REVIEW

Narrative review of therapies for chronic enteropathies in dogs and cats

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Background: The optimal medical treatment for chronic enteropathy (CE) in dogs and cats is controversial. Sequential treatment using diet, antimicrobials, and immunosuppressive drugs is the most common strategy used by clinicians.

Objectives: To review the evidence for the effectiveness of dietary, drug, and alternative health interventions for inducing clinical remission in dogs and cats with CE.

Animals: Retrospective study of dogs and cats with a diagnosis of chronic enteropathy.

Methods: MEDLINE and Centre for Agriculture and Bioscience International (CABI) databases (1950 to March 2017) were searched for randomized controlled trials (RCTs), observational studies, and case series. The primary outcome was induction of clinical remission. All studies were evaluated using the quality of evidence grading guidelines (I-IV), which assign a score defining the strength and quality of the evidence.

Results: Twenty-two studies (11 RCTs in dogs and 2 in cats and 9 cohort studies or case series) met the inclusion criteria for inducing remission of gastrointestinal (GI) signs. Of the 13 RCTs achieving grade I scores, 10 studies (totaling 218 dogs and 65 cats) compared single treatment: diet (n = 3), immunosuppressives (n = 3), antimicrobials (n = 2), anti-inflammatory drugs (n = 1), and probiotics (n = 1). Three case series (grade III) reported clinical remission using an elimination diet fed to 55 cats and use of enrofloxacin to induce remission in dogs with granulomatous colitis (2 studies totaling 16 dogs).

Conclusions and Clinical Importance: The current evidence for treatment of CE is much greater in dogs than in cats. There is sufficient strong evidence to recommend the use of therapeutic GI diets, glucocorticoids, enrofloxacin, or some combination of these in dogs with CE. Therapeutic GI diets and glucocorticoids are most useful in cats with CE.

KEYWORDS

antibiotics, cyclosporine, diet, drug treatment, immunosuppressives, inflammatory bowel disease, prednisone, quality of evidence guidelines, randomized controlled trial

1 | INTRODUCTION

Chronic enteropathies (CE) are a common cause for persistent or recurrent gastrointestinal (GI) signs in dogs and cats. Although the different forms of CE, including food-responsive enteropathy (FRE),[1,2] antimicrobial-responsive diarrhea (ARD),[3] and corticosteroid or immunosuppressive-responsive inflammatory bowel disease (IBD) (steroid-responsive disease, SRD)[4,5] have different etiologies, clinical signs often overlap and distinguishing among these disorders may be

difficult, even with GI endoscopy and histopathologic review of mucosal biopsy specimens. Alternatively, the different phenotypes of CE might reflect a single disease process of increasing severity affecting the intestinal immune system and selectively responsive to different interventions over time. A prevailing hypothesis is that most forms of CE involve a complex interplay among host genetics, the intestinal microenvironment (primarily bacteria and dietary constituents), and the immune system.[6] Accordingly, sequential treatment using specially formulated diets, antimicrobials, and immunosuppressive drugs is the most common strategy used to achieve clinical remission, with a final diagnosis often made in response to treatment, histopathologic evaluation of intestinal biopsy specimens, or both.

Over the past 3 decades, many therapeutic interventions have been developed for CE in dogs and cats, but scientific evidence of efficacy and effectiveness often is lacking or highly variable. Still other published studies are small (and often underpowered), and very few properly designed clinical trials have been performed. Evidence-based medicine (EBM) has emerged in different veterinary disciplines to aid in clinical decision-making regarding patient care.[7–10] It has been defined as the integration of the best research evidence with clinical expertise and owner and clinician preferences. The basic tenet of EBM is that integration of these elements (ie, relevant clinical research, clinical expertise, patient and owner preferences, and available resources) will result in the formation of diagnostic and therapeutic plans that optimize clinical outcome and quality of life.[11]

The purpose of this narrative review based on an extensive literature search was to examine the evidence regarding clinical efficacy and effectiveness of dietary, drug, and alternative or complementary treatments for inducing remission in dogs and cats with CE. We first performed a structured and reproducible search for RCTs and cohort studies and used expert opinion (Albert E. Jergens and Kelly Makielski as experienced board-certified internists and Annette O'Connor and Jonah Cullen as clinical epidemiologists) to identify relevant case series and then evaluated the quality of the intervention using quality of evidence grading guidelines.[12]

2 | MATERIALS AND METHODS

2.1 | Search strategy

The search strategy was developed to identify veterinary studies that assessed dietary, drug, and alternative or complementary health interventions for CE in dogs and cats indexed in the MEDLINE and Centre for Agriculture and Bioscience International (CABI) databases through March 2017. The MEDLINE and CABI databases were accessed via Web of Science through Iowa State University. Identical search terms for each database included the following as text words and medical subject headings: canine, dog, feline, cat, inflammatory bowel disease (IBD), colitis, enterocolitis, and CE. Only publications written in English that included an abstract were considered. In addition, the reference lists of relevant articles were searched for other appropriate articles, and clinician experts in gastroenterology were consulted to identify additional studies.

2.2 | Study selection

For the electronic search, studies that used a comparison group were considered relevant (ie, controlled clinical trials reporting the effect of various treatments on clinical remission, cohort studies, and case-control studies). Studies must also have provided a minimum treatment duration of 14 days, must have contained a description of how clinical remission was defined, and must have included histopathologic confirmation of intestinal inflammation if a diagnosis of IBD was made. A single reviewer (Kelly Makielski) assessed the eligibility of these studies, after a training to ensure high agreement with the expert about relevant studies.

In addition to the structured search, a nonstructured search was conducted for non-peer-reviewed articles (eg, scientific proceedings from major veterinary meetings), review papers, and some expert opinion papers. Two reviewers (Kelly Makielski and Jonah Cullen) independently conducted an initial screen of abstracts for eligibility of these sources and evaluated the full-text articles of identified abstracts for final eligibility. The nonstructured search did not limit relevant studies to those with a comparison group (ie, case series were included).

2.3 | Data extraction and quality assessment

For all relevant studies identified by the structured and nonstructured search, 2 reviewers (Kelly Makielski and Albert E. Jergens) performed data extraction and assigned an evidence grade based on the study design. Extracted data included study treatment characteristics, participant characteristics, and outcomes. All studies were evaluated using the quality of evidence grading guidelines, which assign a score defining the strength and quality of the evidence.[12] This tool previously has been applied to establish EBM recommendations regarding veterinary nutrition and nephrology.[8,11,12] These guidelines categorize the quality of evidence into grades I-IV, based on the applicability to clinical case management (Table 1). Grades I and II are evidence of the highest quality, whereas grade IV evidence is of the lowest quality. The quality and strength of the evidence then can be used to make a recommendation about the use of a specific treatment intervention.

2.4 | Summation of evidence

The corresponding author (Albert E. Jergens) compiled the data and summarized the findings by treatment options and evidence grade of the relevant studies. For each treatment, a summary of the findings was provided for the available relevant study by evidence grade. The recommendations were developed based on the opinion of the 2 clinical authors after reviewing the literature (Albert E. Jergens and Kelly Makielski).

3 | RESULTS

3.1 | Eligible studies

The combined (structured and nonstructured) search strategy identified 1112 canine and 486 feline citations. The original search was conducted in 2015, and then a second search was performed from November-December 2016 through March 2017. Figures 1 and 2 show the flow-charts of the selection of retrieved studies from both searches. Thirteen

TABLE 1 Quality of evidence grading guidelines

Score	Descriptor	
Grade I	Evidence obtained from 1 or more properly designed RCT in clinical patients of the target species	Strong
Grade II	Evidence obtained from a properly designed RCT using the target species with spontaneous disease in a research or laboratory setting	
Grade III	Evidence obtained from controlled studies, without randomization, such as cohort studies, case control trials, or prospective case series having significant clinical impact	
Grade IV	Evidence obtained from reports of expert committees descriptive studies, key case reports, and opinions from recognized experts based on their clinical experience	Weak

Abbreviation: RCT, randomized controlled trial.
Adapted from Roudebush et al, 2004.

