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Randomized controlled trial demonstrates nutritional management is superior to metronidazole for treatment of acute colitis in dogs

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OBJECTIVE
To describe the outcome of dietary management of canine noninfectious acute colitis with or without concurrent oral administration of metronidazole using a randomized controlled clinical trial.

ANIMALS
59 client-owned dogs with noninfectious acute colitis.

PROCEDURES
Dogs with acute noninfectious colitis were enrolled in a 30-day diet trial after exclusion of parasitic infectious etiologies (fecal centrifugation floatation, *Giardia/Cryptosporidium* antigen testing) and systemic disease (CBC, biochemistry, urinalysis). Dogs were randomized into 3 placebo-controlled groups: group 1, easily digestible diet + placebo tablet; group 2, easily digestible diet + metronidazole tablet; and group 3, psyllium-enhanced easily digestible diet + placebo tablet. Dogs were evaluated serially using fecal scoring for time to remission, average fecal score, relapse after remission, and dysbiosis index.

RESULTS
Median remission time was significantly different among the 3 groups ($P < .01$) with median times of 5 days (range, 4 to 10) for group 1, 8.5 days (range, 7 to 12) for group 2, and 5 days (range, 3 to 6) for group 3. Metronidazole addition affected the fecal dysbiosis index negatively at days 7 to 10. No adverse effects or complications were noted throughout the study.

CLINICAL RELEVANCE
For canine noninfectious acute colitis, dietary management with an easily digestible diet with or without psyllium enhancement proved a superior management strategy compared to metronidazole. The omission of metronidazole reduced the adverse impact significantly on intestinal microbiota. Longitudinal clinical trials are necessary to compare the long-term response, stability, and complications associated with dietary management alone versus combined dietary and antimicrobial therapy for canine acute colitis.

Acute colitis is one of the most common syndromes in veterinary medicine.[1,2] In most cases, a definitive cause for the clinical signs is rarely discovered, and treatment is empirical.[3,4] Affected dogs often exhibit a self-limiting disease course, lack of an identifying underlying cause (eg, infectious pathogen), and have no history of chronic gastrointestinal or other systemic disease. Reported empirical management strategies include dietary modification, probiotics, antimicrobials, and fiber supplementation.[1,5] However, there is limited evidence on the effectiveness of these treatments as well as insufficient comparisons of the relative efficacy of these therapies.

Among these treatments, the antimicrobial metronidazole is particularly popular and is used as a first-line treatment for canine acute colitis. Metronidazole is used for its anti-inflammatory, antimicrobial, and antiprotozoal effects.[6–8] However, infectious etiologies in canine acute colitis are rare, and adverse effects of this medication may include peripheral neuropathies, inappetence, nausea, vomiting, seizures, neutropenia, and adverse effects on the gastrointestinal microbiome.[4,9–13] From the global health perspective, there are also antimicrobial resistance concerns regarding the overprescribing of antimicrobials in human and veterinary medicine.[14]

Dietary management of acute colitis is also recommended as an effective option without major adverse effects. There is substantial evidence outlining the benefits of early enteral nutrition in promoting intestinal integrity and improving patient outcome in acute infectious gastrointestinal disease such as canine parvoviral enteritis.[15] There are also several studies that have investigated the nutritional management of chronic colitis in dogs. These studies used various dietary approaches, including home-cooked (mostly cottage cheese and rice), easily digestible, low-fat, high-fiber, and hypoallergenic (limited-ingredient or hydrolyzed) diets.[16–19] Although available dietary studies in acute colitis have been performed in combination with other therapies such as antibiotics, it remains unclear which nutritional strategy is optimal and how these approaches apply to canine acute colitis management.[5] Therefore, prospective studies comparing the efficacy of nutritional strategies in acute colitis in comparison to current empirical antimicrobial recommendations are needed.

We hypothesized that dietary modification, using an easily digestible adult canine maintenance diet, will be as effective in controlling clinical signs of acute colitis as that same diet with either additional psyllium fiber supplementation or antibiotic (metronidazole) administration. The objectives of this study were to compare the impact of 3 acute colitis treatments—group 1, easily digestible diet alone with a placebo tablet; group 2, easily digestible diet with antibiotic (metronidazole) tablet; and group 3, psyllium-enhanced easily digestible diet with a placebo tablet—to time to resolution of colitis clinical signs and effect on the canine dysbiosis index.

Materials and Methods

Dogs between the ages of 1 and 10 years were eligible for enrollment into a prospective, block randomized, blinded clinical trial when presented to the Emergency Service, Community Practice Service, or Internal Medicine Service at The Ohio State University Veterinary Medical Center (OSU-VMC) for evaluation of acute colitis (Institutional Animal Care and Use Protocol No. 2017A00000135). All animals were enrolled after (1) discussing the study specifics with owners, (2) providing an opportunity for owners to ask questions regarding the study, and (3) obtaining informed consent for each study animal. Age inclusion was limited to dogs between the ages of 1 and 10 based on retrospective data acquired at the OSU-VMC demonstrating an increased risk of parasitic causes of diarrhea in dogs younger than 1 year of age and increased frequency of concurrent disease in those older than 10 years of age.[20] There were no restrictions on breed or body weight for study enrollment. Dogs were eligible for enrollment if they had acute signs (< 3 days) of colitis, in the absence of other clinical signs. To be included, dogs had to exhibit 2 or more of the following clinical signs: watery consistency of feces, dyschezia, increased frequency of defecation (> 6 per day), presence of fecal mucus, small-volume defecations, hematochezia, or tenesmus. Enrolled dogs were required to have no parasitic organisms detected on centrifugation fecal flotation and no antigen detected on the *Giardia/Cryptosporidium* antigen test (ImmunoCard Stat Crypto/Giardia; Meridian Biosciences).

Dogs were excluded from the study if other gastrointestinal clinical signs were present (eg, vomiting, anorexia, abdominal pain, small bowel diarrhea [eg, increased fecal volume, melena, vomiting, or weight loss]). Dogs were excluded if gastrointestinal clinical signs of any kind were reported in the 90 days prior to evaluation or if current clinical signs had been observed for more than 3 days. Dogs were excluded from the study if they were diagnosed with acute hemorrhagic diarrhea syndrome or required hospitalization.

