

Determining optimal therapy of dogs with chronic enteropathy by measurement of serum citrulline

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Background: Serum concentration of citrulline is a useful biomarker in human intestinal disease and indicates globally reduced enterocyte mass and absorptive function in various disease states.

Objectives: To determine whether serum citrulline concentration is a biomarker in chronic enteropathy (CE) in dogs, to provide useful information regarding optimal treatment or to predict outcome.

Animals: Seventy-four dogs with CE and 83 breed- and age-matched hospital controls with no clinical signs of intestinal disease.

Methods: Retrospective study. Outcome was determined and dogs were categorized by response to treatment as having food-responsive enteropathy (FRE), antibiotic-responsive diarrhea (ARD), or idiopathic inflammatory bowel disease (IBD). Disease severity was quantified by the CIBDAI scoring index.

Results: Serum citrulline concentration did not differ between dogs with CE (median, 8.4 µg/mL, 5th-95th percentile 2.0-19.6) and controls (median, 8.1 µg/mL, 5th-95th percentile 2.2-19.7, $P = .91$). Serum citrulline concentration was similar between dogs with FRE (median, 9.1 µg/mL, 5th-95th percentile 2.0-18.9), ARD (median, 13.0 µg/mL, 5th-95th percentile 1.6-19.2), IBD (median, 8.4 µg/mL, 5th-95th percentile 2.1-21.0; $P = .91$). Serum citrulline did not correlate to CIBDAI or to serum albumin concentration.

Conclusions and Clinical Importance: In our study, serum citrulline concentration was not associated with efficacy of treatment or outcome in dogs with CE.

KEYWORDS

biomarker, diarrhea, IBD

1 | INTRODUCTION

Chronic enteropathy (CE) is a common condition in dogs.¹ Causes of CE can include adverse reaction to food, apparent antibiotic responsive diarrhea (ARD) and putative idiopathic inflammatory bowel disease

(IBD), with these disorders best diagnosed retrospectively, by exclusion of other causes and response to treatment.^{1,2} As histopathological diagnosis does not reliably distinguish different causes of CE, determining the best treatment is currently undertaken on a trial-and-error basis.^{1,3} Further, outcomes for individuals vary widely and are difficult to predict, with some dogs responding to one treatment or another, and others responding poorly.² As a result, there is a need for novel tests that predict the best treatment and help to determine the likely outcome. Unfortunately, despite recent investigations into potential

Abbreviations: ARD, antibiotic-responsive diarrhea; CCECAI, canine chronic enteropathy clinical activity index; CE, chronic enteropathy; CIBDAI, canine IBD activity index; FRE, food-responsive enteropathy; IBD, idiopathic inflammatory bowel disease; SATH, Small Animal Teaching Hospital.

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new tests,^{4–10} serum biomarkers that are specific to CE in dogs have not yet been identified.

Citrulline, a nondietary amino acid involved in intermediary metabolism, is produced almost exclusively by the enterocytes of the small intestinal mucosa, and is a potential biomarker in intestinal disease. Circulating citrulline is dependent on *de novo* synthesis, as it is not found in food (except for watermelons). Therefore, decreased serum or plasma citrulline concentration corresponds to a reduction in functioning enterocyte mass.¹¹ In human medicine, citrulline is considered to be a reliable biomarker of remnant small intestinal enterocyte mass and absorptive capacity, independent of intestinal inflammation.¹² It is used to determine, quantitatively, intestinal epithelial integrity at the enterocyte level and is not greatly influenced by nutritional status or systemic inflammatory status.¹¹ Decreased plasma citrulline concentration correlates with reduced enterocyte mass in short bowel syndrome,^{13–15} villous atrophy states,¹⁶ and during follow-up of patients after small bowel transplantation.¹⁷ Various cut-offs are employed in humans to quantify the degree of intestinal failure and are useful in predicting prognosis where there is intestinal compromise.^{18,19}

To date, there have been few studies of citrulline in chronic intestinal diseases of dogs.^{20,21} Therefore, the aims of our study were to determine the value of citrulline as a biomarker in canine CE. The hypothesis was that serum citrulline concentration in dogs with CE will differ between dogs that respond to dietary management (adverse food reaction), those that have ARD, and those that have idiopathic IBD.