RCTs (11 in dogs, 2 in cats) were considered relevant. For the specific treatments in which few or no RCTs were available, the best available evidence was described, resulting in the description of an additional 9 cohort studies and case series. The quality of these selected studies was moderate (grade III), and clinical outcome was considered impactful because they demonstrated innovative treatment strategies that promoted positive patient outcome.

3.2 | Diet as primary and adjuvant treatment for CE

Adverse reactions to food are a common cause for GI signs through immunologic (ie, dietary sensitivity triggered by aberrant immune responses) and nonimmunologic (including food intolerance and dietary indiscretion) mechanisms.[13] Clinical studies attest to the central role that diet plays in management of dogs and cats with CE (Table 2).

3.2.1 | Grade I evidence studies

In 1 RCT, 26 dogs with small intestinal diarrhea randomized in a 2 : 1 ratio to be fed either a diet containing hydrolyzed soy protein (test diet) or an intestinal diet containing proteins from a variety of sources.[14] Outcome measures included subjective response to treatment, change in body weight, and disease activity using the canine IBD activity index (CIBDAI) score. The short-term (3 months) response was 88% in both groups, however, only 1 in 6 dogs fed the intestinal diet versus 13 of 14 dogs fed the hydrolysate diet maintained clinical remission over a 3-year period. For the final examination (median treatment
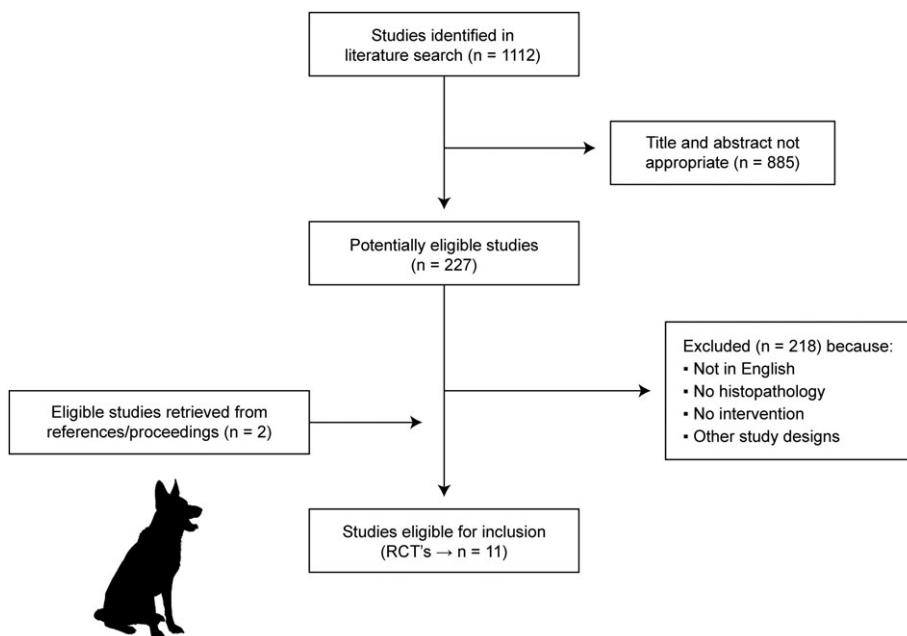
FIGURE 1 Literature search flowchart for canine CE
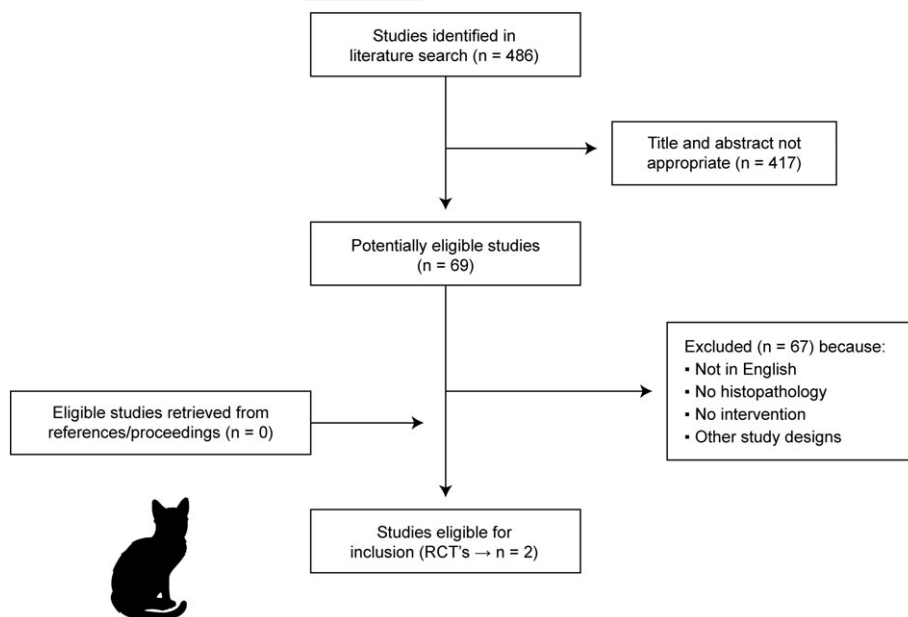
FIGURE 2 Literature search flowchart for feline CE

duration of 1284 days), body weight and CIBDAI scores were unavailable for comparison among cohorts of dogs.

Results of 2 RCT evaluating the effect of diet in cats with CE have been reported. In 1 randomized, double-blinded clinical trial, 55 pet cats with chronic diarrhea were randomized to receive either a low-fat (10%) or high-fat (23%) diet fed exclusively for 6 weeks as a primary intervention.[15] Clients were instructed to record fecal scores and the occurrence of vomiting episodes weekly, with the results analyzed between groups at 0, 1, 3, and 6 weeks. Results indicated that there was no difference in clinical responses between test diets, with fecal scores improving as early as 1 week and with maximal improvement at 3 weeks. In the 2nd RCT, the efficacy of a hydrolyzed soya diet was assessed in 10 cats with CE.[16] Cats were randomized on entry to be fed either a hydrolyzed soya protein diet or a commercial prescription intestinal diet. A positive clinical response was defined as cessation of GI signs. The use of the hydrolyzed soy-based diet

resolved GI signs in 7 of 10 cats versus 3 of 10 cats who fed the prescription diet over a 4-week trial period. Although different clinical responses to dietary intervention were observed, the effect of the hydrolyzed soy diet as compared to the prescription diet was not statistically different. Importantly, this observation may have been influenced by the number of cats enrolled in the trial, which was too small to detect a difference.

3.2.2 | Grade III evidence studies

In 1 cohort study, 39 of 65 (60%) dogs with FRE or IBD responded when fed an antigen-restricted diet of salmon and rice for at least 10 days.[1] The severity of clinical signs was scored by means of CIBDAI.[5] The CIBDAI score decreased significantly after treatment in both groups (in dogs with FRE, 74% moderate to severe before versus 8% after treatment; in dogs with IBD, 85% moderate to severe before versus 32% after treatment).