All dogs were evaluated for infectious parasitic causes of diarrhea with both an ova/cyst centrifugation zinc sulfate fecal flotation and *Giardia/Cryptosporidium* antigen testing, as well as for systemic illness with a CBC, serum biochemistry profile, and urinalysis. All results were reviewed by a board-certified veterinary internist. Any dog that tested positive for an infectious parasitic etiology or had signs or diagnostic results consistent with systemic disease were excluded. Dogs receiving antibiotics or probiotics were excluded. Early removal criteria for the study included development of other medical conditions; colitis signs that did not resolve by the study conclusion; dogs that were given treats, nonprescribed foods, supplements, or other medications at any time point during the study; or dogs that did not willingly eat or tolerate the study diet.

When inclusion and exclusion criteria were met, dogs were block-randomized using online software into 1 of 3 study groups and enrolled in the 30-day trial **(Supplementary Figure S1)**. Prior to the study, a sample size calculation indicated that 19 dogs per study group would be necessary to maintain a statistical power of 80% and an alpha error of 0.05. Clinical trials and pharmacy team members were aware of group assignment and associated treatments. Study veterinarians and owners were blinded to group assignment and associated treatments. Group 1 dogs were fed an experimental control diet and a placebo tablet. The base experimental control dietary formula was designed to be easily digestible for the general management of nonspecific

gastrointestinal disease (total dietary fiber = 15.3 g/Mcal). Group 2 dogs received the same control diet as dogs in group 1. In addition, group 2 dogs received oral metronidazole (Viona Pharmaceuticals) as recommended for management of acute colitis (5 to 10 mg/kg PO every 12 hours for 7 to 10 days). Metronidazole dose was selected based on available tablet sizes to achieve a dose between 5 and 10 mg/kg. Group 3 dogs received an experimental test diet and a placebo tablet. This experimental test diet was formulated using the same base formula as the experimental control diet, but it was enhanced with psyllium husk **(Supplementary Table S1)**. The total dietary fiber in the diet was 28.3 g/Mcal. Study diets were manufactured and tested by Royal Canin Research and Development for the purpose of this study and are not currently available commercially at the time of publication. All diets used in this study were dry formulations. The placebo was repacked to match metronidazole in appearance and included inactive ingredients found in metronidazole tablets. The placebos were manufactured in-house by registered pharmacists at The Ohio State University Veterinary Medical Center Pharmacy.

During the entire study, all other diets the dogs may have received, including wet food, treats, and table scraps, were discontinued. If treats were requested by the owner, a portion of the daily kibble allowance was retained and used for treats at the owner's discretion. Dogs were fed based on their estimated maintenance energy requirement (1.2 to 1.4 X resting energy requirement [70 X Body $weight_{kg}^{0.75}$]) for the entire study period. Body weight taken at baseline was monitored throughout the study at recheck days 7 to 10 and recheck day 30, and approximate caloric recommendations were adjusted as necessary to ensure maintenance of body weight during the 30-day study period.

At study enrollment, all dogs had, at a minimum, a physical examination and parasitic fecal examination performed for infectious disease. Additional diagnostics at the initial visit were at the discretion of the attending clinician. All treatments were started at study day 0. Dogs were fed exclusively the treatment diets until the end of the study at day 30 (± 2 days). Metronidazole and placebos were discontinued at the first recheck on days 7 to 10. At that recheck, all dogs had a physical examination, CBC, serum biochemical profile, and urinalysis performed. At day 30, all dogs were evaluated a final time to conclude the study.

Naturally voided fecal samples were collected into cryovials and stored at −80 °C for evaluating the canine dysbiosis index at study enrollment (day 0), recheck 1 (days 7 to 10), and at completion of the study (day 30).[21] Samples were shipped overnight on dry ice and were confirmed to have arrived frozen for analysis at the diagnostic lab (Gastrointestinal Laboratory, Texas A&M University). The canine dysbiosis index uses mathematical modeling based on the abundance of specific fecal bacteria measured in test samples relative to a normal canine reference set. The mathematical model provides a single numeric value that can then be interpreted based on published reference intervals: < 0 is normal, 0 to 2 indicates mild to moderate shifts in the microbiota, and > 2 represents significant shifts likely indicating dysbiosis.[21] For each day after hospital discharge, the owners were instructed to perform daily fecal scoring (using the Mars Global Method 5-point scoring system; **Supplementary Figure S2**), photograph feces for verification by investigators, and complete a wellness survey to monitor for complications **(Supplementary Appendix S1)**.[22] Fecal scores were measured for each bowel movement daily and were recorded in a provided study diary **(Supplementary Appendix S2)**. A modified behavioral assessment **(Supplementary Appendix S3)** was completed at study enrollment, at the day 7 to 10 recheck, and at completion of the study (day 30) to capture general behavioral data, occurrence of additional clinical signs (lethargy, appetite, discomfort, etc) of acute colitis, and owner perception of diet palatability.

All data collection was monitored, collated, and stored using an electronic database (REDCap) and physical printed records by the OSU-VMC Clinical Trials Office (CTO). The CTO contacted owners by phone and email multiple times throughout the study to ensure data were collected appropriately. Scheduled contact time points included 2 to 3 days after enrollment, at both recheck evaluations, and weekly between recheck examinations to ensure compliance. The CTO also facilitated client follow-up to ensure recheck evaluations were completed in the outlined timeframes. Specific data of interest for each group included time to remission, daily fecal score, recurrence after remission, average fecal score after achieving remission, fecal canine dysbiosis index (using mean quantitative PCR concentration), and behavioral assessment scores.[21]

Time to remission was defined as 3 consecutive days with no fecal score > 3. The third of the 3 consecutive days was considered the date of remission. Recurrence after remission was defined as a fecal score > 3 after achieving remission. All data were assessed for normality using the Shapiro-Wilk test. Kaplan-Meier analysis was used to compare time to remission between groups. Pairwise comparisons of remission time between groups was performed using the log-rank test. One-way ANOVA was used for testing the impact of study group on the number of recurrences (fecal score worse or > 3) after the first remission (3 days with fecal score worse or ≤ 3). Tukey's honest significant difference (HSD) test was used for multiple comparisons for correcting the false discovery rate. Cohen's d effect size was also estimated. Linear mixed models (LMMs) were used with visit, study group, and their respective interaction as fixed effects, and animal as a random term for the analysis of the canine dysbiosis index. Statistical assumptions of LMMs, normally distributed residuals, and homoscedasticity were verified. Tukey's HSD was used for pairwise comparisons between study groups within visits and between visits within study groups.

