PAPER

The use of hydrolysed diets for vomiting and/or diarrhoea in cats in primary veterinary practice

A. Kathrani[1,*], D. B. Church*, D. C. Brodbelt†, C. Pegram† and D. G. O'Neil†

*Clinical Science and Services, Royal Veterinary College, North Mymms, Hatfield, AL9 7TA, UK
†Pathobiology and Population Science, Royal Veterinary College, North Mymms, Hatfield, AL9 7TA, UK

Corresponding author email: akathrani@rvc.ac.uk

Objective: To describe responses of cats prescribed a hydrolysed diet with or without concurrent medication for chronic vomiting and/or diarrhoea of undetermined aetiology.

Materials and Methods: Anonymised records of 512,213 cats under UK veterinary care in 2016 from the VetCompass database were searched using relevant terms for hydrolysed diets. The records of 5000 (90%) of 5569 cats with evidence of receiving a hydrolysed diet were randomly reviewed for gastrointestinal indication, prior and concurrent medication and response after hydrolysed dietary intervention. A poor response was defined as evidence of receiving antibiotic or glucocorticoid treatment for vomiting/diarrhoea at visits after the onset of the diet or death from gastrointestinal signs for at least 6 months follow-up.

Results: Of 977 cats prescribed a hydrolysed diet for chronic vomiting/diarrhoea, 697 (71%) were first prescribed the diet without concurrent antibiotics or glucocorticoids while 280 (29%) first received the diet with these medications. Thirty-four per cent of cats in the former group and 61% in the latter had a poor response. Cats older than 6 years and cats prescribed antibiotic and/or glucocorticoid for vomiting/diarrhoea before and concurrently with the diet had higher odds of poor response.

Clinical Significance: Although variations in our observations may reflect severity of signs or prescribing habits of primary-care veterinary surgeons, our study suggests there is merit in trialling a hydrolysed diet first as a sole therapy in cats with chronic vomiting/diarrhoea when diagnostic investigations do not reveal a cause, before resorting to antibiotic and/or glucocorticoid therapy for cases that respond poorly.

Journal of Small Animal Practice (2020), 1–9
DOI: 10.1111/jsap.13214

Accepted: 30 July 2020

INTRODUCTION

Feline chronic enteropathy (CE) describes a spectrum of diseases resulting in chronic gastrointestinal (GI) signs, with unknown aetiology (Willard 1999). However, the pathogenesis is hypothesised to involve the variable interplay of four key components; genetic susceptibility, environmental risk factors, intestinal dysbiosis and altered GI mucosal immune response (Jergens 2012). Definitive diagnosis of CE requires ruling out all known causes of chronic GI signs with extensive laboratory and faecal testing, trans-abdominal ultrasound and GI histopathology. Treatment often requires a sequential or combination approach with diet, antibiotics and immunosuppressive medication depending on the severity of the disease (Jergens 2012). However, the number of cats in primary practice that are treated empirically for CE, without extensive diagnostic tests, due to financial or logistical constraints or contraindications to general anaesthesia for collection of GI biopsies is suspected to be high.

Commercial hydrolysed, limited ingredient novel protein, highly digestible or high fibre diets have been used for suspected or confirmed feline CE (Nelson *et al.* 1984, Dennis *et al.* 1992, 1993, Hart *et al.* 1993, Guilford *et al.* 2001, Mandigers *et al.* 2010a, Laflamme *et al.* 2012, Perea *et al.* 2017). Although, only one small published study specifically evaluated the response to hydrolysed diets in cats with CE (Mandigers *et al.* 2010a), it is suspected that this category of diets is frequently used in suspected or confirmed cases of CE in cats in primary practice. Unfortunately, no information is currently available with regards to the use of hydrolysed diet for chronic GI signs of undetermined aetiology in cats in primary practice. Therefore, it is unknown how many cats that are empirically treated with a hydrolysed diet with or without concurrent medication for chronic vomiting and/or diarrhoea in primary practice subsequently return with on-going GI signs requiring treatment with antibiotic and/or glucocorticoid or are euthanased due to these signs. These results could assist veterinary practitioners and owners to build an evidence base for the application of hydrolysed diets within clinical management protocols for chronic GI signs in cats in the general population. These results will also help to provide a benchmark for the use of, and response to, hydrolysed diets in primary practice for chronic vomiting and/or diarrhoea in cats to allow for comparisons to future similar studies utilising alternative diets.