TABLE 2 Characteristics of included studies—dietary interventions

Study	Species	Inclusion diagnosis	No. of patients	Study quality	Intervention	Treatment duration	Outcome
Guilford et al, 2001[2]	Feline	CE	55	Grade III	Elimination diet	3 y	Elimination diet resolved GI signs in 27 of 55 (49%) cats
Luckschander et al, 2006[1]	Canine	FRE	39	Grade III	Salmon + rice diet	10 d	All dogs showed decreased CIBDA post-treatment
Allenspach et al, 2007[34]	Canine	FRE	39/70	Grade III	Elimination diet	3 y	Elimination diet induced long-term remission in dogs with FRE
Mandigers et al, 2010[14]	Canine	CE	18	Grade I	Hydrolyzed protein versus control diet	3 y	Hydrolyzed diet superior to control diet for long-term clinical remission
Jergens et al, 2010[18]	Feline	FRE	6	Grade III	Elimination diet	3 wk	All cats showed decreased FCEAI scores post-treatment
Waly et al, 2010[16]	Feline	CE	10	Grade I	Hydrolyzed soya diet	4 wk	Hydrolyzed diet superior to control diet for clinical remission
Laflamme et al, 2011[15]	Feline	CE	55	Grade I	High-fat versus low-fat diet	6 wk	No difference in treatment response
Allenspach, et al, 2016[17]	Canine	FRE	131/203	Grade III	Elimination or hydrolyzed diet	12 wk	Outcome at 1 y best for dogs with FRE versus dogs with ARD and SRD

Abbreviations: ARD, antimicrobial-responsive diarrhea; CE, chronic enteropathy; CIBDAI, canine IBD activity index; FCEAI, feline chronic enteropathy activity index; FRE, food-responsive enteropathy; SRD, steroid/immunosuppressive-responsive disease.

In a retrospective cohort study of short-term and long-term outcome in 203 dogs with CE, outcomes of 131 dogs (64%) with FRE were compared to 33 dogs (16%) treated with antimicrobials (ie, ARD) and 39 dogs (19%) treated with immunosuppressive drugs (ie, SRD).[17] Diets prescribed to dogs with FRE included an elimination diet (55%), a hydrolyzed diet (44%), and a homemade diet. Dogs with FRE showed significantly better outcome (decreased clinical activity score) at 4-8 weeks after discharge than those with ARD, and at 6 months to 1 year after discharge as compared to both ARD and SRD groups. There was no difference in outcome in dogs with FRE who fed an elimination diet or a hydrolyzed diet.

Another study[2] reported the clinical response of 55 cats with clinical signs of CE challenged with dietary elimination trials. In this descriptive single-group cohort study, 49% of the enrolled cats having chronic GI signs responded to dietary modification as the primary treatment intervention. When fed 1 of 2 commercial selected diets, 16 (29%) of the 55 cats with CE were diagnosed as food-sensitive. The GI signs of another 11 cats (20%) resolved on the elimination diet but did not recur after challenge with their original food. Clinical signs in the most food-sensitive cats resolved quickly within 3-5 days on the elimination diet. Food-sensitive cats most commonly showed adverse reactions to beef and cereal grains, including wheat, corn, and barley.

In a separate prospective nonrandomized cohort study, 23 cats with IBD (74%) or FRE (26%) responded completely to an elimination dietary trial alone (FRE) or in combination with PO-administered prednisolone (IBD).[18] Clinical response in affected cats was assessed using a combination of GI signs and laboratory markers (eg, feline CE activity index) to define remission.

3.2.3 | Summary

There is strong evidence from RCTs to support a recommendation to feed elimination diets to dogs and cats with CE (grade I evidence). Moreover, several other descriptive cohort studies and nonrandomized trials (grade III evidence) support a recommendation for dietary trials in the short-term and long-term maintenance of clinical remission. Evidence supporting a recommendation for further limiting some dietary ingredients (eg, selected proteins, cereal grains) in the management of CE in cats is based on dietary elimination trials and controlled clinical reports (grade III evidence). It is not possible to ascertain which form of diet (eg, novel intact protein or hydrolysate) is most effective in modulating GI signs in dogs and cats.

3.3 | Antimicrobials as primary and adjuvant treatment for CE

Antimicrobials are often advocated as a principal component of sequential treatment (eg, diet, antimicrobials, corticosteroids, and then other immunosuppressive drugs) for dogs and cats with CE. Antimicrobials presumably are used to counter the effects of microbial dysbiosis which may initiate and drive host inflammatory responses.[19,20] Antimicrobial trials using metronidazole or tylosin have shown efficacy in a subset of animals diagnosed with CE (Table 3).[21,22] Although numerous trials report remission with the use of metronidazole in dogs and cats, the antimicrobial often was combined with diet and other drugs (eg, glucocorticoids) confounding interpretation as to what portion of the clinical response was attributable to the antimicrobial alone.

3.3.1 | Grade I evidence studies

Tylosin-responsive diarrhea (TRD) is described in dogs as a form of ARD, which typically affects middle-aged, large-breed dogs causing chronic or intermittent small or large intestinal diarrhea.[3,22] In 1 RCT, the effect of tylosin was investigated in 71 dogs with histories of intermittent diarrhea previously responsive to tylosin administration.[23] Using a placebo-controlled, randomized, double-blinded study design, dogs were assigned in a 2 : 1 ratio to receive tylosin versus placebo and followed over 2 months. Treatment outcome was evaluated as the mean of fecal consistency scores assigned during the last 3 days of the treatment period. Results indicate that 27 of 61 enrolled dogs developed diarrhea during the study period with a greater percentage ($P < .05$) of dogs that received tylosin (17/20, 85%) versus placebo (2/7, 29%) having normal fecal consistency at study completion.

Another RCT compared the clinical efficacy of rifaximin (RIF) to metronidazole (MET) for treatment of dogs with CE.[24] All dogs enrolled in the study had chronic GI signs and histopathologic lesions of lymphocytic-plasmacytic intestinal inflammation suggestive of idiopathic IBD. Twenty-four dogs were randomized to receive either RIF (n = 14 dogs) or MET (n = 10 dogs) for 21 days, with changes in disease activity (CIBDAI) and serum C-reactive protein (CRP) concentrations measured at the end of the study period. Remission was

TABLE 3 Characteristics of included studies—antimicrobial interventions

Study	Species	Inclusion diagnosis	No. of patients	Study quality	Intervention	Treatment duration	Outcome
Hostutler et al, 2004[26]	Canine	GC	9	Grade III	Enrofloxacin	1 mo	Enrofloxacin effective for remission
Mansfield et al, 2009[27]	Canine	GC	7	Grade III	Enrofloxacin	2 wk	Enrofloxacin effective for remission
Jergens et al, 2010[29]	Canine	IBD	54	Grade I	MTZ + prednisone vs prednisone	3 wk	No difference in treatment response
Kilpinen et al, 2011[23]	Canine	CE	20	Grade I	Tylosin	2 mo	Tylosin superior to placebo for remission
Rossi et al, 2014[25]	Canine	IBD	20	Grade I	MTZ + prednisone vs probiotic	2 mo	No difference in treatment response
Menozzi et al, 2016[24]	Canine	IBD	24	Grade I	MTZ vs rifaximin	3 wk	No difference in treatment response
Allenspach et al, 2016[17]	Canine	ARD	33/203	Grade III	MTZ or tylosin	2 wk	Outcome at 1 y best for dogs with FRE vs dogs with ARD and SRD

Abbreviations: ARD, antimicrobial-responsive diarrhea; CE, chronic enteropathy; FRE, food-responsive enteropathy; GC, granulomatous colitis; IBD, inflammatory bowel disease; MTZ, metronidazole; SRD, steroid/immunosuppressive-responsive disease.

defined as a ≥75% decrease in the baseline CIBDAI score. Results showed that treatment with RIF or MET decreased clinical disease severity and serum CRP concentrations in both groups similarly. No adverse effects were noted. Potential study limitations included the small number of dogs evaluated and the possible contribution of antiemetic drugs to improve CIBDAI scores.