Results

A total of 71 dogs were screened for enrollment into the study and randomized into 3 groups (Supplementary Figure S1). Twelve dogs were eliminated from the study because of the following: infectious etiology (n = 9), lost to follow-up (n = 2), or voluntary withdrawal by the owner because of the inability to meet the study requirements (n = 1). A total of 59 dogs completed the 30-day study (group 1, n = 19; group 2, n = 20; group 3, n = 20). For the groups, there were no significant differences in age (mean ± SD: group 1, 4.45 ± 3.09 years; group 2, 4.91 ± 3.38 years; group 3, 3.52 ± 3.16 years; *P* = .29), body weight (mean ± SD: group 1, 26.2 ± 12.72 kg; group 2, 21.56 12.1 kg; group 3, 20.6 ± 13.04 kg; *P* = .25), body condition score (group 1, 5 [range, 4 to 7]; group 2, 5 [range, 4 to 8]; group 3, 5 [range, 4 to 8]; *P* = .61), or sex (group 1, 42% male and 58% female; group 2, 40% male and 60% female; group 3, 55% male and 45% female; *P* = .49) between groups. All dogs in the study were neutered. All dogs enrolled were considered to have normal muscle condition scores. Breeds represented in the study included mixed-breed dogs (n = 15), Labrador Retrievers (n = 10), German Shepherd Dogs (n = 8), American Staffordshire Terriers (n = 3), Greyhounds (n = 3), French Bulldogs (n = 2), Samoyeds (n = 2), Yorkshire Terriers (n = 2), Boston Terriers (n = 2), Newfoundlands (n = 2), Standard Poodle (n = 1), Belgian Sheepdog (n = 1), Boxer (n = 1), Siberian Husky (n = 1), Chihuahua (n = 1), American Pitbull Terrier (n = 1), German Shorthair Pointer (n = 1), Border Collie (n = 1), Chinese Crested (n = 1), and Pug (n = 1).

No complications associated with the diets, metronidazole, or placebos were encountered throughout the study in any of the groups. All dogs received exclusively the metronidazole or placebo, as well as the diet as directed for the duration of the 30-day study, and owner compliance was documented in study diaries. Both the control diet and test diet were considered highly palatable by owners, and no dogs required removal from the study because of an unwillingness to eat the diet. Diet palatability assessed at recheck evaluations was rated as good or better in all enrolled dogs. Screening laboratory test results (CBC, serum biochemical profile, urinalysis) performed during the study were unremarkable. No dogs enrolled and completing the study had detectable parasitic infections. No dogs experienced significant changes in weight or required caloric intake adjustments throughout the study.

There were no differences in fecal score (*P* = .604) or duration of clinical signs (*P* = .731) at the time of enrollment between groups. Time to remission of colitis based on fecal score was significantly different between groups (*P* = .003) **(Figures 1 and 2)**. Median remission time was 5 days (range, 4 to 10) for group 1, 8.5 days (range, 7 to 12) for group 2, and 5 days (range, 3 to 6) for group 3. There was a statistically significant difference in time to remission between the 3 groups as assessed by 1-way ANOVA

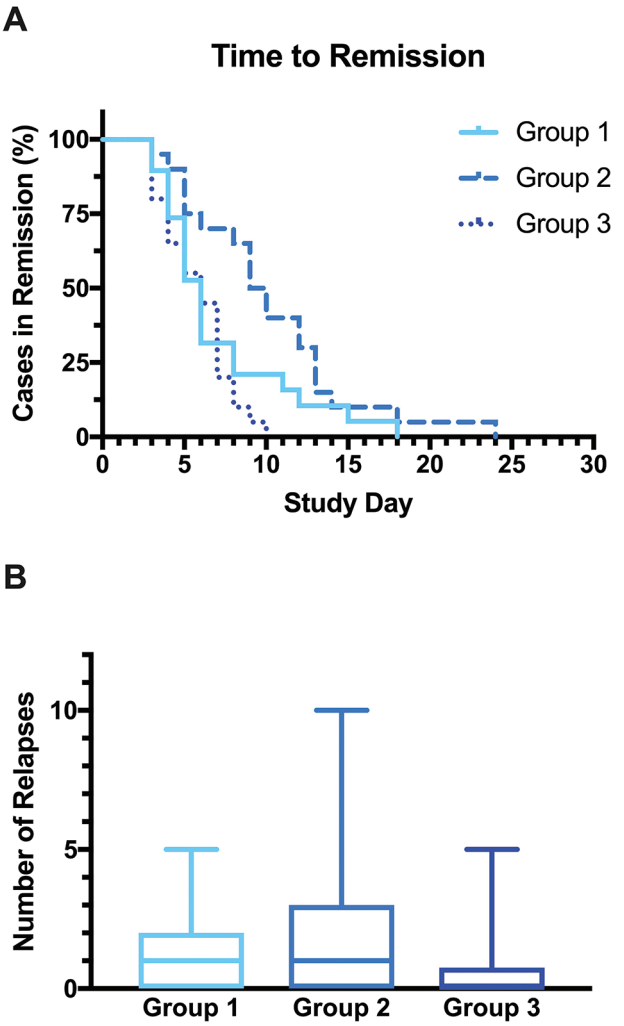

Figure 1—A—Kaplan-Meier time-to-event curves of outcome data for canine acute colitis remission (defined as a minimum of 3 days with a fecal score < 3; N = 59; group 1, n = 19; group 2, n = 20;, group 3, n = 20). B—Number of recurrences after first remission among the 3 study groups. Data are shown as median, range, and quartiles. Dogs in group 1 were fed an easily digestible experimental control diet and a placebo tablet. Group 2 dogs received the same control diet as the dogs in group 1 in addition to oral metronidazole. Group 3 dogs received a fiber-enhanced experimental test diet and a placebo tablet.

(F[2 df, 56 df] = 6.501, *P* < .01). Multiple comparisons testing found that the mean time to remission was significantly different between groups **(Table 1)**. Pairwise comparison of mean time to remission revealed significant differences between group 1 and group 2 (*P* = .03), and group 2 and group 3 (*P* < .01).

