowel thickness compared to weight in normal dogs. *Vet Radiol Ultrasound*. 2003;44:577-580. https://doi.org/10.1111/j.1740-8261.2003.tb00510.x
267. Gladwin NE, Penninck DG, Webster CRL. Ultrasonographic evaluation of the thickness of the wall layers in the intestinal tract of dogs. *Am J Vet Res*. 2014;75:349-353. https://doi.org/10.2460/ajvr.75.4.349
268. Makielski K, Cullen J, O'Connor A, Jergens AE. Narrative review of therapies for chronic enteropathies in dogs and cats. *J Vet Intern Med*. 2019;33:11-22. https://doi.org/10.1111/jvim.15345
269. Roudebush P, Allen TA, Dodd CE, Novotny BJ. Application of evidence-based medicine to veterinary clinical nutrition. *J Am Vet Med Assoc*. 2004;224:1765-1771. https://doi.org/10.2460/javma.2004.224.1766
270. Ryu MO, Lee SY, Kim SH, Youn HY, Seo KW. Fecal microbiota transplantation via commercial oral capsules for chronic enteropathies in dogs and cats. *J Vet Clin*. 2024;41:150-156. https://doi.org/10.17555/jvc.2024.41.3.150

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