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Treatment response and long term follow up in nineteen dogs diagnosed with chronic enteropathy in Australia

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Structured abstract

Chronic enteropathy (CE) in dogs is common worldwide, but little data is available from Australia. The aim of this study was to describe treatment response and long-term outcome in a cohort of dogs with CE.

Dogs were prospectively enrolled at Murdoch University and the University of Melbourne. After diagnostic investigation to rule out diseases other than CE, dogs underwent sequential therapeutic trials until achieving a clinical response (diet then antibiotics, and finally immunosuppressants). Success was defined as 75% reduction of clinical severity for a minimum of five weeks.

A total of 21 dogs were enrolled, and 19 completed the study. One dog was euthanised for lack of response to treatment and one excluded for lack of owner compliance. Most dogs responded to diet (n=10), followed by antibiotics (n=7) and immunosuppressants (n=2). Long-term remission (median 21.1 months, [3.0-44.7]) was achieved in eight out of ten dietary responders without additional treatment. In contrast, only two dogs with antibiotic response remained in long-term remission, of which one needed on-going antibiotic treatment. Longer term remission was achieved in the two dogs treated with immunosuppressants with on-going low dose therapy.

This study concludes that most dogs referred for CE in Australia respond to dietary treatment (even after previous dietary interventions), and remission is long-term compared to dogs treated with an antibiotic. Furthermore, the need for long-term antibiotics in some dogs to

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maintain response may lead to antibiotic resistance. This study supports adequate dietary trials for CE in dogs, and a need for alternative second-line treatments.

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Keywords dog; chronic enteropathy; treatment; inflammatory bowel disease; diet; antibiotic

Abbreviation

ARE: antibiotic-responsive enteropathy.

BCS: body condition score.

CCECAI: canine chronic enteropathy clinical activity index.

CE: Chronic enteropathy.

FRE: food-responsive enteropathy.

IBD: inflammatory bowel disease.

IRE: immunosuppressant-responsive enteropathy

MU: Murdoch University.

UoM: University of Melbourne.

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Introduction

Chronic enteropathy (CE) is defined as primary gastrointestinal disease of at least three weeks duration, with no evidence of infectious aetiologies.[1] The aetiology of CE is thought to be similar to inflammatory bowel disease (IBD) in humans, and arises from an imbalance between the microbiota, genetics, environment (including diet), and immune system of the host.[2]

In contrast to adult people, where immunomodulation is needed to treat IBD, dogs with CE may respond to a diet trial or an antibiotic trial without requiring immune suppression.[3] This is similar to findings in paediatric Crohn's disease where a meta-analysis report similar success with enteral nutrition than corticosteroid in a paediatric population.[4] Interestingly, in a referral setting, several studies report that a majority of dogs respond to diet alone. This has been the case in North America, several European countries, and Japan, but to the best of our knowledge, no information is currently available in Australia.[5–10] There is evidence that IBD in people is affected by geographical location, dietary intake, and genetic background.[11–13] For this reason, it cannot be assumed that studies in dogs in Europe and North America reflect the clinical findings in Australia, without further analysis.

Typical treatment includes stepwise trials starting with diet, then antibiotics, and finally the use of immune-suppressive drugs, such as prednisolone, in non-responders. Dogs are retrospectively classified as having food-responsive enteropathy (FRE), antibiotic-responsive enteropathy (ARE), or immunosuppressant-responsive enteropathy (IRE).[14]

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Although most dogs will respond to one of these treatment trials initially, their long-term response has not been as well characterised. Only a few studies have had follow-up over six months with prolonged response in a majority of FRE dogs, but not in dogs with ARE or IRE.[1,7,9] This raises a concern that dogs with ARE or IRE might require pulse or on-going antibiotic or immunosuppressant treatment to maintain clinical response. This is of particular concern when considering the risk of antibiotic resistance development, as described in people with IBD.[15]

The aims of our prospective study were to (1) describe treatment response in a cohort of dogs with CE in an Australian referral setting and (2) to determine long-term response to the different trials.

Material and methods

Prospective enrolment took place at Murdoch University (MU) and the University of Melbourne (UoM). Full Animal Ethics Committee institutional approval was obtained for all dogs used in these two institutions (respectively MU, R2262/09 and UoM, UMVH 2014-06).