2 | MATERIALS AND METHODS

2.1 | Dogs

This was a retrospective study involving client-owned dogs referred to the Small Animal Teaching Hospital (SATH), University of Liverpool, UK. Computer records were searched to identify dogs diagnosed with CE between January 2012 and July 2015. The study was approved by the University of Liverpool, Institute of Veterinary Science Research Ethics Committee (reference no. VREC160).

2.2 | Eligibility criteria

Dogs were eligible for the study if they had clinical signs consistent with CE, including vomiting, diarrhea, or weight loss, for a duration of at least 3 weeks; no identified systemic or nonintestinal causes of the clinical signs, such as exocrine pancreatic insufficiency, pancreatitis, or hypoadrenocorticism; and normal serum or plasma creatinine concentration (as advanced kidney disease might falsely increase serum citrulline by reduced renal clearance). Further, sufficient surplus serum had to be available for use in the study, after diagnostic tests had been performed. Control dogs were dogs presented to the SATH for reasons other than gastrointestinal disease and included dogs with orthopedic or dermatological disease, and blood donors. For each dog that was identified with CE, computer records were used to identify 2 control dogs of the same breed and of similar age (date of birth within 6 months of the dog with CE). Control dogs were included if they had

had a blood sample taken, had no signs of intestinal disease, and had normal serum creatinine and albumin concentrations. Two possible controls were identified for each case because not every dog had sufficient residual stored serum for citrulline assay after diagnostic testing.

2.3 | Diagnostic investigations and therapeutic trials

Hematological and serum biochemical analyses were performed on blood samples from all dogs with CE. Hypoadrenocorticism was excluded in all dogs by cortisol assay and/or ACTH stimulation test. Exocrine pancreatic insufficiency was excluded in all dogs by measurement of serum trypsin-like immunoreactivity. All dogs subsequently underwent abdominal radiography and ultrasonography. In dogs that were clinically well and where findings of these investigations were normal, dogs were treated with fenbendazole to exclude occult parasitism (when this had not already been done by the referring veterinarian) and then started on a therapeutic dietary exclusion trial, most commonly using a commercial hydrolyzed protein diet (eg, Royal Canin Hypoallergenic, or Hill's z/d diet), again unless a rigorous dietary exclusion trial already been done by the referring veterinarian. If there was no improvement in signs of gastrointestinal disease after the dietary exclusion trial, a therapeutic antibiotic trial was started, using either oxytetracycline (10–20 mg/kg q8h) or tylosin (20 mg/kg q8h). For dogs that failed both dietary and antibiotic trials, or had protein losing enteropathy (PLE, serum albumin <2.3 g/dL), intestinal biopsy was performed, most commonly by endoscopy (31 dogs underwent endoscopy and biopsy, and 8 dogs underwent full thickness intestinal biopsy at coeliotomy). In 4 cases in which owners declined intestinal biopsy, a therapeutic trial with prednisolone was started in the same way as in dogs that underwent biopsy. After diagnostic testing, dogs were followed either by revisits to the clinic or, in a few cases, by telephone contact with the owners (every 3–4 weeks, or more often if dictated by the clinical situation). This refers to telephone contact at the time rather than later.

Dogs with CE that showed resolution of their signs of gastrointestinal disease after the therapeutic food trial were diagnosed with food responsive enteropathy (FRE). Dogs with CE that did not improve by 2 weeks after starting the therapeutic food trial, but showed resolution of their signs of gastrointestinal disease after the antibiotic trial, were diagnosed with ARD. Dogs that did not improve on the food trial or antibiotic trial and where intestinal inflammation was documented on intestinal histopathology were diagnosed with idiopathic IBD.¹ Inflammatory bowel disease was a presumptive diagnosis in dogs whose owners declined biopsy but had unremarkable imaging findings and who had failed to improve on the food trial or antibiotic trial. Dogs with IBD were treated with an immunosuppressive dose (2 mg/kg/day) of prednisolone, with the dose being subsequently reduced in dogs that responded well. This empirical approach using therapeutic trials is currently the most accurate way to determine a diagnosis in CE, and is in keeping with accepted criteria for the diagnosis of FRE, ARD, and IBD in dogs.^{1,22,23} Dogs with IBD were further subdivided into those that responded well to immunosuppressive therapy and those that were refractory to treatment. Finally, all study dogs were also

separately classified as PLE or non-PLE based on serum albumin concentration. The CIBDAI scoring index was used to quantify the severity of clinical signs and assess progression of disease.²⁴