Therefore, using anonymised veterinary clinical data from the VetCompass™ Programme (VetCompass 2019), our study aimed to describe responses of cats prescribed a hydrolysed diet with or without concurrent antibiotic and/or glucocorticoid for chronic vomiting and/or diarrhoea of undetermined aetiology. A second aim was to determine if antibiotic or glucocorticoid use for vomiting and/or diarrhoea before or concurrently with the hydrolysed diet was associated with response.

METHODS

Study outcomes

The primary outcome of our study was to describe responses of cats prescribed a hydrolysed diet with or without concurrent antibiotic and/or glucocorticoid for chronic vomiting and/or diarrhoea of undetermined aetiology. A secondary outcome was to determine if antibiotic or glucocorticoid use for vomiting and/or diarrhoea before or concurrently with the hydrolysed diet was associated with response. The study population included all cats under primary veterinary care at clinics participating in the VetCompass Programme during 2016. Cats under veterinary care were defined as those with either (1) at least one electronic patient record (EPR) (VeNom diagnosis term, free-text clinical note, treatment or bodyweight) recorded during 2016 or (2) at least one EPR recorded during both 2015 and 2017. VetCompass collates de-identified EPR data from primary-care veterinary practices in the UK for epidemiological research (VetCompass 2019). Data fields available to VetCompass researchers include a unique animal identifier along with species, breed, date of birth, colour, sex and neuter status, and also clinical information from free-form text clinical notes, summary diagnosis terms (The VeNom Coding Group 2019) and treatment with relevant dates.

Study design

A cohort study of cats prescribed a hydrolysed diet for chronic vomiting and/or diarrhoea was undertaken within this VetCompass population. A single operator reviewed and performed all data extraction from the medical records. Chronic was defined as evidence of at least 2 weeks of clinical signs, and was consistent with previous publications assessing the effects of diet in cats with idiopathic GI signs (Dennis *et al.* 1992, 1993, Hart *et al.* 1993, Guilford *et al.* 2001). Identification of cats that were prescribed a hydrolysed diet involved initial screening of all 512,213 study cats for candidate hydrolysed diet cases by searching the treatment field using the terms zd, z/d, HA, hypoallergenic, anallergenic and allergy (Paiva 2013). This resulted in 5569 potential or candidate cases. Candidate hydrolysed diet cases were randomly ordered by the VetCompass programme and the clinical notes of 5000 (90%) candidate animals were reviewed in detail to evaluate for case inclusion.

Inclusion criteria

Inclusion criteria were: (1) first received a hydrolysed diet for persistent or intermittent vomiting and /or diarrhoea of at least 2 weeks duration, (2) there was no evidence of concurrent conditions that might additionally be associated with receiving these therapeutic diets, *e.g.* dermatological disease, (3) no evidence that the diet was refunded or discontinued within 1 month of dispensing, (4) referral notes were available if cases were referred for their GI signs, (5) had at least 6 months follow-up at the same practice unless they died or were euthanased due to their GI signs and (6) diagnostic investigations did not reveal an aetiology for the chronic vomiting and/or diarrhoea, apart from chronic inflammatory enteropathy (Table 1).

Exclusion criteria

Additional exclusion criteria included: (1) the cat was already receiving a hydrolysed diet for vomiting and/or diarrhoea at the first available EPR and therefore prior medical records regarding the GI signs were not available for review and (2) glucocorticoids were started within 1 week of first prescribing the diet for concurrent non-GI condition (Table 1, Fig. 1).

Data extraction

The medical records from all cats within the 5000 candidate cases selected, that met the inclusion criteria and none of the exclusion criteria, were reviewed in detail and the following information was extracted for each case: (1) whether dewormer, antibiotic or glucocorticoid had ever been prescribed for vomiting/diarrhoea at any visits before the visit where the hydrolysed diet was first prescribed. There was no time limit to when prior visits for vomiting/diarrhoea were evaluated and therefore this was dependent on the duration of medical records that were available for each case, (2) whether antibiotic or glucocorticoid was concurrently prescribed at the same visit as when the hydrolysed diet was first prescribed, (3) whether antibiotic or glucocorticoid was

Table 1. Summarises the methodology used for determining the response in cats to a hydrolysed diet with or without concurrent antibiotic and/or glucocorticoid for chronic vomiting and/or diarrhoea of undetermined aetiology