Inclusion criteria - Dogs with signs consistent with chronic enteropathy (weight loss, hyporexia, diarrhoea and/or vomiting), of three weeks or longer duration, were included in this study after ruling out extra-intestinal disease as described elsewhere.[16] All dogs also had a negative faecal flotation examination (performed with saturated sodium nitrate, specific gravity of 1.2, and a centrifugation step) and were wormed with fenbendazole (Coopers®, NSW, Aust; 50mg/kg PO q24 for three days,) prior to enrolment. No diet change, treatment

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with antibiotics or immune-suppressive drugs were allowed in the four weeks preceding enrolment.

Parameters collected at time of inclusion included breed, age, sex, weight, body condition score (BCS), clinical signs (upper, lower, or mixed gastrointestinal signs), dietary history and duration of signs. Extra-intestinal disease was ruled out with a combination of laboratory testing and abdominal ultrasound. Laboratory examination included haematology and biochemistry, serum trypsin-like immunoreactivity (TLI), and canine pancreatic lipase (cPL). Cobalamin was either supplemented with subcutaneous injections once a week for 6 weeks with one additional injection after a month (Troy Laboratories Pty Ltd, NSW, Aust; 250µg to 1000µg per injection according to weight) or measured to determine the need for supplementation at clinician discretion. Basal cortisol or adrenocorticotropic hormone (ACTH) stimulation test was performed in cases where hypoadrenocorticism was considered possible. A basal cortisol concentration >55nmol/L was used to rule out hypoadrenocorticism as described previously.[17]

Clinical investigation included upper and lower gastro-intestinal endoscopy at the time of enrolment including histology grading, and again after clinical response. Histology results for this cohort of dogs has been already published and the reader is referred to this article for further detail.[18] In brief, all dogs had 12 to 15 biopsies taken from the stomach, duodenum, and colon. Ileal biopsies were taken in the last dogs enrolled (n=6). Histology grading was performed using the criteria from the World Small Animal Veterinary Association for intestinal histopathology assessment.[19] A summary of the histology scores is available in Supplement 1.

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Following this work up, all dogs were diagnosed with chronic enteropathy with the combination of clinical signs, exclusion of extra-intestinal disease or parasitic disease, and presence of gastro-intestinal inflammation on histology. The canine chronic enteropathy clinical activity index (CCECAI) was used to determine the clinical severity at enrolment and throughout the study.[1]

The first trial consisted of a diet trial (hydrolysed or selected protein diets not previously prescribed) for a minimum of 2 weeks. The diets selected included Hill's z/d™ (Hill's Pet Nutrition, NSW, Australia), Royal Canin™ Sensitivity Control, and Royal Canin™ Hypoallergenic (Royal Canin™, VIC, Australia). Responders were classified as FRE. Non-responders were then treated with oxytetracycline (Slade Pharmacy, VIC, Australia) at a dose of 10mg/kg PO q12h. Responders were classified as ARE. If there was continued poor to no response for a minimum of 2 weeks, then prednisolone (Apex Laboratories Pty Limited, NSW, Australia) was started at a dosage of 2mg/kg PO q24h for dogs less than 20kg and 40mg/m^2 for dogs 20kg or more. Dogs could also be treated with chlorambucil at an initial dosage of 2 to 4mg/m^2 q24h (Leukeran, Aspen Australia, VIC, Australia) as necessary. Responders were classified as IRE rather than steroid-responsive enteropathy to account for the combined therapy. The same diet was continued throughout the trial. Treatment success for each trial was defined as a 75% reduction in CCECAI maintained for a minimum of 5 weeks.[1] At that point, the dog exited the study.

At the end of the trial, the owners were given the choice of continuing to feed the same diet or to transition to a new one. An attempt was made to wean ARE dogs off antibiotics with reduction in frequency monthly. If the dogs relapsed, the last effective dosing was re-started.

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Similarly, immunosuppressants were weaned off monthly, but if the dogs relapsed, the last effective dosing was re-started. Most dogs were returned to their primary care giver after the end of the study. No repeat diagnostic, including cobalamin concentration determination, was performed after finishing the study.