2.4 | Blood sampling and sample storage and citrulline assays

Blood samples were collected from the jugular vein. Given possible postprandial variation in plasma citrulline concentration,²⁵ all dogs were routinely fasted for at least 12 hours before blood collection. The blood was centrifuged and the serum separated. Serum was stored at -20°C until citrulline assays were performed. All serum samples were shipped frozen via courier at the end of the study period, to the same laboratory (Laboratorio d'Analisi Veterinarie San Marco, Padova, Italy). Time in storage was between 53 and 825 days. Serum citrulline was measured by ultra-high performance liquid chromatography with tandem mass spectroscopy. The method was validated for selectivity, linearity, precision, accuracy, recovery, and stability. Selectivity was assessed by comparing the chromatogram of blank serum with those of corresponding plasma samples spiked with L-citrulline. Sensitivity was determined by analyzing samples spiked with L-citrulline. Intraday and interday variation were assessed by analysis of five batches on different days with coefficient of variation 6% and 7%, respectively. Limit of detection was determined to be 0.050 ng/mL. The assay was found to be linear over a citrulline concentration range of 0.194–198.8 ng/mL.

2.5 | Statistical analysis

Computer software was used to perform the analysis (GraphPad Prism 5.0). Continuous variables were assessed for normality using the Shapiro-Wilk method. Where data were normally distributed, comparison between groups was by unpaired Student's *t*-test. Where data were not normally distributed, comparison between groups was by Mann-Whitney *U*-test (for 2 groups) or the Kruskal-Wallis test (for more than 2). Correlation between serum citrulline concentration and CIBDAI or albumin concentration was performed by Spearman's rank correlation. The level of statistical significance was set at $P < .05$.

3 | RESULTS

3.1 | Dogs

A total of 286 dogs were seen for investigation of chronic signs of gastrointestinal disease during the study period, and of these, 74 met the eligibility criteria. Of the control dogs identified, 83 dogs had sufficient stored serum for citrulline analysis, meaning that a total of 157 dogs were included in the study. The CE group comprised 29 females and 45 males, with a median age of 6.9 years (range, 0.3–15.3 years). In the control group, there were 39 females and 44 males with a median age of 6.5 years (range, 0.7–15.4 years). As expected, ages and breeds were very similar between both groups with Border Collies, Cross Breed dogs, Labrador Retrievers, and German Shepherd dogs being the most numerous dogs included.

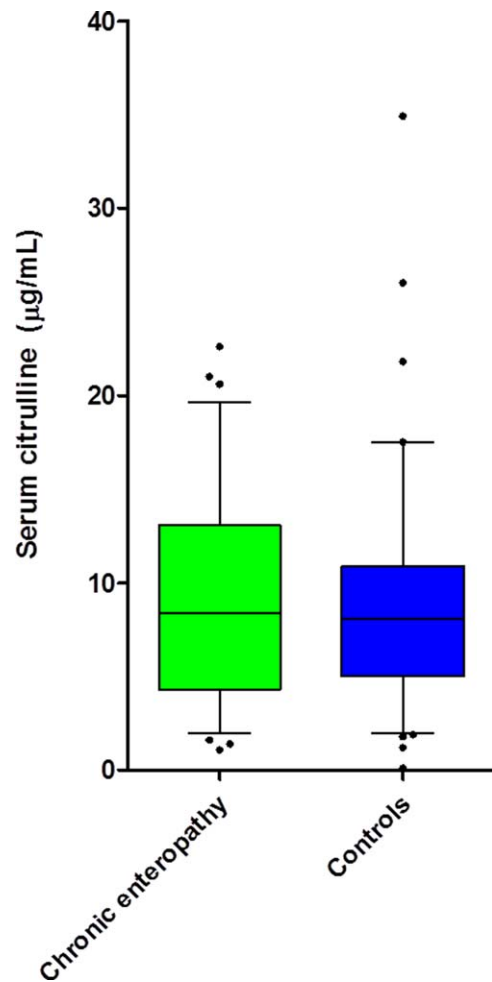


FIGURE 1 Box plot comparing serum citrulline concentration between 74 dogs with CE and 83 controls. $P = .91$ (Mann-Whitney)

3.2 | Diagnosis based on investigations performed and the results of therapeutic trials with food, antibacterials, or prednisolone

Of the 74 animals with CE, 32 responded to a dietary trial and were diagnosed with FRE, 4 failed a dietary trial but responded to antibacterials and were diagnosed with ARD, and 38 failed to respond either to diet or antibacterials and were diagnosed with idiopathic IBD, of which 34/38 had intestinal inflammation confirmed by biopsy. In the other 4 dogs, owners declined biopsy, and a presumptive diagnosis of IBD was made. Of the 38 dogs with idiopathic IBD, 18 responded well to immunosuppressive treatment, 18 responded poorly, and response was unknown in 2.