Two other RCTs investigated the efficacy of MET in treating dogs with IBD. In separate studies, the combination of MET and prednisone was compared to either prednisone alone or a multi-strain probiotic.[25] In both trials, differences between treatments in the rate of clinical remission (CIBDAI) were not observed. Additional details of these separate trials are included below.

3.3.2 | Grade III evidence studies

In an early descriptive single-group cohort study, the responsiveness of histopathologic GC in 9 dogs (8 Boxer dogs and 1 English Bulldog) treated with enrofloxacin alone or in combination with MET and amoxicillin was evaluated.[26] Clinical signs, including diarrhea, resolved in all 9 dogs within 12 days after beginning enrofloxacin alone or in combination with either MET or amoxicillin and MET. Five dogs that underwent repeat colonic biopsy showed marked histopathologic improvement characterized by a decrease in the numbers of PAS-positive macrophages in biopsy specimens. All 9 dogs were free of clinical signs up to 21 months after treatment, and medications were discontinued in 3 dogs with resolution of clinical signs for up to 14 months.

A 2nd descriptive single-group cohort on GC in dogs investigated the association between eradication of mucosal adherent/invasive *Escherichia coli* (AIEC) and clinical remission with antimicrobial treatment.[27] Colonic biopsy specimens obtained in 7 Boxer dogs with GC were evaluated for their content of AIEC before and after treatment with enrofloxacin. Clinical response was observed in all 7 dogs within 2 weeks of antimicrobial treatment. Furthermore, fluorescence in situ

hybridization (FISH) was negative for AIEC in 4 of 5 dogs after enrofloxacin treatment. *Escherichia coli* resistance to enrofloxacin was present in the FISH-positive dog that relapsed.

A single study describing long-term outcome of dogs with CE reports successful use of tylosin or MET to treat ARD.[17]

3.3.3 | Summary

There is evidence from a single RCT (grade I evidence) to support a weak recommendation to use tylosin in treatment of ARD in dogs. The recommendation is weak because not all dogs developed diarrhea during the treatment period, decreasing the anticipated distribution of dogs in both treatment groups. There is no strong evidence to support the use of MET as a component of combination treatment for treatment of dogs with IBD. The clinical response of Boxer dogs with GC to antimicrobial regimens containing enrofloxacin suggests an infectious cause (eg, AIEC) for the inflammatory process (grade III evidence).

3.4 | Immunosuppressive drugs as primary and adjuvant treatment for CE

Chronic enteropathy nonresponsive to diet and antimicrobial interventions often are designated as idiopathic IBD, which is confirmed by intestinal biopsy results showing mucosal inflammation. In these instances, treatment typically requires immunosuppressive drugs, with glucocorticoids being a mainstay of most treatment regimens (Table 4).[19] Immunosuppressive drug treatment also may include administration of other drugs, especially when adverse effects of corticosteroids are present or when animals fail to respond adequately to systemic corticosteroids.[28]

3.4.1 | Grade I evidence studies

One RCT compared the efficacy of prednisone versus prednisone and MET in induction therapy for dogs with IBD.[29] Fifty-four dogs with

TABLE 4 Characteristics of included studies—steroid/immunosuppressive drug interventions

Study	Species	Inclusion diagnosis	No. of patients	Study quality	Intervention	Treatment duration	Outcome
Allenspach et al, 2006[33]	Canine	IBD	14	Grade III	Cyclosporine for steroid refractory disease	10 wk	12 of 14 dogs show clinical remission
Allenspach et al, 2007[34]	Canine	IBD/PLE	18/70	Grade III	Prednisolone first then cyclosporine for steroid refractory disease	10 wk for prednisolone; 10 wk for CsA	10 of 21 dogs with IBD respond to prednisolone; 2 of 8 dogs respond to CsA; 7 of 10 dogs with PLE respond to CsA
Jergens et al, 2010[29]	Canine	IBD	54	Grade I	MTZ + prednisone vs prednisone	3 wk	No difference in treatment response
Jergens et al, 2010[18]	Feline	IBD	17	Grade III	Prednisolone	3 wk	All cats showed decreased FCEAI scores post-treatment
Heilmann et al, 2012[30]	Canine	IBD	34	Grade I	MTZ + prednisone vs prednisone	3 wk	Prednisone ↑ serum cCP
Dye et al, 2013[31]	Canine	IBD	34	Grade I	Prednisone vs budesonide	6 wk	Prednisone is as effective as budesonide for remission
Allenspach et al, 2016[17]	Canine	SRD	39/203	Grade III	Combination of prednisolone, CsA, and/or azathioprine	Not stated	Outcome at 1 y best for dogs with FRE versus dogs with ARD and SRD
White et al, 2017[39]	Canine	IBD	26	Grade I	Prednisone + diet (ST) versus ST + probiotic	8 wk	No difference in treatment response

Abbreviations: ARD, antimicrobial-responsive diarrhea; cCP, canine calprotectin; CsA, cyclosporine A; FCEAI, feline chronic enteropathy activity index; FRE, food-responsive enteropathy; IBD, inflammatory bowel disease; MTZ, metronidazole; SRD, steroid/immunosuppressive-responsive disease; ST, standard IBD treatment (diet + prednisone).

IBD were randomized to receive single or combination drug treatment (CT) with clinical (CIBDAI) scores, and serum CRP concentrations determined at diagnosis and after 21 days of drug treatment. Results indicated that the rates of remission (>80%) were similar in both treatment groups. Both treatments decreased CRP in comparison with pretreatment concentrations. In a related study, dogs from this earlier RCT were shown to have increased serum calprotectin concentrations compared with those of control dogs.[30] Although results indicated that measurement of serum calprotectin concentration was useful for the detection of baseline inflammation, treatment with glucocorticoids resulted in increased serum calprotectin concentrations despite clinical remission.

A separate double-blinded RCT compared budesonide and prednisone for induction therapy of IBD in dogs.[31] Forty dogs with IBD were randomized to receive budesonide or prednisone administered daily for 6 weeks with remission rates (>75% reduction in baseline CIBDAI after treatment) and adverse effects serving as outcome measures. Differences in remission rates were not observed between the treatment groups. The frequency and severity of adverse effects reported by pet owners were similar for the 2 treatment groups.

3.4.2 | Grade III evidence studies

Although most dogs with IBD respond to immunosuppressive doses of corticosteroids, a subset of animals will not respond initially to induction or will relapse after months of treatment.[17,32] Separate studies have investigated the efficacy of cyclosporine A (CsA) as a single-agent treatment for steroid-refractory IBD in dogs. In a single-group descriptive cohort, 14 dogs with IBD treated previously with prednisolone for up to 2 years with minimal clinical response were treated with CsA once daily for 10 weeks.[33] Outcome measures included clinical disease activity (CIBDAI score) and histopathology score. Results indicated significant clinical improvement in 12 of 14 dogs with IBD and decreased numbers of intestinal mucosal cellular infiltrates (eg, CD3+ T cells) after CsA treatment. Another descriptive cohort study investigated CsA as treatment in 8 dogs with IBD that failed to respond to glucocorticoid treatment.[34] These dogs

underwent the same treatment protocol as described above and were evaluated using similar clinical and histopathologic indices of inflammation. Long-term follow-up showed that 2 of 8 dogs with IBD and 7 of 10 dogs with PLE responded favorably to CsA treatment and were rescued from euthanasia.

3.4.3 | Summary

Several RCTs provide high-quality evidence to support a recommendation to administer glucocorticoids as induction treatment to dogs with idiopathic IBD. Separate trials show that single-drug treatment with prednisone is as efficacious as treatment with budesonide alone or prednisone combined with MET. A single prospective cohort study indicates that prednisolone treatment is effective in cats with IBD (grade III evidence).[18] Evidence supporting a recommendation for use of CsA in dogs with steroid-refractory IBD is based on several, small descriptive cohort studies (grade III evidence).