Long-term follow-up was performed at 2 to 3-month intervals either at the respective clinics, or by phone after successful treatment was achieved. The outcome was defined as (1) **remission** for dogs with on-going 75% reduction in CCECAI, (2) **partial remission** for dogs with self-limiting CE signs $\leq$ once a month, (3) **relapse** for dogs with signs more frequent or CCECAI with less than 75% reduction compared to pre-enrolment.

IBM SPSS Statistics for Windows was used for statistical analysis (IBM Corp. 2016. Version 24.0. Armonk, NY). Given that some of the variables were not normally distributed (using the Shapiro-Wilk Test), non-parametric analyses were used. For comparison of age, weight, body condition score, duration of signs, CCECAI at diagnosis and follow up between treatment groups (FRE vs ARE), the Mann-Whitney U test was used. For comparison of outcome and odds ratio calculation (remission vs partial remission or relapse), a two-sided Fisher's exact was used. For comparison of CCECAI before and after treatment for each group, a Wilcoxon Signed Rank Test was used. A *P-value* of less than 0.05 was considered significant.

Results

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A total of 21 dogs were included in the study. Six dogs were enrolled at MU from June until October 2010 and 15 at UoM from June 2012 until June 2015. Two dogs were excluded from the study. One MU dog did not complete the treatment trial (marked hypoalbuminaemia at enrolment and euthanasia because of lack of response with immune-suppressive treatment), and one UoM dog did not complete the trial because of poor owner compliance. The remaining 19 dogs responded to one of the three treatment trials for a minimum of five weeks (i.e. reduction of at least 75% of CCECAI). Ten dogs had a diagnosis of FRE, seven of ARE, and two of IRE. As the sample size of IRE dogs was small (only 2 dogs), statistical analysis was limited to FRE and ARE dogs. A summary of the study design and outcome is available in figure 1.

Signalment, clinical history, clinical scoring before and after treatment, and histology scoring before and after treatment for each dog (including the two dogs that were excluded) are summarised in Supplement 1. The most represented breeds included German shepherd dogs (n=4), followed by Labrador retriever (n=3) and golden retriever (n=2). All remaining breeds were represented by one dog each.

Comorbidities in the FRE group included atopy or otitis externa (n=3). In the ARE group, two dogs were treated for behavioural problems (one with fluoxetine) and one dog was treated for incontinence with oestriol. In the IRE group, one dog had previously been diagnosed with auto-immune retinopathy and polyarthropathy but was not receiving medical therapy at the time of enrolment.

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Only mild abnormalities were noted on haematology and biochemistry. The most common finding was an absence of stress leukogram (five FRE and three ARE dogs), and eosinophilia was noted in three dogs (two FRE and one ARE dogs). Only two dogs were hypoalbuminaemic: one dog from the IRE group (dog 17, 16g/L [24 - 38]) and the dog excluded due to lack of response to all treatments.

Both cTLI (n=15) and cPL (n=14) were normal in all dogs tested. Hypoadrenocorticism was ruled out in fifteen dogs via basal cortisol (n=11) or an ACTH stimulation test (n=4). Seven dogs had cobalamin measured, which was within normal limits and the remaining dogs received supplementation.

There was no significant difference in age, weight, BCS, duration of clinical signs, CCECAI at diagnosis, histology score at diagnosis and after response, and follow up duration between FRE dogs and ARE dogs. Results per group are summarised in table 1. The inflammation was characterised by a lymphocytic or lympho-plasmacytic infiltrate in 15 of 19 dogs.

The different diets used for the diet trial are listed in table 2. In the FRE group, eight dogs were fed strictly dry food of which five responded to hydrolysed diets and three to a single protein diet. One dog was fed a mix of canned and dry hydrolysed diet and one dog a mix of dry hydrolysed and canned single protein diet.

At the last follow up, the owners of six out of ten FRE dogs had decided to continue the trial diet long term. Of these six dogs, five were in remission and one in partial remission. Of the four dogs with diet change, three were transitioned from a hydrolysed to either a single protein diet (n=2) or commercial diet (n=1) and the diet was not recorded for one . At the last

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follow up of dogs with diet change, three dogs remained in remission (including the dog without diet recorded) and one was in partial remission.

The median follow-up for all dogs was 32 months (range three to 59 months). There was no significant difference between groups in the length of follow-up (table 1).