3.3 | Comparison of citrulline concentration between dogs with CE and controls

Serum citrulline concentration was similar between dogs with CE (median 8.4 $\mu\text{g/mL}$, 5th-95th percentile 2.0–19.6) and controls (median 8.1 $\mu\text{g/mL}$, 5th-95th percentile 2.2–19.7; $P = .91$, Figure 1).

3.4 | Comparison of citrulline concentration amongst dogs with different categories of CE

Serum citrulline concentration was similar between dogs with FRE (median 9.1 $\mu\text{g/mL}$, 5th-95th percentile 2.0-18.9), ARD (median 13.0 $\mu\text{g/mL}$, 5th-95th percentile 1.6-19.2), IBD (median 8.4 $\mu\text{g/mL}$, 5th-95th percentile 2.1-21.0), and controls (median 8.1 $\mu\text{g/mL}$, 5th-95th percentile 2.2-19.7; $P = .91$). When, the IBD group was further divided into those that responded well and those that responded poorly to immunosuppressive therapy, serum citrulline concentration was again not different amongst groups (median 8.3 $\mu\text{g/mL}$, 5th-95th percentile 2.3-22.6 for dogs that responded well, and median 7.7 $\mu\text{g/mL}$, 5th-95th percentile 1.4-16.8 for those that responded poorly, $P = .79$, Figure 2).

3.5 | Comparison of citrulline concentration amongst CE dogs with different disease severity

Serum citrulline concentration was compared between 16 dogs with clinically unimportant CE (median 11.2 $\mu\text{g/mL}$, 5th-95th percentile 2.6-19.2), 22 dogs with mild CE (median 9.9 $\mu\text{g/mL}$, 5th-95th percentile 2.4-20.9), 27 dogs with moderate CE (median 8.0 $\mu\text{g/mL}$, 5th-95th percentile 1.3-20.9), and 9 dogs with severe CE (median 3.3 $\mu\text{g/mL}$, 5th-95th percentile 1.4-16.4), as determined by CIBDAI and was similar between groups ($P = .10$). Further, there was no significant

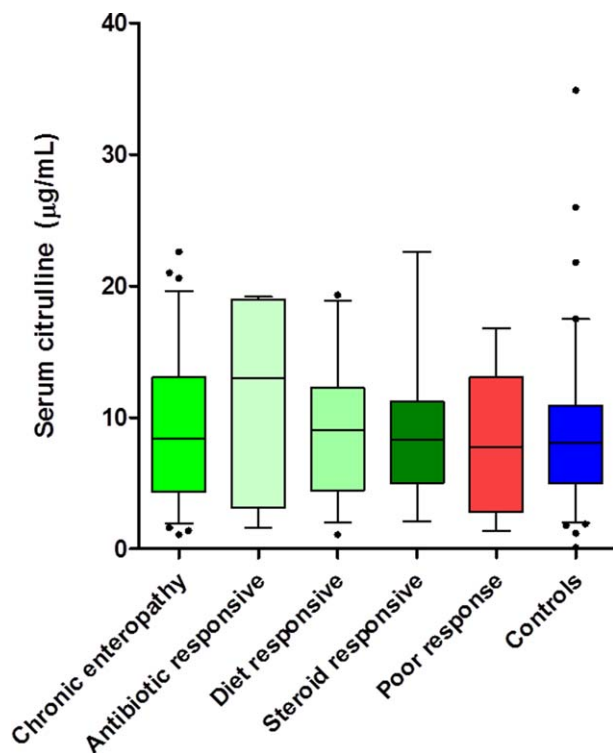


FIGURE 2 Box plot comparing serum citrulline concentration between dogs with different types of CE. Data are shown from 74 dogs with CE (including 32 dogs with CE that responded to dietary management, 4 dogs with CE that responded to antibiotic trials, 18 dogs with IBD that responded well to immunosuppression, and 18 dogs with IBD that were refractory to treatment) and 83 controls. $P = .79$ (Kruskal-Wallis)