There was not a statistically significant difference in number of recurrences after achieving remission between the 3 groups as assessed by 1-way ANOVA (F[2 df, 56 df] = 2.565, *P* = .08). Multiple comparisons testing found that the mean values of number of recurrences was not significantly different between groups (**Table 2**; Figure 1). There was no statistically significant difference in reported

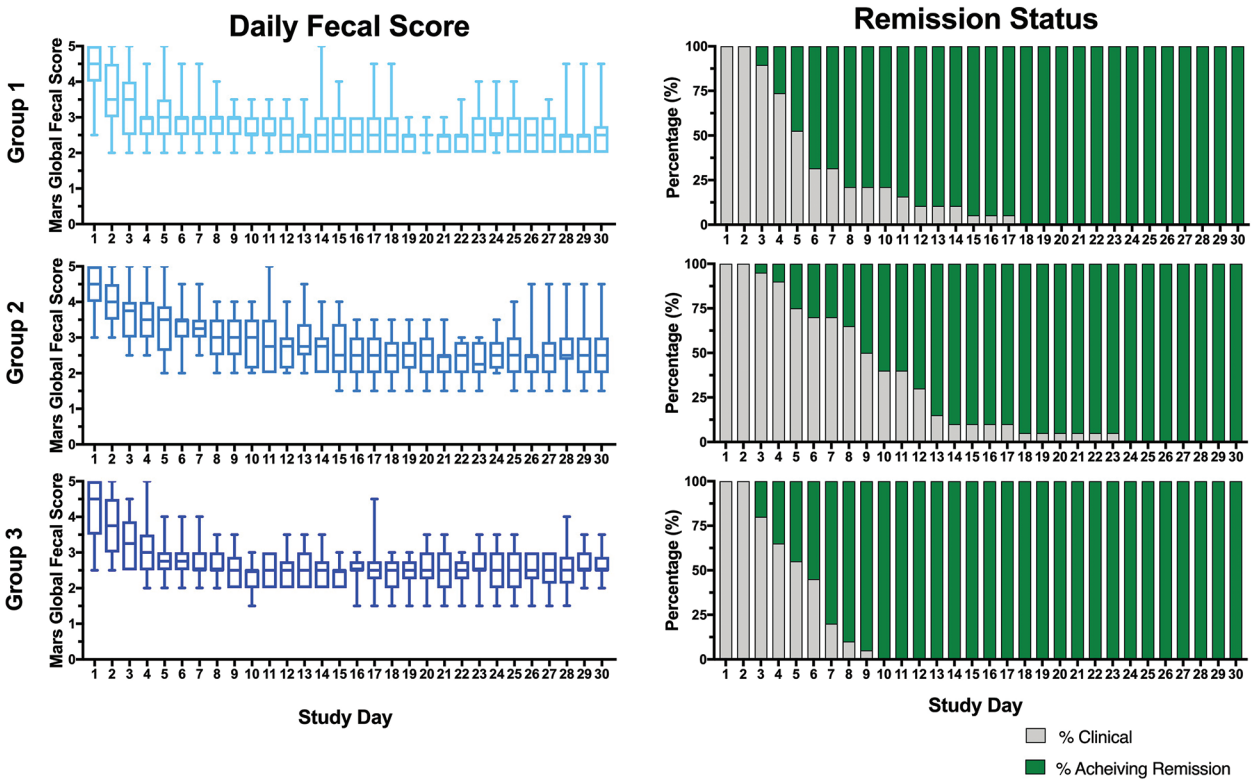

Figure 2—Fecal score and remission rate during the 30-day study (N = 59; group 1, n = 19; group 2, n = 20; group 3, n = 20). Dogs in group 1 were fed an easily digestible experimental control diet and a placebo tablet. Group 2 dogs received the same control diet as the dogs in group 1 in addition to oral metronidazole. Group 3 dogs received a fiber-enhanced experimental test diet and a placebo tablet. Left—Daily fecal scores for enrolled dogs per study group. Data are shown as median, range, and quartiles. Right—Percentage of dogs with acute colitis achieving remission (defined as a minimum of 3 days with a fecal score < 3) by study day.

Table 1—Results of the 1-way ANOVA model and pairwise testing for time to remission (in days).

Study group	Time to remission (days)	SE	Lower confidence interval	Upper confidence interval
1	6.00	0.94	4.12	7.88
2	9.30	0.91	7.47	11.13
3	4.80	0.91	2.97	6.63
Pairwise comparison	**Estimated difference (days)**	**SE**	**t Ratio**	***P* value**
Group 1 and group 2*	−3.30	1.31	−2.52	.03
Group 1 and group 3	1.20	1.31	0.92	.63
Group 2 and group 3*	4.50	1.29	3.49	.001
Effect size between	**Effect size**	**SE**	**Lower confidence interval**	**Upper confidence interval**
Group 1 and group 2	−0.81	0.33	−1.47	−0.15
Group 1 and group 3	0.29	0.32	−0.35	0.94
Group 2 and group 3	1.10	0.33	0.44	1.77

Data reported include estimated group means for time to remission calculated by the model, pairwise comparisons between groups, and the effect size between groups. The asterisk indicates statistically significant comparisons.

fecal scores after achieving remission between the 3 groups (P = .86).

There were no differences in canine dysbiosis index in group 1 and group 3 across the 3 time points. Group 2 had a significant difference in dysbiosis index between the 3 study visits **(Figure 3)**. Multiple comparisons testing found that the dysbiosis index was significantly different in group 2 dogs between baseline and days 7 to 10 (P < .001) as well as between days 7 to 10 and day 30 (P < .001; **Table 3**). In addition, multiple comparisons testing found that the dysbiosis index was significantly different at days 7 to 10 for dogs in group 1 and dogs in group 2 (P < .001), as well as dogs in group 2 and dogs in group 3 (P < .001; Table 3). The individual bacterial taxa in the dysbiosis index

Table 2—Results of the 1-way ANOVA model and pairwise testing for recurrences per dog after remission.

Study group	Mean No. of recurrences	SE	Lower confidence interval	Upper confidence interval
1	1.68	0.33	1.02	2.35
2	1.30	0.32	0.65	1.95
3	0.65	0.32	0.002	1.30
Pairwise comparison	**Estimated difference**	**SE**	**t Ratio**	***P* value**
Group 1 and group 2	0.38	0.46	0.83	.69
Group 1 and group 3	1.03	0.46	2.23	.07
Group 2 and group 3	0.65	0.46	1.42	.34
Effect size between groups	**Effect size**	**SE**	**Lower confidence interval**	**Upper confidence interval**
Group 1 and group 2	0.27	0.32	-0.38	0.91
Group 1 and group 3	0.72	0.33	0.06	1.37
Group 2 and group 3	0.45	0.32	-0.19	1.09

Data reported include estimated group means for number of recurrences calculated by the model, pairwise comparisons between groups, and the effect size between groups. The asterisk indicates statistically significant comparisons.