Remission was reported at the last follow-up in eight out of ten dogs with FRE, in two out of seven dogs with ARE, and in both dogs with IRE. Partial remission (self-limiting signs once or less a month) was reported in two FRE dogs and four ARE dogs. One dog in the ARE relapsed while on treatment with antibiotics q48h and was then lost to follow up (at five months). The odds ratio for FRE dogs to go into remission compared to ARE dogs was 10 (95%-confidence interval: 0.73 – 162.7) but did not reach significance (p=0.058). The power of our study to assess the outcome was 0.41, and a total of 36 dogs would be required to reach a power of 0.82.

In the ARE group, apart from the dog lost to follow up, two dogs were still receiving antibiotics at the last follow up (respectively 14 and 23 months) at dosing intervals ranging from q12h to q72h, and one dog as pulse therapy, when clinical signs were recurring. Antibiotic was stopped completely in only three dogs of which one was in remission and two in partial remission.

In the IRE group, both dogs were receiving a low dose of prednisolone (<0.3mg/kg q48h) and chlorambucil (2mg q48-72h). Neither dog could be weaned off these medications without recurrence of clinical signs.

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Discussion

This study describes a population of dogs diagnosed with CE recruited at two universities in Australia. Similar to reports from other countries, a majority of dogs with CE were food-responsive, despite having had previous dietary intervention.[5,7,8,16,20] In our population, the second most frequent presentation of CE was ARE, and immunosuppressant treatment was needed in only two dogs. A step-up approach (sequential treatment trials) was selected in this group of dogs as none had severe signs (for example a dog with hypoalbuminaemia, ascites, and decreased appetite) where a step-down approach with steroid treatment earlier would have potentially been considered.[21]

Dogs with FRE and ARE had a median age of less than three years old and there was no statistically significant difference between both groups as previously reported.[1,22] However, of note is that two dogs with FRE in the present study were over nine years old and for this reason, a diet trial should be considered regardless of the age in dogs that are otherwise well. FRE dogs of similar age have also been previously reported.[8]

Similarly, the CCECAI was consistent with severe disease (>8) in four dogs, of which two responded to diet alone and one to antibiotics. A dietary trial was commenced despite the severity of clinical signs in these cases, as the dogs' general demeanour was good, and their appetite remained adequate. The last dog, which was also hypoalbuminaemic, did not respond to any treatment and euthanasia was elected by the owners.

As previously described, treatment response was achieved in dogs with FRE by feeding either single protein or hydrolysed diet.[20] Remission was achieved for a long duration in a majority

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of dogs with FRE (eight out of ten dogs) and no dogs relapsed during the follow-up period (median 21 months; range 3-45 months). The remaining two dogs with FRE achieved partial remission with infrequent GI signs. Overall, the owners considered the dogs to be clinically much improved compared to enrolment and did not feel the need to achieve better control. This long-term response in FRE dogs is consistent with a recent study from the UK.[7] Mucosal healing is the gold standard to assess treatment response in human IBD with reduced risk of relapse when achieved.[23] FRE dogs have been shown to have improvement in their mucosal ultrastructure after successful response to a diet trial, which is likely to account for this long-term response despite the lack of resolution of histological changes reported in other studies.[1,24,25]

To determine if the diet response was due to eliminating hypersensitivity (by removing or altering protein antigens) would require a dietary rechallenge. Diet re-challenge was not part of our study protocol, and the decision to continue feeding the same diet or change to another diet was left to the owners at the end of the study period. Three dogs did transition to new diets after successful response, with two remaining in remission and one in partial remission. Most owners elected not to change the diet as their dogs were clinically well. Due to the lack of recrudescence in some of our dogs, it is possible that other dietary factors contributed to success, such as alteration of the microbiome or improvement of mucosal health due to dietary macronutrients.

Another interesting aspect of the dogs with FRE is that many of them had undergone dietary trials prior to referral to the study institutions, yet still responded to an alternate diet. This mirrors the situation worldwide, where the majority of dogs with CE have been classified as

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FRE for over ten years in referral centres.[9,1,5,7,8] A reason for the improved success after referral may be that clients willing to seek referral are more receptive to following a strict diet trial. Therefore, it would be beneficial to develop strategies in general practice to improve client compliance when prescribing a diet trial, so that diagnosis of FRE is made earlier during the disease. It would be of interest to see if strategies used in people with coeliac disease to increase dietary compliance, such as education, professional support and use of online tools, could also be implemented in veterinary medicine.[26,27] .