Search terms for HA diet revealed 5569 cats out of 512,213 (1.1%)

5000 out of 5569 (90%) cats randomly selected and coded

Inclusion criteria
- First received HA diet for V ± D of at least 2 weeks duration
- No concurrent conditions that might also be associated with receiving the HA diet (*e.g.* dermatological)
- Diet not refunded or discontinued within 1 month of dispensing
- Referral notes available if cases were referred for GI signs
- At least 6 months follow-up at same practice unless died or were euthanased due to GI signs
- Diagnostic investigations did not reveal an aetiology for the V ± D, other than CIE

Exclusion criteria
- Prior medical records unavailable if already receiving a HA diet for GI signs
- GC started within a week of starting the diet for non-GI condition

977/5000 cats (19.5%) met criteria

Following extracted from medical records of all 977 cats:

1. VISITS BEFORE HA DIET: whether DW, AB or GC prescribed for V/D
2. VISIT WHEN HA DIET FIRST PRESCRIBED: whether AB or GC prescribed with diet:

A. No concurrent AB or GC
B. Concurrent AB (without GC)
C. Concurrent GC (±AB)

3. VISITS AFTER THE HA DIET (at least 6 months FU):
- For cats in Group A: if AB or GC prescribed for on-going V/D
- For cats in Group B: if more AB or GC prescribed for on-going V/D
- For cats in Group C: if more GC or AB prescribed for on-going V/D at least 3 months after first starting the diet
- For all cats:
  - If non-GC anti-inflammatory/immunosuppressives prescribed for V/D
  - If cat died or was euthanased for GI condition
- SEX/NEUTER STATUS, BREED, COAT COLOUR AND AGE WHEN HA DIET FIRST PRESCRIBED

Abbreviations: HA hydrolysed, V vomiting, D-diarrhoea, GI gastrointestinal, DW dewormer, AB antibiotic, GC glucocorticoid, CIE chronic inflammatory enteropathy, FU follow up.

prescribed for vomiting/diarrhoea at a subsequent visit after the hydrolysed diet was first prescribed for a minimum follow-up period of 6 months. For those cases that received the diet with concurrent glucocorticoids, whether this medication was tapered and discontinued within the 3-month period after initiation of the diet was also extracted. Further information included (4) whether non-glucocorticoid anti-inflammatory or immunosuppressive medication was prescribed at subsequent visits for vomiting/diarrhoea after the hydrolysed diet was first prescribed and (5) whether the cat died or was euthanased for signs associated with their GI disease (Table 1).

Definition of poor response

A poor response was defined as evidence in the records of the cat receiving intervention with antibiotic or glucocorticoid for vomiting/diarrhoea at a subsequent visit after the diet was first prescribed or death was reported associated with the GI signs within the follow-up period of a minimum of 6 months. For those cases that received the diet with concurrent glucocorticoid, a poor response was defined as receiving intervention with further glucocorticoid or antibiotic for vomiting/diarrhoea at least 3 months after the diet was first prescribed or death from GI signs (Table 2).

Statistical analysis

Data were checked for internal validity and cleaning in Excel (Microsoft Office Excel 2013, Microsoft Corp.). The sex and neuter status, coat colour, breed and age of the cat when the hydrolysed diet was first prescribed were described.

Analyses were performed using a computer software package (IBM SPSS Statistics Version 26). Univariable and multivariable binary logistic regression modelling was used to assess the following variables for associations with the odds of a poor response: (1) age when the hydrolysed diet was first prescribed, (2) coat colour, (3) sex and neuter status, (4) breed, (5) pre-treatment subcategory; consisting of whether antibiotic and/or glucocorticoid had been prescribed for vomiting/diarrhoea at any visit before the hydrolysed diet being first prescribed and (6) treatment subcategory; consisting of whether antibiotic and/or glucocorticoid had been prescribed concurrently with the diet when first prescribed. Age was categorised as equal/less than 6 years or greater than 6 years based on the median cut-off of age for all cats. Coat colour and breed were categorised into 11 categories each, as depicted in Table 3. Sex and neuter status were categorised as male entire, male neutered, female entire and female neutered. Pre-treatment subcategory was categorised as (1) no antibiotic or glucocorticoid prescribed for vomiting/diarrhoea before the diet, (2) antibiotic but no glucocorticoid prescribed for vomiting/diarrhoea before the diet, (3) glucocorticoid but no antibiotic prescribed for vomiting/diarrhoea before the diet and (4) both antibiotic and glucocorticoid prescribed for vomiting/diarrhoea before the diet. Treatment subcategory was categorised as (1) hydrolysed diet without concurrent antibiotic or glucocorticoid, (2) hydrolysed diet with concurrent antibiotic (without glucocorticoid) and (3) hydrolysed diet with concurrent glucocorticoid (with or without antibiotic).