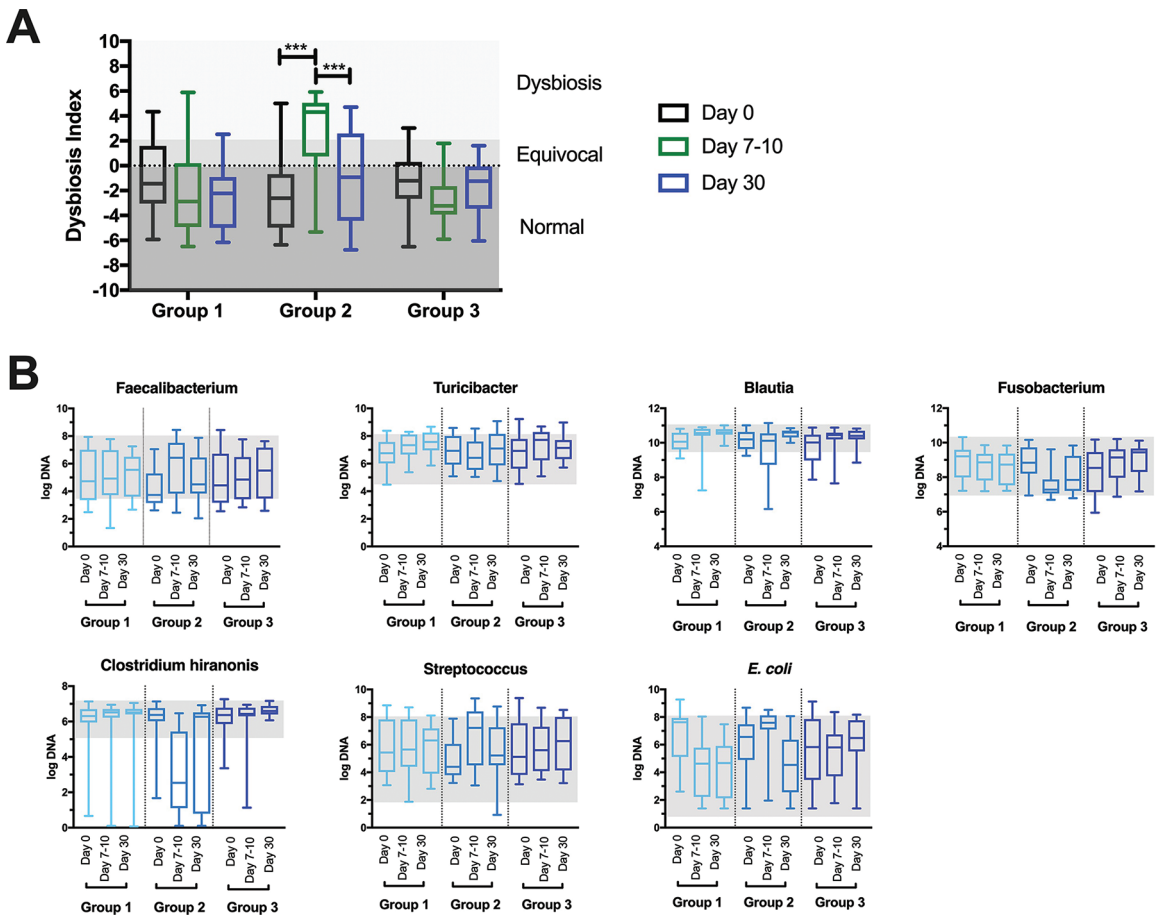

Figure 3—The dysbiosis index (DI), a quantitative PCR-based assay, used to assess the fecal microbiome in individual study participants at baseline, day 7, and at the conclusion of the study at day 30. Dogs in group 1 were fed an easily digestible experimental control diet and a placebo tablet. Group 2 dogs received the same control diet as the dogs in group 1 in addition to oral metronidazole. Group 3 dogs received a fiber-enhanced experimental test diet and a placebo tablet. A—The DI quantifies the fecal abundance of 7 bacterial taxa as well as the total bacterial abundance. A normal DI < 0 indicates that no shifts in the overall diversity of the intestinal microbiota have been detected. If individual bacterial groups are outside the reference interval, this is suggestive of mild dysbiosis. A DI between 0 and 2 is a mild increase, suggesting a mild to moderate shift in the overall diversity of the intestinal microbiota. A DI > 2 is consistent with a marked shift in the overall diversity of the intestinal microbiota. Data are shown as median, range, and quartiles. B—The specific taxa and their associated reference intervals in healthy dogs include *Faecalibacterium* (3.4 to 8.0), *Turicibacter* (4.6 to 8.1), *Blautia* (9.5 to 11.0), *Fusobacterium* (7.0 to 10.3), *Clostridium hiranonis* (5.1 to 7.1), *Streptococcus* (1.9 to 8.0), and *Escherichia coli* (0.9 to 8.0). Reference intervals are indicated by gray shading. This figure shows the relative abundance of these taxa from individual study participants at baseline, day 7, and at the conclusion of the study at day 30. Data are shown as median, range, and quartiles.

Table 3—Results of the 1-way ANOVA model and pairwise testing for the canine dysbiosis index (DI) at each study time point.

Study group and day of study visit	Average dysbiosis index	SE	Lower confidence interval	Upper confidence interval
Group 1, day 0	−0.80	0.67	−2.14	0.53
Group 1, days 7–10	−2.01	0.67	−3.35	−0.68
Group 1, day 30	−2.43	0.67	−3.77	−1.10
Group 2, day 0	−2.32	0.66	−3.62	−1.02
Group 2, days 7–10	2.79	0.66	1.49	4.09
Group 2, day 30	−1.00	0.66	−2.30	0.30
Group 3, day 0	−1.36	0.64	−2.63	−0.09
Group 3, days 7–10	−2.35	0.64	−3.62	−1.08
Group 3, day 30	−1.68	0.68	−3.03	−0.33
Pairwise comparison	**Estimated difference**	**SE**	**t Ratio**	***P* value**
Group 1, day 0 and days 7–10	1.21	0.77	1.57	.26
Group 1, day 0 and day 30	1.63	0.77	2.11	.09
Group 1, days 7–10 and day 30	0.42	0.77	0.54	.85
Group 2, day 0 and days 7–10*	−5.11	0.75	−6.81	< .001
Group 2, day 0 and day 30	−1.31	0.75	−1.76	.19
Group 2, days 7–10 and day 30*	3.80	0.75	5.06	< .001
Group 3, day 0 and days 7–10	0.99	0.73	1.35	.37
Group 3, day 0 and day 30	0.32	0.77	0.41	.91
Group 3, days 7–10 and day 30	−0.67	0.77	−0.87	.66
Pairwise comparison	**Estimated difference**	**SE**	**t Ratio**	***P* value**
Day 0, groups 1 and 2	1.51	0.94	1.61	.25
Day 0, groups 1 and 3	0.55	0.93	0.60	.82
Day 0, groups 2 and 3	−0.96	0.92	−1.04	.55
Days 7–10, groups 1 and 2*	−4.81	0.94	−5.11	< .001
Days 7–10, groups 1 and 3	0.33	0.93	0.36	.93
Days 7–10, groups 2 and 3*	5.14	0.92	5.60	< .001
Day 30, groups 1 and 2	−1.43	0.94	−1.52	.28
Day 30, groups 1 and 3	−0.75	0.96	−0.78	.71
Day 30, groups 2 and 3	0.68	0.95	0.71	.76