In contrast to dogs with FRE, only a minority of dogs with ARE achieved long-term remission (two out of seven dogs). Three dogs were receiving on-going antibiotic treatment to maintain remission or partial control of their clinical signs. This is again very similar to the findings in the UK study.[7] Although the odds ratio between FRE and ARE dogs was elevated, our study was underpowered to reach significance, and a larger number of dogs would be necessary to confirm the poorer outcome in ARE dogs long-term. The power of our study to assess the outcome was 0.41, and a total dog of 36 would have been required to reach a power of 0.82.

Although antibiotics have been used widely in human medicine, their real benefit in IBD remains uncertain, except for specific entities such as pouchitis or in cases with infectious complications.[15] Conversely, the use of antibiotics has been shown to be a risk factor for the development of *Clostridium difficile* associated diarrhoea and the development of antibiotic resistance both in human and veterinary medicine. [28–30]

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Antibiotics such as tylosin and oxytetracycline have been shown to be effective in some dogs with CE. However, the response is typically short-lived after cessation of treatment with one report of over 80% of dogs relapsing within a month.[31,32] It remains unclear if response to treatment is due to modification of the microbiota via an antibiotic effect or other mechanisms such as anti-inflammatory properties as shown *in vitro* for tylosin and oxytetracycline.[30,33–35] However, there is a paucity of *in vivo* studies to support this effect and conflicting *in vitro* results for oxytetracycline.[36] Studies using members of the tetracycline family in mice models of colitis (acute inflammation) showed that tetracyclines not only affect the gut microbiota composition, but also have immunomodulatory properties that can secondarily alter the microbiota.[37] A pronounced decrease in the proportion of reads of *Actinobacteria* was observed in antibiotic-treated mice. An additional concern is the metabolic effect of using antibiotics over a long period, either at low dose or with pulse therapy. Both tylosin and metronidazole has been shown to cause marked alterations of the jejunal and colonic microbiome and metabolome in healthy dogs.[38–40] There is limited information in dogs with CE, but no significant changes in the bacteria species studied were observed in ten healthy dogs treated with a combination of metronidazole and prednisolone after a 30 day washout.[41]

Only one antibiotic, oxytetracycline, was used in our study. Metronidazole, oxytetracycline, and tylosin are the most frequently used antibiotics for trials in dogs with CE.[21] There is no literature available to determine if one type should be favoured or to support the use of a different one in the absence of response with the first one. For this reason, it was decided to limit the trial to one type of antibiotic.

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The limited success of antibiotics and the need of on-going antibiotic treatment in some dogs in our study raises the question on whether antibiotics should play a role in the treatment of CE, or if alternative methods of manipulating the microbiome should be used instead. In one study in dogs, the use of a probiotic after tylosin treatment or of steroids after relapse was not successful in achieving long-term remission.[42] Similarly, sporadic studies of the benefit of probiotics in dogs with CE have not shown any tangible benefit.[41,43,44]

In the past decade, faecal microbiota transplantation (FMT) has been used to treat people affected by recurrent *Clostridium difficile* associated diarrhoea.[45] The evidence is sparse for FMT in the treatment of people with IBD, and there is currently no published information in small animal medicine for dogs with CE.[45] This treatment needs to be further assessed especially in dogs not responding to diet trials as an alternative to antibiotic trial.[46]

In our study, only two dogs required immunosuppressant treatment and a good outcome was achieved for both. However, ongoing low dose treatment was required. Chlorambucil was added as a steroid-sparing agent in one case that was diagnosed with protein-losing enteropathy and in the other case due to the requirements of long-term immunosuppressant treatment to control the polyarthropathy and excessive side-effects of steroids. Interpretation of this data remains limited given the small number of dogs in the IRE group.

Limitations of our study include the relatively small number of dogs that could be enrolled over several years. Another limitation was the case distribution (FRE vs ARE vs IRE) could not be predicted prior to starting the study. As a result, only two dogs with IRE were recruited precluding statistical analysis for this group. Recruitment occurred in two

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universities with a majority of FRE in both centres. The same core group investigators were present in both institutions so that the findings from this study is likely to be a true reflection of dogs' response rather than differences between institutions.