3.5 | Alternative/complementary therapies as primary and adjuvant treatment for CE

The most commonly prescribed treatments for dogs and cats with CE are directed toward suppressing the overactive immune responses causing chronic GI signs. However, there is an important role for nonimmunosuppressive therapies that may decrease mucosal inflammation, counter microbial dysbiosis, and promote a more favorable risk-benefit profile in patients.[35] This need has prompted clinical evaluation of several alternative/complementary treatments including probiotics, prebiotics, and synbiotics for treatment of CE (Table 5).

3.5.1 | Grade I evidence studies

Probiotics, defined as bacteria with beneficial effects on the host, have broad appeal to clinicians and clients wishing to use "natural" therapeutic approaches. In an open-label trial,[25] the efficacy of a multi-strain probiotic (VSL#3) was investigated for treatment of IBD in dogs. After IBD diagnosis, 20 dogs were randomized to receive treatment with a multi-strain probiotic (n = 10) or combination drug

TABLE 5 Characteristics of included studies—Complementary/alternative treatment interventions

Study	Species	Inclusion diagnosis	No. of patients	Study quality	Intervention	Treatment duration	Outcome
Rossi et al, 2014[25]	Canine	IBD	20	Grade I	MTZ + prednisone vs probiotic	2 mo	No difference in treatment response
Schmitz et al, 2015[43]	Canine	CE	12	Grade I	Hydrolyzed diet + synbiotic (EF + FOS) or placebo	6 wk	No difference in treatment for inflammasome gene expression
Schmitz et al, 2015[42]	Canine	FRE	12	Grade I	Hydrolyzed diet + synbiotic (EF + FOS) or placebo	6 wk	No difference in treatment for intestinal cytokine gene expression
Segarra et al, 2016[41]	Canine	IBD	19	Grade I	Hydrolyzed diet + chondroitin sulfate with prebiotics or placebo	6 mo	No difference in treatment response
White et al, 2017[39]	Canine	IBD	26	Grade I	Prednisone + diet (ST) vs ST + probiotic	8 wk	No difference in treatment response
Webb et al, 2015[44]	Feline	CE but no histology	14	Grade IV	Mesenchymal stem cells (MSCs) or placebo IV	2 wk	5 of 7 MSC-treated cats showed clinical improvement

Abbreviations: CE, chronic enteropathy; EF, *Enterococcus faecium*; FOS, fructo-oligosaccharides; FRE, food-responsive enteropathy; IBD, inflammatory bowel disease; MSC, mesenchymal stem cell; ST = standard IBD treatment (diet + prednisone).

(prednisone + MET) treatment (n = 10) given daily for 8 weeks. Outcomes included disease activity (CIBDAI score), histologic indices, epithelial tight junction protein (TJP) expression, and fecal microbiota composition. During the short course (8 weeks) of the study, clinical signs of GI disease resolved in dogs of both treatment groups. Although treatment with either probiotic or drugs was associated with clinical and histopathologic improvement, only the probiotic was shown to upregulate the expression of TJP in the intestines of dogs with IBD. The increased expression of TJPs in these dogs might suggest enhanced epithelial barrier integrity associated with probiotic treatment.[36–38]

A separate RCT investigated the effects of a multi-strain probiotic on the mucosal microbiota in dogs with IBD.[39] Thirty-four dogs with IBD were randomized to receive standard treatment (ie, elimination diet + prednisone) with or without probiotic. Tissue sections from endoscopic biopsy specimens were evaluated for mucosal bacteria using FISH on a quantifiable basis. Disease activity (CIBDAI scores) and changes in mucosal microbiota and TJP expression were assessed before and after 8 weeks of IBD treatment. Both treatments increased the numbers of total bacteria and individual species residing within adherent mucus in a similar fashion. Although both treatments were associated with rapid and progressive clinical remission, significant improvement in histopathologic inflammation was not observed in either group. Similar to the earlier clinical trial, epithelial TJP expression was increased in probiotic-treated dogs.

The effect of galacto-oligosaccharides (GOS) on the fecal microbiota of healthy cats and cats with IBD recently has been evaluated during a randomized, double-blind, crossover feeding study.[40] A GOS-supplemented diet was fed to control cats and cats with IBD for a period of 3 weeks with fecal microbiota evaluated using an 8-probe FISH array. Overall, inter-animal variation of microbial composition was high. Although a trend for increased *Bifidobacterium* spp. was seen with GOS supplementation, it was not statistically significant in either the healthy cats or cats with IBD. The low number of animals enrolled coupled with extensive inter-animal variation in microbiota limited the statistical power of our study.

Another RCT investigated the long-term management (180 days) of dogs with IBD using a supplement containing chondroitin sulfate and prebiotics (ie, resistant starch, β-glucans, and manno-oligosaccharides) combined with a hydrolyzed diet.[41] End points included clinical signs, intestinal histopathology, fecal microbiota, and serum biomarkers of inflammation and oxidative stress. Final data analysis (supplement: n = 9 dogs; placebo: n = 10 dogs) indicated no differences between groups at any time point for CIBDAI score, histopathologic lesions, and fecal microbiota. Although results suggested favorable alterations in selected serum biomarkers in response to supplement administration, the sample size was small and the study was likely underpowered.

One RCT has investigated the clinical efficacy of PO prebiotics in combination with probiotics (synbiotic) in dogs with CE.[42] Dogs diagnosed with CE were prospectively recruited to receive a hydrolyzed elimination diet plus either a synbiotic product containing *Enterococcus faecium* (EF) or placebo for 6 weeks. Of the 45 dogs recruited, 12 finished the clinical trial with 7 dogs treated with synbiotic and 5 dogs treated with placebo. There was no difference between groups or

treatments regarding clinical efficacy, histology, or expression of any inflammatory genes. Because the study was underpowered, it was not possible to determine whether EF had a beneficial effect within the time of 6 weeks. A 2nd RCT, using the same synbiotic and a hydrolyzed antigen diet, showed no difference in inflammasome-related gene expression in 12 dogs undergoing treatment for chronic FRE.[43]

3.5.2 | Grade IV evidence studies

Stem cell therapy in cats with CE recently has been reported in a small proof-of-concept study.[44] Mesenchymal stem cells (MSCs) have been shown to alter host responses and decrease inflammation in humans by changes in cytokine secretion; direct interactions with T cells, natural killer cells, neutrophils, and dendritic cells; and, by increasing numbers of regulatory T cells.[45–48] In this single report, allogenic adipose-derived feline MSCs (fMSCs) were used to treat 7 cats with chronic diarrhea (>6 months duration), whereas 4 cats with similar GI signs received placebo in a blinded fashion. Study objectives included determination of the safety and efficacy of stem cell therapy using a client questionnaire. Owner responses were tabulated before and 2 weeks after the second of 2 fMSC or placebo treatments. No adverse effects were observed in the fMSC-treated cats. Owners of 5 of 7 fMSC-treated cats reported substantial improvement in or resolution of GI signs. Owners of placebo-treated cats reported no change or worsening of clinical signs. During the study, no change in diet, supplements, or prescribed medications was performed or no histopathologic diagnosis was required for study entry.

3.5.3 | Summary

There is grade I evidence from different RCTs that multi-strain probiotics modulate the expression of TJPs, which may positively affect intestinal barrier function to decrease intestinal inflammation. However, dogs in both trials[25,39] also were fed an elimination diet, and it remains possible that the beneficial clinical response was at least partially attributable to the dietary intervention. These different studies show variable effects of probiotic treatment on mucosal histopathology before versus after treatment when evaluated after 2 months of continuous treatment. The efficacy and effectiveness of probiotics for maintenance of long-term clinical remission of CE have not been reported. Separate studies evaluating the treatment effects of either prebiotics or synbiotics for dogs and cats with CE are underpowered and therefore provide no clinically relevant data to evaluate. A single report exists for use of MSCs in cats with poorly defined CE (grade IV evidence).