Variables associated with a poor response with a P-value <0.2 in the univariable analysis were taken forward into multivariable analysis. Multivariable models were built using a backward stepwise elimination method. All promoted variables were initially included, and the variable with the highest P-value was removed until all remaining variables had a P-value <0.05. Potential confounders were assessed by checking the removed variables for a marked change in the OR after re-addition to the final model. Collinearity was investigated by examining the variance inflation factor (VIF) and tolerance of

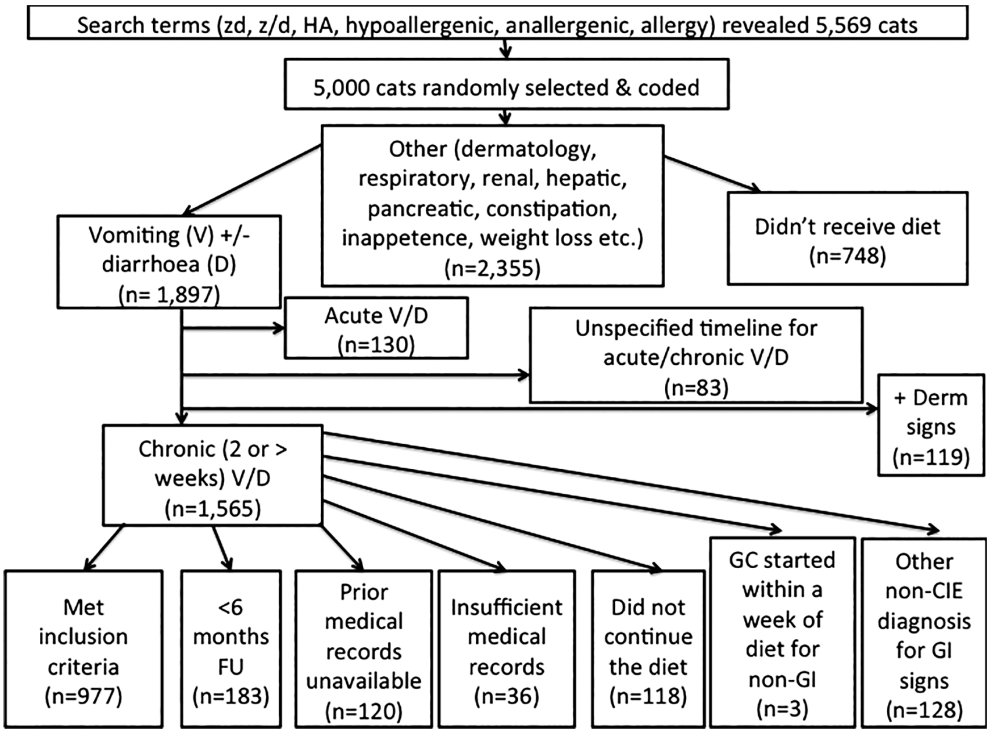

FIG 1. Flow chart demonstrating exclusion criteria used for our study. Cats were excluded if they were not receiving a hydrolysed diet (for example medical records subsequently showed the cat to be consuming hypoallergenic treats, or "allergy" was flagged as a treatment but did not pertain to a hydrolysed diet) (n = 748) or received a hydrolysed diet for other reasons that did not include vomiting and/or diarrhoea (n = 2355). Cats were excluded if they first received the diet for less than 2 weeks of vomiting and/or diarrhoea (n = 130) or the time-line for these signs were not specified in the records (n = 83). Also, those cats that had concurrent dermatological signs and this was also a reason for prescribing the hydrolysed diet were excluded (n = 119). For those cats that had first received the diet for vomiting and/or diarrhoea of at least 2 weeks duration but had less than 6 months of follow-up at the same practice, unless the cat died or was euthanased for GI signs were excluded (n = 183). Also, for those cats that were already receiving a hydrolysed diet for vomiting and/or diarrhoea at the time of first visit to the practice and therefore the duration, diagnostic investigations and prior treatment of these signs were unavailable for review were excluded (n = 120). Those cats that had been referred for the GI signs but the referral notes were unavailable for review were also excluded (n = 36). Additional exclusion criteria also included those cats that did not continue the diet, as the medical record showed that the diet had been refunded or specifically stated that the owners had stopped feeding the diet within 1 month of it being prescribed (n = 118) and if diagnostic investigations revealed an aetiology for the vomiting and/or diarrhoea that was not chronic inflammatory enteropathy (n = 128). Finally, three cats were excluded as they were prescribed glucocorticoids for non-gastrointestinal conditions (eosinophilic granuloma complex, regenerative anaemia and possible asthma) within 1 week of starting the diet. Abbreviations: Derm dermatology, FU follow-up, GC glucocorticoid, GI gastrointestinal, CIE chronic inflammatory enteropathy