Another limitation includes the use of different food for the diet trials. However, as seen in our study, there is evidence that both hydrolysed and non-hydrolysed diet can be successful although long-term result is reported to be better with hydrolysed diet.[20] This flexibility also allowed for the use of dry and tinned food to accommodate for the preference of each dog, and was important in ensuring good compliance from the owners during the first two weeks of diet trial.

We did not use the option of home-cooked diet, but only commercially available diets. In a recent review, mislabelling (additional ingredients found) was reported in 33 to 83% of limited antigen diets tested, which could preclude the success of a diet trial.[47] We cannot exclude that some of the dogs that did not respond to our diet trial would have benefited from a home-cooked, limited-antigen diet.

Finally, some of the cases had a long-term follow up obtained by phone rather than a clinical assessment mostly due to travel distance. Although the information obtained cannot be verified, the assessment of the pet by the owner is the most important criteria of success.

In summary, our study suggests that in Australia, most dogs diagnosed with CE in a referral population have FRE. Strategies should be implemented to improve diagnosis and management of FRE dogs in general practice, as a majority of FRE dogs go into remission for a long duration. Also like other reports, ARE dogs were the second most represented

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group and although a good response was noted in the short term, the long-term remission was rare. Only two dogs required immunosuppressant treatment, and both were stabilised long-term on a low dose of prednisolone and chlorambucil.

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Tables

Table 1. Differences in demographics, duration of clinical signs, CCECAI, and follow up time between dogs diagnosed with FRE, ARE, and IRE.

	FRE (N=10)				ARE (N=7)				IRE (N=2)			
	n	Median	Min	Max	n	Median	Min	Max	n	Median	Min	Max
Age (months)	10	30	14	114	7	26	18	60	2	90	60	120
Weight (kg)	9	29.5	4.1	72.7	7	29.2	9.4	38.9	2	12.5	11.3	13.7
BCS (out of 9)	9	4	2	6	6	4	2	5	2	2.5	1	4
Duration of signs (months)	10	11.5	2	36	7	5	3	36	2	14	12	16
CCECAI before	10	6	3	12	7	7	5	12	2	6.5	6	7
CCECAI after	10	0	0	3	7	1	0	2	2	0	0	0
Follow up (months)	10	21.1	3.0	44.7	7	32.9	5.1	59	2	33.5	25.0	41.9

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ARE, antibiotic-responsive enteropathy; BCS, body condition score; CCECAI, canine chronic enteropathy clinical activity index (maximum score 24); IRE, immune-suppressive enteropathy; N, number in each group; n, number of dogs within each group.

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Table 2. Diet and long term follow up of dogs with CE after response to empiric trial.

Dog		Diet		Follow up		
		Trial	At follow up	Length (mo)	Current therapy	Outcome[1]
2	FRE	S	NR	3	None	R
3	FRE	H	H	36	None	R
4	FRE	S	S	3	None	R
5	FRE	S	S	3	None	R
6	FRE	H	S	32	None	PR[2]
9	FRE	H + S[3]	H	4	None	R
13	FRE	H	H	45	None	R
15	FRE	z/d	z/d	34	None	PR
16	FRE	H	Commercial	39	None	R
19	FRE	H + z/d[3]	S	11	None	R
1	ARE	S	S	5	AB q48h	Relapse
7	ARE	H + S	H	33	None	PR
8	ARE	H + S	H	23	AB q12h	PR
10	ARE	H + S	Limited antigen	59	AB pulse therapy Fluoxitine	PR
11	ARE	H + S	Commercial	34	None	R
12	ARE	H	H + chicken	14	AB q72h	R
18	ARE	H + z/d	Commercial	33	None	PR
14	IRE	H + z/d + SP	Commercial	42	Pred 2.5mg q48h	R[4]

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					Chlorambucil 2mg q72h	
17		z/d	z/d	25	Pred 5mg q48h Chlorambucil 2mg q48h Pancreatic enzymes	R[5]

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Supplement 1. Demographics, clinical signs, diagnosis, and clinical scoring of the dogs enrolled. Nineteen dogs responded to treatment and two dogs were excluded (dog 20 and 21).