4 | DISCUSSION

Our narrative review based on an extensive literature search comprehensively summarizes the available evidence regarding treatment of CE in dogs and cats. A challenge in critical review of therapies for CE in dogs is the overlapping features of the 3 major types (FRE, ARD, and SRD), which makes it difficult to distinguish the different forms of the disease except by response to treatment. Importantly, therapeutic approaches are influenced by suspicion of a breed-related problem, age of the patient, severity of GI signs, serum albumin and cobalamin concentrations, endoscopic mucosal appearances, and the presence of

histopathologic changes, such as the type and magnitude of cellular infiltrate, the presence of mucosal bacteria, and architectural alterations of villus atrophy, ulceration or erosions, lymphangiectasia, or crypt abscesses, or some combination of these.[49,50]

Most clinicians favor treatment trials first, reserving endoscopy or surgery to obtain intestinal biopsy specimens in poor-responder or nonresponder patients and to confirm the presence and severity of intestinal inflammation while eliminating other intestinal disorders such as GI histoplasmosis and lymphoma.[51] In several reports, dogs with FRE were younger than dogs with SRD and most often presented with signs of large bowel disease.[17,34] They also usually showed low clinical disease activity and normal serum albumin concentrations as compared with dogs with ARD and SRD. Clinical response to dietary change typically is rapid within 1-2 weeks of changing the diet. If dietary trials with 2 different diets are unsuccessful, then adjunct treatments along with diet should be attempted. Dogs responding to antimicrobials usually are younger predominantly large-breed dogs (German Shepherd dogs, Rough Collies, and Golden Retrievers). Although short-term response to both MET and tylosin have been observed in dogs with ARD, studies describing long-term control of GI signs are few.[17,23] The use of FISH to identify mucosal-associated bacteria, such as AIEC found in Boxers and French Bulldogs with GC, may confirm the presence of an infectious agent and the need for an antimicrobial trial. Generally speaking, dogs with SRD are middle-aged or older and have a more severe clinical disease phenotype, abnormal serum albumin and cobalamin concentrations, endoscopic mucosal abnormalities, and variable degrees of histopathologic (predominantly lymphocytic-plasmacytic cellular infiltrates) inflammation within intestinal biopsy specimens. Dogs having mild-to-moderate disease often are treated using a step-up approach (ie, first dietary trial, followed by antimicrobial trial, and then use of immunosuppressive drugs such as prednisone or prednisolone if inadequate or failed prior responses are observed).[51] For other dogs having moderate-to-severe clinical disease, a step-down approach is used, with concurrent treatment of diet, antimicrobials, and corticosteroids or other immunosuppressive drugs given from the outset and then withdrawing immunosuppressive drugs and antimicrobials in patients with a favorable response.[28]

The retrieved literature yielded a few well-designed RCTs (dogs: n = 11; cats: n = 2) involving dietary, antimicrobial, immunomodulatory, or alternative or complementary treatments, with most interventions targeting IBD. Of concern is the fact that several of the clinical studies were small, underpowered investigations that yielded data of no or limited statistical significance.[24,40–43] Therefore, we supplemented these RCT data with cohort studies (ie, studies that follow dogs or cats over an extended period of time to look for the development of the outcome) to provide additional evidence-based appraisal of non-RCT treatments.

There is strong evidence from RCTs to support a recommendation to feed elimination diets to dogs and cats with CE (grade I evidence). Beyond the aforementioned RCTs, other EBM data in dogs and cats utilizing a spectrum of controlled,[52–55] elimination,[1,2,4,18] and hydrolyzed[16,56] diets suggest that nutritional treatment for CE is overwhelmingly beneficial. Moreover, 2 studies provide convincing evidence of long-term (up to 3 years after intervention) clinical remission

in dogs with CE when fed antigen-restricted diets.[14,17] Although the overall response rate for dogs generally exceeds 50%, it is even greater for cats regardless of whether the diet is used as a primary[2,16,18] or adjunct[4,18,53–55] intervention. The reason why some patients do not relapse on rechallenge (if performed) with their original diet is not fully known, and this strategy remains a trial-and-error approach used by individual clinicians.

Considerations for drug selection with CE include drug class (glucocorticoids, antibiotics, immunosuppressives), disease phenotype (ARD, IBD, protein-losing enteropathy [PLE], steroid-refractory disease), treatment stage (induction therapy, maintenance therapy, flare, refractory disease), and histopathologic lesions (lymphocytic-plasmacytic enterocolitis, granulomatous colitis, intestinal lymphangiectasia). There is grade I evidence that most dogs with IBD respond to single drug glucocorticoid for induction therapy of clinical disease.[31] Studies evaluating long-term (over a 3-year period) control using immunosuppressive drug protocols provide less convincing evidence of remission success.[17,32] Only sparse evidence (grade III evidence) in few animals (n = 22) is available regarding the use of CsA for treatment of steroid-refractory CE in dogs.[33] Anecdotally, other drugs including azathioprine, chlorambucil, leflunomide, and mycophenolate have been used for treatment of CE in dogs and cats, but well-designed studies have not been reported.

Protein losing enteropathy in dogs was not a specific form of CE included in our review based on selection of our search terms. Rather, we chose not to include studies with a diagnosis of primary intestinal lymphangiectasia because treatment recommendations for this distinct form of PLE seem less arbitrary and primarily based on dietary intervention with low-fat diets.[57,58] However, several other studies describe dogs with CE with PLE that have histopathologic lesions of villus lacteal changes accompanied by lamina propria cellular inflammation.[34,48,49] In 1 descriptive cohort study, combination treatment with chlorambucil + prednisolone versus azathioprine + prednisolone was associated with better 6-month survival in dogs with CE complicated by PLE.[59]

Antimicrobials have a legacy of use as empirical treatment in dogs and cats with CE. Unfortunately, this historic use of antimicrobials has relatively weak support by large, randomized, placebo-controlled trials.[23] Several small case series uphold a role (grade III evidence) for enrofloxacin in treating GC in dogs.[26,27] Studies providing support (grade III evidence) for use of MET in cats with IBD are largely based on results derived from 4 retrospective case series.[4,53–55] Moreover, complications from acute and chronic administration of antimicrobials remain a clinical concern. For example, broad-spectrum antimicrobials can cause GI signs including diarrhea,[3] the emergence of enrofloxacin-resistant AIEC is seen in some dogs with GC,[27] and both MET[60] and tylosin[61] have been associated with disturbances in the microbiome of healthy dogs after antimicrobial administration. In addition, recent epidemiological data in humans[62] and dogs with infectious enteritis[63] implicate exposure to antimicrobials as a risk factor for developing IBD later in life for a subset of patients.