Data reported include estimated group means for the DI calculated by the model, pairwise comparisons between time points, and pairwise comparisons between groups. The DI was interpreted based on published reference intervals, where < 0 is normal, 0 to 2 indicates mild to moderate shifts in the microbiota, and > 2 represents significant shifts, likely indicating dysbiosis. The asterisk indicates statistically significant comparisons.

was affected by the addition of metronidazole to dietary management.

Discussion

The results demonstrate that implemented dietary management alone is superior to metronidazole in combination with dietary management for treatment for canine noninfectious acute colitis. Dietary management can be accomplished with an easily digestible diet with or without psyllium enhancement, both of which outperformed metronidazole in this study in terms of faster times to remission and minimized impact on the canine dysbiosis index. Although there was no statistically significant difference in this study between the dogs assigned to groups 1 and 3 (easily digestible with or without psyllium), the effects of treatments in group 3 and group 1 improved clinical outcome significantly when compared to dogs receiving treatment in group 2. Based on these results, time to remission was achieved 3.3 days sooner (P = .03) with an easily digestible diet and 4.5 days sooner (P = .001) with a psyllium-enhanced, easily digestible diet when compared to management with an easily digestible diet in combination with oral metronidazole. This difference in response time between dietary management and metronidazole is likely of clinical relevance for clients caring for a dog with acute colitis and the associated increased husbandry demands. Furthermore, although there were no documented impacts on the dysbiosis index associated with dietary management, the use of metronidazole had a significant detrimental impact on selected gut microbiota in dogs with acute colitis. These results demonstrate that dietary management provided a nutritionally complete, antibiotic-sparing option for dogs with acute colitis while avoiding collateral damage to the gut microbiota compared to metronidazole.

There were no reported complications or adverse effects of dogs receiving dietary management in our study. The diets were accepted by all enrolled dogs, and owner-perceived palatability was good, with many owners requesting to keep their dogs on the study diets indefinitely. Dietary management has been shown to be the preferred option for canine noninfectious acute colitis in which complete and balanced nutritional support was imperative for both the general health- and illness-related medical outcomes.[23,24]

Diets such as those used in our study represent an easy management approach for many owners, and limit patient and owner stress surrounding oral medication administration. High-quality diets are also usually readily available, making this a feasible and accessible treatment option for many patients.

Previously, chronic colitis has been reported to be responsive to home-cooked (eg, cottage cheese and rice), easily digestible, low-fat, high-fiber, or hypoallergenic (limited-ingredient or hydrolyzed) diets.[16–19] The 2 diets in this study were formulated to be easily digestible and comparable in nutrient profiles with the exception of dietary fiber content; otherwise, the nutrient profile differences between the 2 diets were minimal (Table 1). In comparison between these 2 diets, our study was unable to document whether an easily digestible diet performed better for management of noninfectious acute colitis with or without psyllium fiber enhancement. Although not significant (P = .07), the mean number of recurrences was greater in the control diet (n = 1.7) when compared to the psyllium fiber-enhanced test diet (n = 0.7), which suggests there may be some benefits in a fiber-enhanced diet in maintaining resolution of acute diarrheal episodes, but additional studies are needed to explore this further. A previous study[5] documented a benefit of a fiber-enhanced diet in combination with metronidazole for treatment of acute diarrhea when compared to a standard fiber diet in combination with metronidazole. In contrast, our study demonstrated that without the addition of metronidazole, either an easily digestible diet or a psyllium fiber-enhanced diet performed better than a diet with antimicrobial administration.

Clinical response times in our study were longer than those reported in other studies,[5,25] which might be a result of the different definition of response time used in our study. In dogs with acute diarrhea, it is common to observe an improved or acceptable fecal score during recovery, followed by soft feces or diarrhea the next day. Because of this, we instituted a more stringent definition of remission to ensure that dogs were not considered resolved prematurely until not a single fecal score > 3 was observed for 3 full consecutive days.

Use of metronidazole for managing noninfectious acute colitis is an increasing area of focus in acute diarrhea literature. The main study[25] supporting the use of metronidazole for this indication suggested that metronidazole could shorten duration of diarrhea compared to a placebo. Recent studies[5,13,26–28] have begun to examine the impact of probiotics, nutraceuticals, fiber, and fecal microbiota transplant (FMT) in combination with or in comparison to metronidazole. The 2 published probiotic studies[26,27] failed to document a clinical benefit to probiotics in combination with or comparison to metronidazole. The study by Shmalberg et al[26] comparing dogs with acute diarrhea receiving probiotic, oral metronidazole, or placebo failed to demonstrate a clinical benefit of the probiotic over metronidazole in terms of clinical outcome. Interestingly, in that study,[26] there was no difference in response time between metronidazole and placebo, in contrast to the study by Langlois et al.[25] Similarly, the fiber-enhanced diet study[5] was performed in dogs concurrently receiving metronidazole. Two more recent studies[13,28] compared separately the effects of a commercial nutraceutical product and FMT in comparison to metronidazole. Both of these studies examined clinical outcomes and also investigated impacts on the fecal microbiome. The nutraceutical improved clinical outcomes compared to metronidazole, but did not affect the microbiome outcomes significantly.[28] The nutraceutical was a symbiotic with added minerals, vitamins, and electrolytes.[28] In contrast, FMT improved both clinical and microbiome outcomes significantly.[13] Based upon the results of that study,[13] nutritional management is the second treatment strategy to show both a clinical and microbiome benefit over metronidazole in noninfectious acute colitis management. This adds to the growing body of evidence that metronidazole is not the optimal management strategy for dogs with noninfectious acute colitis, especially considering the long-lasting effects of metronidazole on the microbiome.