Dog	Origin	Breed	Sex	Age	Weight	BCS	Signs		Outcome	CCECAI		Histology	
				(Mo)	(kg)	(out of 9)	Localisation	Duration (Mo)		Before	After	Before	After
1	MU	Labrador R.	FS	26	29.2	5	Lower GI	5	ARE	7	1	2	0
2	MU	Great Dane	MC	30	72.7	5	Lower GI	25	FRE	4	0	3	3
3	MU	SBT	MC	29	23	5	Mix GI	24	FRE	11	2	4	1
4	MU	GSD	M	15	31.3	4	Upper GI	2	FRE	3	0	1	4
5	MU	Toy Poodle	MC	30	6.7	5	Lower GI	18	FRE	9	0	5	0
6	UoM	Weimaraner	MC	21	27.6	2	Mix GI	3	FRE	4	0	2	0
7	UoM	Japanese Spitz	FS	18	9.4	5	Mix GI	4	ARE	8	2	1	0
8	UoM	GSD	M	44	38.9	4	Upper GI	3	ARE	9	0	2	0
9	UoM	Maltese cross	FS	60	NR	NR	Upper GI	12	FRE	6	0	3	4
10	UoM	GSD	FS	18	25.4	2	Mix GI	3	ARE	12	1	1	1
11	UoM	Basset Hound	M	35	33.2	NR	Mix GI	24	ARE	5	0	4	4
12	UoM	Border Collie	MC	60	21.0	3	Mix GI	36	ARE	5	1	3	0
13	UoM	Golden R.	MC	60	30.8	4	Mix GI	36	FRE	7	1	3	3
14	UoM	Spoodle	M	60	11.3	4	Lower GI	12	IRE	6	0	2	1
15	UoM	Labrador R.	FS	114	40.2	6	Mix GI	11	FRE	12	3	4	2
16	UoM	GSD	FS	14	29.5	3	Lower GI	6	FRE	6	0	2	0
17	UoM	Labrador R.	FS	120	13.7	1	Upper GI	16	IRE	7	0	4	1
18	UoM	Greyhound	FS	24	29.2	4	Upper GI	12	ARE	7	1	2	2
19	UoM	Chihuahua	MC	108	4.1	3	Mix GI	2	FRE	6	0	2	4
20	MU	Rottweiler	M	60	30.5	3	Mix GI	1	NA	12	NA	NA	NA
21	UoM	Whippet	FS	48	9.5	3	Mix GI	12	NA	9	NA	NA	NA

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ARE, antibiotic-responsive enteropathy; BCS, body condition score; CCECAI, canine chronic enteropathy clinical activity index; F, female; FRE, food-responsive enteropathy; FS, female spayed; GI, gastro-intestinal; GSD, German shepherd dog; IRE, immunosuppressant-responsive enteropathy; M, male; MC, male castrated; Mo, months; UoM, University of Melbourne; MU, Murdoch University; NA, not applicable; NR, not recorded; SBT, Staffordshire bull terrier.

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Supplementary material

Supplement 1. Demographics, clinical signs, diagnosis, and clinical scoring of the dogs enrolled. Nineteen dogs responded to treatment and two dogs were excluded (dog 21 and 22).

Legends

Figure 1. Flow chart of the treatment trials used in 19 dogs diagnosed with chronic enteropathy. ARE, antibiotic-responsive enteropathy (initial dosage: oxytetracycline 10mg/kg PO q12h); FRE, food-responsive enteropathy (selected protein or hydrolysed protein diet); IRE, immunosuppressant-responsive enteropathy (initial dosage: prednisolone 1mg/kg PO q24h $\pm$ chlorambucil 2-4mg/m^2 PO q24h).

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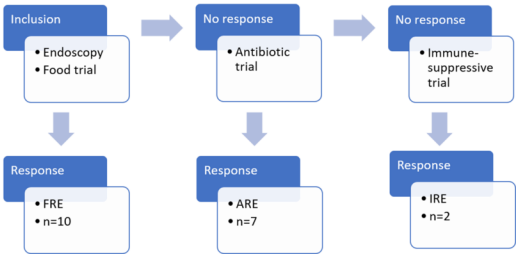

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