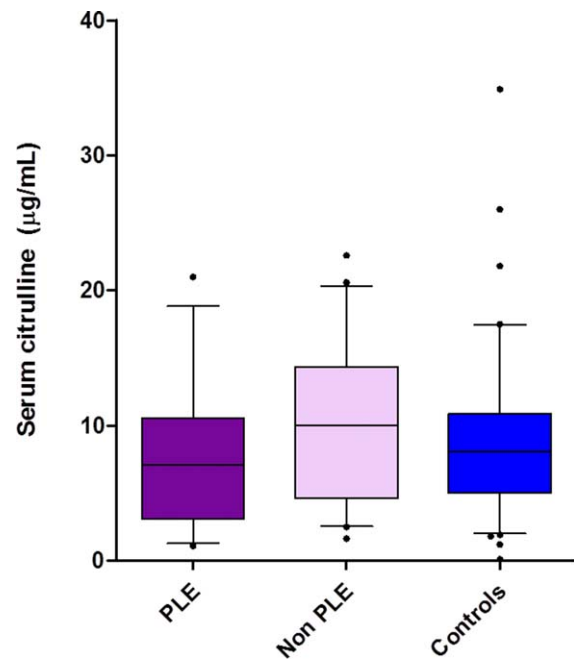


FIGURE 3 Box plot comparing serum citrulline concentration between 31 dogs with CE and associated PLE and 43 dogs with CE and normal serum albumin. $P = .18$ (Kruskal-Wallis)

correlation between CIBDAI and serum citrulline concentration ($r = -0.08$, $P = .68$). Finally, serum citrulline concentration was similar between dogs that were alive at the end of the study period (median 8.1 $\mu\text{g/mL}$, 5th-95th percentile 1.6-20.1), and those that were euthanized before the end of the study period (median 8.5 $\mu\text{g/mL}$, 5th-95th percentile 2.1-16.3, $P = .43$).

3.6 | Comparison between dogs with and without PLE

Serum citrulline concentration was compared between 31 dogs with CE and associated PLE (median 7.1 $\mu\text{g/mL}$, 5th-95th percentile 1.3-18.8), and 43 dogs with CE and normal serum albumin (median 10.0 $\mu\text{g/mL}$, 5th-95th percentile 2.5-20.0), and was similar between groups ($P = .18$, Figure 3). Further, serum citrulline concentration did not correlate with serum albumin concentration ($r = 0.02$, $P = .81$).

4 | DISCUSSION

The main study conclusion was that serum citrulline concentration did not differ between dogs with various types of CE or between dogs with CE of different clinical severity. We had hypothesized that serum citrulline might help to predict response to treatment, as determined by response to sequentially performed therapeutic trials, but the fact that citrulline concentrations did not vary amongst treatment groups would suggest that this will not be possible. Another hypothesis was that serum citrulline concentrations might be useful in predicting whether dogs were likely to respond irrespective of treatment. However, serum citrulline concentrations did not differ between dogs that responded well to treatment and those that failed treatment or between those that were still alive at the end of the study period and those that had

been euthanized because of CE. Moreover, there was no difference in serum citrulline concentration between dogs with CE and concurrent PLE and those with CE but no PLE, and no association was found between serum citrulline concentrations and disease severity, as determined by CIBDAI. The latter finding contrasts with the results of a previous, albeit smaller, study that did find a negative correlation between citrulline and the canine CE clinical activity index in 23 dogs with IBD,²¹ and another study that showed a small but significant increase in citrulline in 10 dogs that received probiotics as treatment for IBD, at the same time that CIBDAI improved, suggesting that citrulline may have been low in affected dogs before treatment started.²⁰ The reason for differences between the studies is not clear, but might relate to differences in the populations studied, and diagnostic approach.