The justification for metronidazole use in clinical practice is often attributed to its utility in treating some infectious causes of acute colitis as well as anti-inflammatory properties. Metronidazole has a broad spectrum of activity against anaerobic bacteria. As such, there are some specific bacterial taxa, such as *Clostridium perfringens*, that are expected to be susceptible and are altered with metronidazole use.[25] However, in general, the frequency of bacterial enteropathogens causing acute colitis appears low, and *C perfringens* in particular is not well documented as a disease-causing organism and can be found in healthy dogs without diarrhea as well.[29,30] Metronidazole also has an antiprotozoal activity and remains a potential treatment for common pathogens such as *Giardia*. The use of diagnostic screening tests for infectious agents such as *Giardia* is helpful to avoid unnecessary prescription of empirical infectious disease treatments. However, when empirical infectious disease treatment is needed, alternative options such as fenbendazole appear to have a broader spectrum of activity, including *Giardia* and many helminths, as well as have minimal impact on the gut microbiome.[31] Last, the evidence for anti-inflammatory effects of metronidazole are limited and have not been documented in dogs, specifically limiting this proposed benefit as justification for use.[32]

Another reason metronidazole has been questioned as a therapy for acute colitis is because of potential concerns that it may delay acute colitis resolution and gastrointestinal tract recovery, and may have significant adverse effects.[7,8,33] In our study, no adverse effects associated with the use of metronidazole were observed. This may have been a result of the fact that metronidazole adverse effects are not as common at the dose range or duration of use typically prescribed for acute colitis management and used in our study.[34] The main adverse effect associated with metronidazole in our study was its

impact on the fecal microbiome as measured by the canine dysbiosis index.[21] Beyond the direct impact on bacterial taxa in our study, recent studies[12,13,35,36] demonstrated that the dysbiosis developing in dogs on metronidazole leads to a negatively altered metabolic state. Recovery from this dysbiosis can take weeks and may not be complete in some patients.[36] If severe, dysbiosis can result in acute antibiotic-associated diarrhea, which is an expensive, ongoing disease in human and veterinary medicine, with potential life-threatening complications resulting from bacterial translocation.[37]

Interestingly, the majority of dogs in our study were medium- or larger breed dogs. The median body weight for each study group was > 20 kg. This is similar to previous studies investigating acute diarrhea in which the majority of dogs were medium- to large-breed dogs.[5] Associations and causality between body weight and frequency of gastrointestinal clinical signs is an important area for future studies. There were also 2 larger breeds that were common in our study population (German Shepherd Dogs and Labrador Retrievers). These are 2 of the most frequently registered purebreds and are also reflective of the breed distribution at OSU-VMC.

Our study had limitations that should be considered when interpreting the results. Because dietary management was a main study variable, all dogs were required to eat the study diets willingly. In our study, dogs that had poor to absent appetites were excluded to ensure the dietary interventions would be consumed. We did observe an excellent palatability of these formulas; therefore, in clinical practice, offering dietary management with high palatability is recommended. If inappetence is persistent, assisted enteral nutrition should be considered. Further study is necessary to examine the best treatment options for anorexic patients with acute noninfectious colitis. The screening process for this study relied on a centrifugation fecal floatation, along with *Giardia/Cryptosporidium* antigen testing, and minimum database laboratory testing. For typical, stable acute colitis patients, this is a thorough workup and is likely to discover most other common infectious etiologies. However, it is possible systemic illness or infectious disease other than idiopathic noninfectious acute colitis could have occurred in some dogs in our study. Based on the lack of treatment failures across all 3 study groups, this is considered less likely in our population. Last, this study examined dogs recovering from acute colitis in the short term. Long-term impacts of dietary management and metronidazole use in these dogs were not evaluated. The long-term stability and impact of these treatments on canine health should be explored in future studies.

In conclusion, dietary management was an effective treatment option for noninfectious acute colitis when compared to dietary management accompanied by metronidazole treatment. Dietary management was accomplished with complete and balanced diets that were easily digestible with or without psyllium fiber enhancement. Metronidazole treatment was associated with slower treatment response times, a significant impact on gastrointestinal health, and an abnormal canine dysbiosis index of patients receiving this therapy. Based on the results of our study, prescription of metronidazole should not be considered for use in canine acute colitis cases; instead, dietary management should be prescribed preferentially. Future studies are needed to evaluate the treatment options more fully in comparison to metronidazole and other treatments when dietary management is not possible.

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References

1. Berset-Istratescu CM, Glardon OJ, Magouras I, Frey CF, Gobeli S, Burgener IA. Follow-up of 100 dogs with acute diarrhoea in a primary care practice. *Vet J.* 2014;199(1):188–190. doi:10.1016/j.tvjl.2013.10.014
2. Saevik BK, Skancke EM, Trangerud C. A longitudinal study on diarrhoea and vomiting in young dogs of four large breeds. *Acta Vet Scand.* 2012;54:8. doi:10.1186/1751-0147-54-8
3. Hubbard K, Skelly BJ, McKelvie J, Wood JL. Risk of vomiting and diarrhoea in dogs. *Vet Rec.* 2007;161(22):755–757. doi:10.1136/vr.161.22.755
4. Stavisky J, Radford AD, Gaskell R, et al. A case-control study of pathogen and lifestyle risk factors for diarrhoea in dogs. *Prev Vet Med.* 2011;99(2–4):185–192. doi:10.1016/j.prevetmed.2011.02.009
5. Lappin MR, Zug A, Hovenga C, Gagne J, Cross E. Efficacy of feeding a diet containing a high concentration of mixed fiber sources for management of acute large bowel diarrhea in dogs in shelters. *J Vet Intern Med.* 2022;36(2):488–492. doi:10.1111/jvim.16360
6. Grove DI, Mahmound AA, Warren KS. Suppression of cell-mediated immunity by metronidazole. *Int Arch Allergy Appl Immunol.* 1977;54(5):422–427. doi:10.1159/000231857
7. Lee JA. Metronidazole risks. *Clin Brief*. Published online September 2014. Accessed March 7, 2022. https://www.cliniciansbrief.com/article/metronidazole-risks
8. Fitzgerald K. Metronidazole. In: Peterson D, Talcott P, eds. *Small Animal Toxicology.* 3rd ed. Saunders Elsevier; 2013:653–658.
9. Dow SW, LeCouteur RA, Poss ML, Beadleston D. Central nervous system toxicosis associated with metronidazole treatment of dogs: five cases (1984–1987). *J Am Vet Med Assoc.* 1989;195(3):365–368.
10. Evans J, Levesque D, Knowles K, Longshore R, Plummer S. Diazepam as a treatment for metronidazole toxicosis in dogs: a retrospective study of 21 cases. *J Vet Intern Med.* 2003;17(3):304–310. doi:10.1111/j.1939-1676.2003.tb02452.x
11. Sekis I, Ramstead K, Rishniw M, et al. Single-dose pharmacokinetics and genotoxicity of metronidazole in cats. *J Feline Med Surg.* 2009;11(2):60–68. doi:10.1016/j.jfms.2008.06.011
12. Pilla R, Gaschen FP, Barr JW, et al. Effects of metronidazole on the fecal microbiome and metabolome in healthy dogs. *J Vet Intern Med.* 2020;34(5):1853–1866. doi:10.1111/jvim.15871