Table 2. The number and percentages of poor response in cats prescribed a hydrolysed diet with or without concurrent antibiotic and/or glucocorticoid for chronic vomiting and/or diarrhoea of undetermined aetiology

Concurrent treatment when hydrolysed diet first prescribed	Definition of poor response	Number (percentage) with poor response	Median follow-up time (range)
No antibiotic nor glucocorticoid (n = 697)	Received intervention with antibiotic or glucocorticoid for vomiting/diarrhoea at subsequent visits after the diet was first prescribed or death from GI signs	240 cats (34%)	818 days (184–3809)
Antibiotic (without glucocorticoid) (n = 127)	Received intervention with additional antibiotic or glucocorticoid for vomiting/diarrhoea at subsequent visits after the diet was first prescribed or death from GI signs	71 cats (56%)	946 days (186–3599)
Glucocorticoid (with or without antibiotic) (n = 153)	Received intervention with further glucocorticoid or antibiotic for vomiting/diarrhoea at least 3 months after the diet was first prescribed or death from GI signs	100 cats (65%)	1082 days (213–3888)

the variables taken forward to the multivariable analysis, with collinearity indicated if VIF > 10 and tolerance <0.1 (Myers 1990, Menard 1995). Pairwise interactions were assessed between the final variables that were significantly associated with poor response. Model fit was assessed using the Hosmer-Lemeshow Test and by calculating the area under the receiver operating characteristic (ROC) curve (Hosmer & Lemeshow 2000).

RESULTS

Population summary of all cats

The study population included 512,213 cats under primary veterinary care at 876 veterinary clinics during 2016. The hydrolysed diet search terms found 5569 candidate cats of which a random subset of 5000 (90%) were randomly reviewed against the inclu-

Table 3. Univariable logistic regression analyses results for associations with the odds of a poor response in cats that were prescribed a hydrolysed diet with or without concurrent antibiotic and/or glucocorticoid for chronic vomiting and/or diarrhoea