Complementary and alternative medicine is used increasingly by humans with digestive disorders, including IBD and irritable bowel syndrome.[64] Some commonly used treatments include probiotics, prebiotics, fish oil, aloe vera, and turmeric (http://www.mayoclinic.org/

TABLE 6 Summary of evidence grades supporting treatment recommendations for canine and feline CE

Grade I evidence	Therapeutic (elimination/hydrolysate) GI diets in dogs for short-term and long-term remission of CE
	Therapeutic (elimination/hydrolysate) GI diets in cats for short-term remission of CE
	Tylosin treatment in dogs with TRD (weak)
	Prednisone treatment for short-term remission in dogs with IBD
	Budesonide treatment for short-term remission in dogs with IBD
	Combination probiotic treatment ± prednisone for short-term remission in dogs with IBD
Grade II evidence	None
Grade III evidence	Metronidazole as adjunct treatment with prednisone for short-term remission in cats with IBD
	Enrofloxacin treatment for granulomatous colitis caused by AIEC
	Prednisolone treatment for short-term remission in cats with IBD
	Cyclosporine treatment for steroid refractory CE in dogs
Grade IV evidence	FMT for refractory IBD[a] and recurrent CPI in dogs
	FMT for refractory IBD[a] in cats
	No evidence to date
	Single strain probiotic, prebiotic, symbiotic, omega-3 PUFA supplementation, and other immunosuppressive treatments

Abbreviations: AIEC, adherent/invasive *Escherichia coli*; CE, chronic enteropathy; CPI, *Clostridium perfringens* infection; GI, gastrointestinal; IBD, inflammatory bowel disease; PUFA, polyunsaturated fatty acids; TRD, tylosin-responsive diarrhea.
[a] Single-case report.

diseases-conditions/inflammatory-bowel-disease/basics/alternative-medicine/con-20034908). However, there are few well-designed studies of their safety and efficacy in humans or dogs and cats. There is evidence (grade I studies) from RCTs that multi-strain probiotics are beneficial for induction of remission in dogs with IBD. As probiotic effects are likely strain-specific, multi-strain products may be most efficacious, but results of these studies should not be extrapolated to different probiotics containing different bacterial strains.[65] Noteworthy, there is clinical evidence that multi-strain probiotics increase the expression of intestinal epithelial TJP, which may improve gut barrier integrity when used with dietary treatment for disease remission.

Fecal microbiota transplantation (FMT) is another potential therapeutic option for nonresponsive CE, but only single case reports have been published. There is a report of preliminary clinical and microbiome assessment in a dog with refractory IBD and a cat with nonresponsive CE after FMT.[66] In this case series, fresh feces was administered by enema to both patients, and the cat also received a fecal suspension into the duodenum by endoscopic delivery. Fecal samples were collected before and after FMT and evaluated for compositional alterations using next-generation sequencing of 16S rRNA bacterial genes. Post-FMT, fecal consistency rapidly (24 hours) improved in both recipients, and other GI signs were mostly attenuated. Fecal samples clustered phylogenetically with the donors by day 2 but were decreased in species richness over time after treatment. In a separate case series,

FMT was used in 8 dogs that had diarrhea associated with refractory *Clostridium perfringens* infection.[67] Donor feces was administered by enema in all 8 dogs as an outpatient treatment. Results indicated that FMT was successful in normalizing fecal character in all 8 dogs with 6 of the 8 dogs having negative post-FMT PCR panels for *C. perfringens* alpha toxin gene expression. A recent report suggests clinical indications and delivery techniques for FMT in dogs and cats with CE.[68]

Intestinal stem cells (ISCs) can be isolated and cultured in vitro giving rise to 3-dimensional self-organizing structures termed organoids.[69] Organoids resemble the intestinal epithelium in vivo as they possess crypt and villus regions that contain multiple cell types that promote mucosal regeneration. Studies have shown that ISCs of mice, humans, and other species are organized into intestinal organoids under appropriate in vitro culture conditions.[70–72] Intestinal organoids derived from canine ISCs recently have been described and may offer regenerative applications in the treatment of IBD and other forms of CE in dogs.[71,73] Successful transplantation of ISCs in experimental colitis models demonstrates that they adhere to and become an integrated part of the epithelium, thereby improving mucosal healing. Lastly, canine ISCs offer a unique drug screening platform for performing high-throughput efficacy and toxicity studies that translate directly to pharmacologic studies in humans with CE.[73]

In summary, there are a few well-designed trials (RCT and others) defining optimal treatment for dogs and cats with CE. Current EBM treatment guidelines for CE are found in Table 6. There is decidedly greater EBM data on treatment for CE in dogs (examples of grade I evidence) as compared to cats with CE (no evidence for grade I trials with less robust evidence for therapeutic recommendations). Treatments with the strongest evidence supporting their efficacy should be recommended first with considerations for financial resources and client preferences taken into consideration. As noted by others, it would be erroneous to assume that treatments supported by weaker forms of evidence may not be beneficial in some patients with CE.[11]

CONFLICT OF INTEREST DECLARATION

Albert E. Jergens currently serves as a consultant for Exegi Pharma. Annette O'Connor serves as Associate Editor for the *Journal of Veterinary Internal Medicine*. She was not involved in review of this manuscript.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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REFERENCES

1. 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.
2. Guilford WG, Jones BR, Markwell PJ, Arthur DG, Collett MG, Harte JG. Food sensitivity in cats with chronic idiopathic gastrointestinal problems. *J Vet Intern Med*. 2001;15:7-13.
3. Hall EJ. Antibiotic-responsive diarrhea in small animals. *Vet Clin North Am Small Anim Pract*. 2011;41:273-286.
4. Jergens AE, Moore FM, Haynes JS, Miles KG. Idiopathic inflammatory bowel disease in dogs and cats: 84 cases (1987-1990). *J Am Vet Med Assoc*. 1992;201:1603-1608.
5. 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.
6. Allenspach K. Clinical immunology and immunopathology of the canine and feline intestine. *Vet Clin North Am Small Anim Pract*. 2011; 41:345-360.
7. Keene BW. Towards evidence-based veterinary medicine. *J Vet Intern Med*. 2000;14:118-119.
8. Polzin DJ. Importance of clinical trials in evaluating therapy of renal diseases. *Vet Clin North Am Small Anim Pract*. 1996;26:1519-1525.
9. Moriello KA. Introducing evidence based clinical reviews in veterinary dermatology. *Vet Dermatol*. 2003;14:119-120.
10. Marr CM. Defining the clinically relevant questions that lead to the best evidence: what is evidence-based medicine? *Equine Vet J*. 2003; 35:333-336.
11. Roudebush P, Polzin DJ, Adams LG, Towell TL, Forrester SD. An evidence-based review of therapies for canine chronic kidney disease. *J Small Anim Pract*. 2010;51:244-252.
12. 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.
13. Gaschen FP, Merchant SR. Adverse food reactions in dogs and cats. *Vet Clin North Am Small Anim Pract*. 2011;41:361-379.
14. 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.
15. Laflamme DP, Xu H, Long GM. Effect of diets differing in fat content on chronic diarrhea in cats. *J Vet Intern Med*. 2011;25:230-235.
16. Waly NE, Biourge V, Day MJ, et al. Use of a hydrolysed soya isolate-based diet in the management of chronic idiopathic inflammatory bowel disease and dietary hypersensitivity in cats. *Assiut Vet Med J*. 2010;56:158-169.
17. Allenspach K, Culverwell C, Chan D. Long-term outcome in dogs with chronic enteropathies: 203 cases. *Vet Rec*. 2016;178:368.
18. Jergens AE, Crandell JM, Evans R, Ackermann M, Miles KG, Wang C. A clinical index for disease activity in cats with chronic enteropathy. *J Vet Intern Med*. 2010;24:1027-1033.
19. Simpson KW, Jergens AE. Pitfalls and progress in the diagnosis and management of canine inflammatory bowel disease. *Vet Clin North Am Small Anim Pract*. 2011;41:381-398.
20. Redfern A, Suchodolski J, Jergens A. Role of the gastrointestinal microbiota in small animal health and disease. *Vet Rec*. 2017;181:370.
21. Jergens AE, Simpson KW. Inflammatory bowel disease in veterinary medicine. *Front Biosci (Elite Ed)*. 2012;E4(4):1404-1419.
22. Westermarck E, Skrzypczak T, Harmoinen J, et al. Tylosin-responsive chronic diarrhea in dogs. *J Vet Intern Med*. 2005;19:177-186.
23. Kilpinen S, Spillmann T, Syrja P, et al. 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.
24. Menozzi A, Dall'Aglio M, Quintavalla F, et al. Rifaximin is an effective alternative to metronidazole for the treatment of chronic enteropathy in dogs: a randomised trial. *BMC Vet Res*. 2016;12:217.
25. 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.
26. Hostutler RA, Luria BJ, Johnson SE, et al. Antibiotic-responsive histiocytic ulcerative colitis in 9 dogs. *J Vet Intern Med*. 2004;18:499-504.
27. 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.
28. Simpson KW, Jergens AE. Pitfalls and progress in the diagnosis and management of canine inflammatory bowel disease. *Vet Clin North Am Small Anim Pract*. 2011;41:381-398.
29. 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.
30. 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.
31. 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.
32. Craven M, Simpson JW, Ridyard AE, Chandler ML. Canine inflammatory bowel disease: retrospective analysis of diagnosis and outcome in 80 cases (1995-2002). *J Small Anim Pract*. 2004;45:336-342.
33. Allenspach K, Rufenacht 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.
34. Allenspach K, Wieland B, Grone A, et al. Chronic enteropathies in dogs: evaluation of risk factors for negative outcome. *J Vet Intern Med*. 2007;21:700-708.
35. Hansen JJ, Sartor RB. Therapeutic manipulation of the microbiome in IBD: current results and future approaches. *Curr Treat Options Gastroenterol*. 2015;13:105-120.
36. Mennigen R, Nolte K, Rijcken E, et al. Probiotic mixture VSL#3 protects the epithelial barrier by maintaining tight junction protein expression and preventing apoptosis in a murine model of colitis. *Am J Physiol Gastrointest Liver Physiol*. 2009;296:G1140-G1149.
37. Dai C, Zhao DH, Jiang M. VSL#3 probiotics regulate the intestinal epithelial barrier in vivo and in vitro via the p38 and ERK signaling pathways. *Int J Mol Med*. 2012;29:202-208.
38. Krishnan M, Penrose HM, Shah NN, Marchelletta RR, McCole DF. VSL#3 probiotic stimulates T-cell protein tyrosine phosphatase-mediated recovery of IFN-gamma-induced intestinal epithelial barrier defects. *Inflamm Bowel Dis*. 2016;22:2811-2823.
39. 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.
40. Abecia L, Hoyles L, Khoo C, et al. Effects of a novel galactooligosaccharide on the faecal microbiota of healthy and inflammatory bowel disease cats during a randomized, double-blind, cross-over feeding study. *Int J Probiotics Prebiotics*. 2010;5:61-68.
41. Segarra S, Martinez-Subiela S, Cerda-Cuellar 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.
42. 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.