13. Chaitman J, Ziese AL, Pilla R, et al. Fecal microbial and metabolic profiles in dogs with acute diarrhea receiving either fecal microbiota transplantation or oral metronidazole. *Front Vet Sci.* 2020;7:192.
14. Mendelson M. Role of antibiotic stewardship in extending the age of modern medicine. *S Afr Med J.* 2015;105(5):414–418. doi:10.7196/SAMJ.9635
15. Mohr AJ, Leisewitz AL, Jacobson LS, Steiner JM, Ruaux CG, Williams DA. Effect of early enteral nutrition on intestinal permeability, intestinal protein loss, and outcome in dogs with severe parvoviral enteritis. *J Vet Intern Med.* 2003;17(6):791–798. doi:10.1111/j.1939-1676.2003.tb02516.x
16. Nelson RW, Stookey LJ, Kazacos E. Nutritional management of idiopathic chronic colitis in the dog. *J Vet Intern Med.* 1988;2(3):133–137. doi:10.1111/j.1939-1676.1988.tb02809.x
17. 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(1):27–32. doi:10.1111/j.1939-1676.2000.tb01495.x
18. Allenspach K, Wieland B, Grone A, Gaschen F. Chronic enteropathies in dogs: evaluation of risk factors for negative outcome. *J Vet Intern Med.* 2007;21(4):700–708. doi:10.1111/j.1939-1676.2007.tb03011.x
19. Simpson JM, Maskell IE, Markwell, PJ. Use of a restricted antigen diet in the management of idiopathic canine colitis. *J Small Anim Pract.* 1994;35:234.
20. Yee H, Arruda AG, Rudinsky AJ, Iazbik C, Millward L, Marsh A. Risk factors and impact of COVID-19-related clinic closures on the detection of gastrointestinal parasites in dogs, a cross-sectional study. *Vet Parasitol Reg Stud Reports.* 2021;26:100647. doi:10.1016/j.vprsr.2021.100647
21. 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):fix136. doi:10.1093/femsec/fix136
22. Waltham faeces scoring system. Waltham. Accessed January 1, 2019. https://www.waltham.com/dyn/_assets/_pdfs/other-resources/waltham-scoring.pdf
23. Wernimont SM, Radosevich J, Jackson MI, et al. The effects of nutrition on the gastrointestinal microbiome of cats and dogs: impact on health and disease. *Front Microbiol.* 2020;11:1266.
24. Bontempo V. Nutrition and health of dogs and cats: evolution of petfood. *Vet Res Commun.* 2005;29(suppl 2):45–50. doi:10.1007/s11259-005-0010-8
25. Langlois DK, Koenigshof AM, Mani R. Metronidazole treatment of acute diarrhea in dogs: a randomized double blinded placebo-controlled clinical trial. *J Vet Intern Med.* 2020;34(1):98–104. doi:10.1111/jvim.15664
26. Shmalberg J, Montalbano C, Morelli G, Buckley GJ. A randomized double blinded placebo-controlled clinical trial of a probiotic or metronidazole for acute canine diarrhea. *Front Vet Sci.* 2019;6:163. doi:10.3389/fvets.2019.00163
27. Fenimore A, Martin L, Lappin MR. Evaluation of metronidazole with and without *Enterococcus faecium* SF68 in shelter dogs with diarrhea. *Top Companion Anim Med.* 2017;32(3):100–103. doi:10.1053/j.tcam.2017.11.001
28. Pignataro G, Di Prinzio R, Crisi PE, et al. Comparison of the therapeutic effect of treatment with antibiotics or nutraceuticals on clinical activity and the fecal microbiome of dogs with acute diarrhea. *Animals (Basel).* 2021;11(6):1484. doi:10.3390/ani11061484
29. Gobeli S, Berset C, Burgener I, Perreten V. Antimicrobial susceptibility of canine *Clostridium perfringens* strains from Switzerland. *Schweiz Arch Tierheilkd.* 2012;154(6):247–250. doi:10.1024/0036-7281/a000340
30. Marks SL, Rankin SC, Byrne BA, Weese JS. Enteropathogenic bacteria in dogs and cats: diagnosis, epidemiology, treatment, and control. *J Vet Intern Med.* 2011;25(6):1195–1208. doi:10.1111/j.1939-1676.2011.00821.x
31. Fujishiro MA, Lidbury JA, Pilla R, Steiner JM, Lappin MR, Suchodolski JS. Evaluation of the effects of anthelmintic administration on the fecal microbiome of healthy dogs with and without subclinical *Giardia* spp. and *Cryptosporidium canis* infections. *PLoS One.* 2020;15(2):e0228145. doi:10.1371/journal.pone.0228145
32. Bamias G, Marini M, Moskaluk CA, et al. Down-regulation of intestinal lymphocyte activation and Th1 cytokine production by antibiotic therapy in a murine model of Crohn's disease. *J Immunol.* 2002;169(9):5308–5314. doi:10.4049/jimmunol.169.9.5308
33. Sadowska A, Kretowski R, Szynaka B, Cechowska-Pasko M, Car H. Metronidazole decreases viability of DLD-1 colorectal cancer cell line. *Cancer Biother Radiopharm.* 2013;28(8):615–622. doi:10.1089/cbr.2013.1485
34. Tauro A, Beltran E, Cherubini GB, et al. Metronidazole-induced neurotoxicity in 26 dogs. *Aust Vet J.* 2018;96(12):495–501. doi:10.1111/avj.12772
35. Suchodolski JS, Markel ME, Garcia-Mazcorro JF, et al. The fecal microbiome in dogs with acute diarrhea and idiopathic inflammatory bowel disease. *PLoS One.* 2012;7(12):e51907. doi:10.1371/journal.pone.0051907
36. 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(9):e107909. doi:10.1371/journal.pone.0107909
37. Bartlett JG. Clinical practice: antibiotic-associated diarrhea. *N Engl J Med.* 2002;346(5):334–339. doi:10.1056/NEJMcp011603

Supplementary Materials

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