Variable		Poor response N (%)	Good response N (%)	Odds ratio (95% confidence interval)	P-value
6 years of age and younger	Yes	153 (16.6%)	292 (31.7%)	–	–
	No	227 (24.7%)	248 (27.0%)	1.75 (1.34–2.28)	<0.001
Sex and neuter status	Male entire	33 (3.4%)	61 (6.3%)	–	–
	Male neutered	194 (19.9%)	246 (25.3%)	1.46 (0.92–2.32)	0.111
	Female entire	54 (5.5%)	55 (5.6%)	1.82 (1.03–3.20)	0.039
	Female neutered	129 (13.2%)	202 (20.7%)	1.18 (0.73–1.90)	0.500
Coat colour	Black and white	65 (6.7%)	91 (9.3%)	–	–
	Black	46 (4.7%)	81 (8.3%)	0.80 (0.49–1.29)	0.351
	Tabby	44 (4.5%)	75 (7.7%)	0.82 (0.50–1.34)	0.431
	Tortoiseshell	26 (2.7%)	39 (4.0%)	0.93 (0.52–1.68)	0.819
	Ginger	18 (1.8%)	29 (3.0%)	0.87 (0.45–1.70)	0.681
	Blue	23 (2.4%)	21 (2.1%)	1.53 (0.78–3.00)	0.212
	Ginger and white	17 (1.7%)	22 (2.3%)	1.08 (0.53–2.20)	0.828
	Tabby and white	11 (1.1%)	27 (2.8%)	0.57 (0.26–1.23)	0.153
	White	13 (1.3%)	14 (1.4%)	1.30 (0.57–2.95)	0.530
	White and grey	11 (1.1%)	15 (1.5%)	1.03 (0.44–2.38)	0.951
	Combination of all remaining coat colours	137 (14%)	152 (15.6%)	1.26 (0.85–1.87)	0.246
Breed	Domestic shorthair	221 (22.6%)	347 (35.5%)	–	–
	Domestic longhair	35 (3.6%)	52 (5.3%)	1.06 (0.67–1.68)	0.814
	British short hair	24 (2.5%)	28 (2.9%)	1.35 (0.76–2.38)	0.308
	Ragdoll	17 (1.7%)	21 (2.1%)	1.27 (0.66–2.46)	0.477
	Persian	13 (1.3%)	16 (1.6%)	1.28 (0.60–2.70)	0.525
	Maine coon	14 (1.4%)	8 (0.8%)	2.75 (1.13–6.66)	0.025
	Bengal	10 (1.0%)	9 (0.9%)	1.75 (0.70–4.36)	0.234
	Burmese	9 (0.9%)	5 (0.5%)	2.83 (0.94–8.54)	0.066
	Birman	6 (0.6%)	5 (0.5%)	1.88 (0.57–6.25)	0.300
	Domestic medium hair	3 (0.3%)	7 (0.7%)	0.67 (0.17–2.63)	0.569
	Combination of all remaining breeds	59 (6.0%)	68 (7.0%)	1.36 (0.93–2.01)	0.118
Pre-treatment subcategory	No AB or GC	139 (14.2%)	296 (30.0%)	–	–
	AB but no GC	168 (17.2%)	210 (21.5%)	1.70 (1.28–2.27)	<0.001
	GC but no AB	30 (3.1%)	13 (1.3%)	4.91 (2.49–9.71)	<0.001
	AB and GC	74 (7.6%)	47 (4.8%)	3.35 (2.21–5.09)	<0.001
Treatment subcategory	No concurrent AB or GC	240 (24.6%)	457 (46.8%)	–	–
	Concurrent AB (without GC)	71 (7.3%)	56 (5.7%)	2.41 1(1.65–3.54)	<0.001
	Concurrent GC (with or without AB)	100 (10.2%)	53 (5.4%)	3.59 (2.49–5.19)	<0.001

sion and exclusion criteria. A total of 977 of 5000 (19.5%) candidate cats met the case definition and inclusion criteria and were included in further analyses (Fig. 1). All 977 cats presented with chronic vomiting and/or diarrhoea of undetermined aetiology, of which 107 had inflammatory changes documented on intestinal histopathology.

The following diagnostic investigations were performed for the cats in our study: feline leukaemia and feline immunodeficiency virus testing in 127 (13%) cats, haematology and serum biochemistry in 704 (72%) cats, serum thyroxine concentration in 292 (30%) cats, faecal analysis (faecal parasitology, ±faecal culture, ±*Giardia* enzyme linked immunosorbant assay ±*Tritrichomonas foetus* polymerase chain reaction) in 424 (43%) cats, empirical deworming for GI signs in 457 (47%) cats, serum vitamin B12 and folate in 325 (33%) cats, pancreatic lipase immunoreactivity in 347 (36%) cats, trypsin like immunoreactivity in 218 (22%) cats, trans-abdominal ultrasound in 349 (36%) cats and intestinal histopathology in 123 (13%) cats, although for 16 cases, the results were not reported or reported as normal/unremarkable.

The median age of the 977 cats at the time the hydrolysed diet was first prescribed was 6.3 years (Interquartile range (IQR) 3.1-10.40, range 0.5-19.9). The most common breeds seen were: domestic shorthair (568, 58%), domestic longhair (87, 8.9%), British shorthair (52, 5.3%), Ragdoll (38, 3.9%), Persian (29, 3.0%) and Maine coon (22, 2.3%) (Table 3). The most common coat colours were: black and white (161, 16.5%), black (128, 13.1%), tabby (119, 12.2%), tortoiseshell (65, 6.7%), ginger (47, 4.8%) and blue (44, 4.5%) (Table 3). There were 107 (11%) entire females, 94 (9.6%) entire males, 333 (34%) neutered females, 440 (45%) neutered males and 3 (0.3%) unknown sex and neuter status.