Therefore, although citrulline is a useful marker in human intestinal diseases as mentioned above, the results of our study do not support its use in the investigation and management of canine gastrointestinal disease. The reasons for such a species difference are not clear. The liver can contribute to circulating citrulline in dogs but not in humans.^{26,27} However, no dogs in our study were diagnosed with liver disease, and in another study canine parvoviral enteritis was associated with a drastic decrease in serum citrulline, even though acute liver damage was considered unlikely.²⁸ This result is consistent with the pathogenesis of canine parvoviral enteritis, in which extensive necrosis of enterocytes is known to occur, and suggests that in principle citrulline can be assayed in dogs as a marker of enterocyte mass.

The disorders in human medicine that are associated with reduced circulating citrulline involve significant loss or absence of functioning enterocytes, such as short bowel syndrome,^{13–15} villous atrophy states,¹⁶ intestinal failure associated with small bowel disruption and transient double enterostomy,¹⁹ Crohn's disease with extensive bowel resection,¹² and critical illness.¹⁸ Decreased circulating citrulline concentration might only occur when the loss of enterocytes is severe.^{12,29,30} Citrulline concentration does not accurately indicate overall absorptive function, especially when there is not a large reduction in enterocyte mass.¹¹ If this is also true in dogs, it might explain why decreases in circulating citrulline were not seen in the dogs with CE in our study, in that the loss of functioning enterocyte mass might not have been severe enough to cause a detectable decrease in serum citrulline concentration. In humans, a citrulline generation test, in which the rate of conversion of glutamine into citrulline measured over time, has been suggested as a dynamic alternative to measurement of fasting serum citrulline concentration. It remains unknown whether this should become standard practice in human medicine²⁹ but to our knowledge, this test has not been assessed in client-owned dogs.

Our study has several limitations that should be considered. First, the cases assessed were from a referral-only population. Therefore, the findings might not be applicable to other populations, for example those visiting primary care practices. Second, the study was retrospective so that samples were not taken for the purpose of the study, and serum samples were stored for a variable time, until they could be analyzed in a batch. It is frequently considered that citrulline concentration is more stable and more reliably measured in plasma than in serum and it is unknown how this may have affected results. Serum samples were

not deproteinized before storage. There was no correlation between time in storage and serum citrulline concentration ($r = 0.01$, data not shown), but these results should be viewed with caution as citrulline degradation could possibly occur with storage at -20°C , and it is also possible that there could be liberation of citrulline from citrullinated proteins that might be present in the sample.

A third limitation, also related to the retrospective nature of the study, was the fact that clinical data were not recorded systematically for the direct purpose of the study. As a result, we were often reliant on the notes made by the attending clinician, and this might have led to errors, for example in how response to treatment was classified. Some of the dogs diagnosed with IBD that responded poorly to treatment may have had alimentary lymphoma, given that histopathology can be unreliable in GI disease and that a small number of dogs did not have biopsies but were instead treated empirically. Further, since dogs with missing data were excluded, the population studied might not have been representative of all affected dogs. A future prospective study could be considered to confirm these findings and to examine changes of serum citrulline concentration over time.

Another limitation is that in humans, citrulline is considered as a marker of the severity of intestinal damage, correlated to the severity of the lesions and the length of gut affected, but this information was not available for all dogs in our study. Neither CIBDAI nor serum albumin have been correlated with the extent of intestinal damage and the true extent of the histopathological damage was not known for most dogs in our study, because most dogs underwent endoscopic biopsy and only a small part of the gut can be examined endoscopically.

5 | CONCLUSIONS

In this retrospective study, serum citrulline concentration did not differ between dogs with CE and dogs attending the hospital for reasons unrelated to intestinal disease. There did not appear to be any relationship between serum citrulline and final diagnosis in canine CE. Therefore, use of serum citrulline cannot currently be recommended in the diagnostic investigation and clinical management of dogs with CE.

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CONFLICT OF INTEREST DECLARATION

One of the authors (MC) is affiliated with a diagnostic laboratory offering commercial citrulline assays. The academic post of one of the authors (AJG) is financially supported by Royal Canin.

OFF-LABEL ANTIMICROBIAL DECLARATION

Some dogs in this study received oxytetracycline or tylosin as part of investigations for possible antibiotic-responsive diarrhea (ARD). These drugs are not licensed for ARD in the United Kingdom. However, no drugs are licensed for use in ARD in the UK and these drugs were chosen as they are considered safe and used widely in management of ARD in dogs.

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

The study was approved by the University of Liverpool, Institute of Veterinary Science Research Ethics Committee (reference no. VREC160).

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