43. 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.

44. Webb TL, Webb CB. Stem cell therapy in cats with chronic enteropathy: a proof-of-concept study. *J Feline Med Surg*. 2015;17:901-908.

45. Panes J, Salas A. Mechanisms underlying the beneficial effects of stem cell therapies for inflammatory bowel diseases. *Gut*. 2009;58:898-900.

46. Uccelli A, Moretta L, Pistoia V. Mesenchymal stem cells in health and disease. *Nat Rev Immunol*. 2008;8:726-736.

47. Kono S, Kazama T, Kano K, Harada K, Uechi M, Matsumoto T. Phenotypic and functional properties of feline dedifferentiated fat cells and adipose-derived stem cells. *Vet J*. 2014;199:88-96.

48. Willard MD, Helman G, Fradkin JM, et al. Intestinal crypt lesions associated with protein-losing enteropathy in the dog. *J Vet Intern Med*. 2000;14:298-307.

49. Wennogle SA, Priestnall SL, Webb CB. Histopathologic characteristics of intestinal biopsy samples from dogs with chronic inflammatory enteropathy with and without hypoalbuminemia. *J Vet Intern Med*. 2017;31:371-376.

50. 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.

51. Dandrieux JR. Inflammatory bowel disease versus chronic enteropathy in dogs: are they one and the same? *J Small Anim Pract*. 2016;57:589-599.

52. Nelson RW, Stookey LJ, Kazacos E. Nutritional management of idiopathic chronic colitis in the dog. *J Vet Intern Med*. 1988;2:133-137.

53. Dennis JS, Kruger JM, Mullaney TP. Lymphocytic/plasmacytic gastroenteritis in cats: 14 cases (1985-1990). *J Am Vet Med Assoc*. 1992;200:1712-1718.

54. Dennis JS, Kruger JM, Mullaney TP. Lymphocytic/plasmacytic colitis in cats: 14 cases (1985-1990). *J Am Vet Med Assoc*. 1993;202:313-318.

55. Hart JR, Shaker E, Patnaik AK, et al. Lymphocytic-plasmacytic enterocolitis in cats: 60 cases (1988-1990). *J Am Anim Hosp Assoc*. 1994;30:505-514.

56. 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.

57. Peterson PB, Willard MD. Protein-losing enteropathies. *Vet Clin North Am Small Anim Pract*. 2003;33:1061-1082.

58. 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.

59. Dandrieux JRS, Noble P-JM, 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.

60. Igarashi H, Maeda S, Ohno K, Horigome A, Odamaki T, Tsujimoto H. Effect of oral administration of metronidazole or prednisolone on fecal microbiota in dogs. *PLoS One*. 2014;9:e107909.

61. Suchodolski JS, Dowd SE, Westermarck E, et al. The effect of the macrolide antibiotic tylosin on microbial diversity in the canine small intestine as demonstrated by massive parallel 16S rRNA gene sequencing. *BMC Microbiol*. 2009;9:210.

62. Ungaro R, Bernstein CN, Gearry R, et al. Antibiotics associated with increased risk of new-onset Crohn's disease but not ulcerative colitis: a meta-analysis. *Am J Gastroenterol*. 2014;109:1728-1738.

63. Unterer S, Kilian E, Mueller RS, et al. Long-term implications of canine parvovirus infection [abstract]. ECVIM Proceedings *J Vet Intern Med*. 2016;31(1):224.

64. Esters P, Dignass A. Complementary therapies in inflammatory bowel diseases. *Curr Drug Targets*. 2014;15:1079-1088.

65. Chandler M. Probiotics: not all created equally. *J Small Anim Pract*. 2014;55:439-441.

66. Weese JS, Costa MC, Webb JA. Preliminary clinical and microbiome assessment of stool transplantation in the dog and the cat [abstract]. *J Vet Intern Med*. 2013;27(3):604-756.

67. Murphy T, Chaitman J, Han E. Use of fecal transplant in eight dogs with refractory *Clostridium perfringens* associated diarrhea [abstract]. *J Vet Intern Med*. 2014;28:976-1134.

68. Chaitman J, Jergens AE, Gaschen F, et al. Commentary on key aspects of fecal microbiota transplantation in small animal practice. *Vet Med: Res Rep*. 2016;7:1-4.

69. Sato T, Vries RG, Snippert HJ, et al. Single Lgr5 stem cells build crypt-villus structures in vitro without a mesenchymal niche. *Nature*. 2009;459:262-265.

70. Jung P, Sato T, Merlos-Suarez A, et al. Isolation and in vitro expansion of human colonic stem cells. *Nat Med*. 2011;17:1225-1227.

71. Meneses AMC, Schneeberger K, Kruitwagen HS, et al. Intestinal organoids—current and future applications. *Vet Sci*. 2016;3(4):31.

72. Powell RH, Behnke MS. WRN conditioned media is sufficient for in vitro propagation of intestinal organoids from large farm and small companion animals. *Biol Open*. 2017;6:698-705.

73. Mochel JP, Jergens AE, Kingsbury D, et al. Intestinal stem cells to advance drug development, precision, and regenerative medicine: a paradigm shift in translational research. *AAPS J*. 2017;20:17.