Four hundred and ninety nine (51%) and 164 (17%) cats were prescribed antibiotic and glucocorticoid, respectively for vomiting/diarrhoea at visits before the hydrolysed diet was first prescribed, while 435 (45%) had no evidence of prior treatment with either therapy before dietary prescription.

Cats first prescribed the diet without concurrent antibiotic and glucocorticoid

Of the 697 cats (71% of all), first prescribed the hydrolysed diet without concurrent antibiotic and glucocorticoid, 457 (66%) did not have a poor response for a median follow-up time of 818 days (range 184-3809) (Table 2). Of the remaining 240 (34%) cats that had a poor response, 5 were euthanased or died due to GI

signs at a subsequent visit without receiving antibiotic or glucocorticoid for their vomiting/diarrhoea, 76 were prescribed antibiotic for vomiting/diarrhoea at a subsequent visit; 1 of which was ultimately euthanased for GI signs and 159 were prescribed glucocorticoid with or without antibiotic for vomiting/diarrhoea at subsequent visits, of which 38 of these ultimately died or were euthanased for GI signs. Of these 240 cats with a poor response, 18 also received other non-glucocorticoid anti-inflammatory or immunosuppressive medication at subsequent visits for vomiting/diarrhoea. Two cats received sulfasalazine, 5 cats cyclosporine, 8 cats chlorambucil, 2 cats chlorambucil and cyclosporine and 1 cat chlorambucil and sulfasalazine. Of these 18 cats, 6 died or were euthanased for GI signs at a subsequent visit.

Cats first prescribed the diet with concurrent antibiotic (without glucocorticoid)

Of the 127 cats (13% of total) first prescribed the diet with concurrent antibiotic (without glucocorticoid), 56 (44%) did not have a poor response for a median follow-up time of 946 days (range 186-3599) (Table 2). Of the remaining 71 cats (56%) that had a poor response, 34 were prescribed further antibiotic for vomiting/diarrhoea at a subsequent visit; 3 of which were ultimately euthanased for GI signs and 37 were prescribed glucocorticoid with or without antibiotic for vomiting/diarrhoea at subsequent visits, of which 8 ultimately died or were euthanased for GI signs. Of these 71 cats, 5 also received other non-glucocorticoid anti-inflammatory or immunosuppressive medication at subsequent visits for vomiting/diarrhoea. One cat received cyclosporine, 3 cats chlorambucil and 1 cat sulfasalazine. Of these 5 cats, 1 was euthanased for GI signs at a subsequent visit.

Cats first prescribed the diet with concurrent glucocorticoid (with or without antibiotic)

In the 153 cats (16% of total) that were first prescribed the diet with concurrent glucocorticoid (with or without antibiotic), 53 cats (35%) did not have a poor response for a median follow-up time of 1082 days (range 213-3888) (Table 2). Of the remaining 100 cats (65%) that had a poor response, 16 were euthanased or died due to vomiting/diarrhoea at a subsequent visit within 3 months of first receiving the hydrolysed diet and concurrent glucocorticoid. Eighty-four cats continued to receive glucocorticoid or were prescribed antibiotic or glucocorticoid for vomiting/diarrhoea at subsequent visits at least 3 months after first receiving the hydrolysed diet and concurrent glucocorticoid; 18 of which ultimately died or were euthanased for GI signs. Of these 100 cats, 8 also received other non-glucocorticoid anti-inflammatory or immunosuppressive medication at subsequent visits for vomiting/diarrhoea. Two cats received cyclosporine, 5 cats chlorambucil and 1 cat both cyclosporine and chlorambucil. Of these 8 cats, 4 were euthanased for GI signs at a subsequent visit.

Univariable and multivariable analysis of poor response for all cats

There were four variables that were liberally significant in univariable analysis and were promoted for multivariable analysis: the age of the cat when the hydrolysed diet was first prescribed, sex and neuter status, pre-treatment subcategory and treatment subcategory (Table 3). After accounting for the other factors, the final multivariable model showed that cats aged over 6 years when first prescribed the diet had increased odds of a poor response compared to cats that were 6 years of age and younger (OR 1.81, 95% CI: 1.37-2.40, $P < 0.001$) (Table 4). For the pre-treatment subcategory, cats that were prescribed antibiotic and cats that were prescribed glucocorticoids before the hydrolysed diet had increased odds of a poor response compared to those cats that received no antibiotic or glucocorticoid before the diet (OR 1.55, 95% CI: 1.14-2.11, $P = 0.005$ and OR 4.11, 95% CI: 2.00-8.43, $P < 0.001$, respectively) (Table 4). Cats that were prescribed both antibiotic and glucocorticoid before the hydrolysed diet had 2.42 times the odds (95% CI: 1.51-3.86, $P < 0.001$) of a poor response compared to those cats that received no antibiotic or glucocorticoid before the diet. In relation to the treatment subcategory, cats that were first prescribed the diet with concurrent antibiotic or glucocorticoid had increased odds of a poor response compared to those cats that received no antibiotic or glucocorticoid when the diet was first prescribed (OR 2.08, 95% CI: 1.38-3.11, $P < 0.001$ and OR 2.66 95% CI: 1.76-4.00, $P < 0.001$, respectively) (Table 4). Sex and neuter status, coat colour and breed were not associated with the odds of a poor response. Pairwise interaction showed no significant associations between the three variables in the final model. The Hosmer-Lemeshow test indicated good model fit ($P = 0.812$), and the area under ROC curve (0.679) indicated moderate predictive ability.

Table 4. Multivariable logistic regression analyses results for associations with the odds of a poor response in cats that were prescribed a hydrolysed diet with or without concurrent antibiotic and/or glucocorticoid for chronic vomiting and/or diarrhoea

Variable		Poor response N (%)	Good response N (%)	Odds ratio (95% confidence interval)	P-value
6 years of age and younger	Yes	153 (16.6%)	292 (31.7%)	–	–
	No	227 (24.7%)	248 (27.0%)	1.81 (1.37–2.40)	<0.001
Pre-treatment subcategory	No AB or GC	139 (14.2%)	296 (30.0%)	–	–
	AB but no GC	168 (17.2%)	210 (21.5%)	1.55 (1.14–2.11)	0.005
	GC but no AB	30 (3.1%)	13 (1.3%)	4.11 (2.00–8.43)	<0.001
	AB and GC	74 (7.6%)	47 (4.8%)	2.42 (1.51–3.86)	<0.001
Treatment subcategory	No concurrent AB or GC	240 (24.6%)	457 (46.8%)	–	–
	Concurrent AB (without GC)	71 (7.3%)	56 (5.7%)	2.08 (1.38–3.11)	<0.001
	Concurrent GC (with or without AB)	100 (10.2%)	53 (5.4%)	2.66 (1.76–4.00)	<0.001

DISCUSSION

This is the first study to describe response to commercial hydrolysed diets in cats with chronic vomiting and/or diarrhoea of undetermined aetiology under primary veterinary care. Overall in our study, 42% of cats that were first prescribed a hydrolysed diet with or without concurrent antibiotic and/or glucocorticoid had a poor response, as evidenced by further prescription of antibiotic and/or glucocorticoid therapy or death associated with the GI condition, for a minimum follow-up period of 6 months. Antibiotic and/or glucocorticoid administration before and concurrent with the diet were associated with higher odds of a poor response, although our study was unable to determine the causality behind this association. Possible explanations include the association of antibiotic and glucocorticoid usage with severity of GI signs, prescribing habits of primary care veterinary surgeons, for example clinicians more likely to use these medications before the diet are more likely to use them after the diet for episodes of vomiting/diarrhoea or, the effects of antibiotic and glucocorticoid on the intestinal microbiota and mucosal immune system, respectively reducing the effectiveness of a hydrolysed diet.

The treatment plan for suspected or confirmed CE often follows a sequential or combination approach with diet, antibiotics and glucocorticoids depending on the severity of signs (Jergens 2012). Therefore, antibiotic and glucocorticoid are likely to be used before, concurrently or subsequent to dietary intervention for those cases with more severe clinical signs. Studies have demonstrated that clinical disease activity scores are negatively correlated with treatment response and outcome in dogs (Allenspach *et al.* 2007, Kathrani *et al.* 2019) and the same is likely true for feline CE. Therefore, cats first prescribed a hydrolysed diet with concurrent antibiotic and/or glucocorticoid might be more severely clinically affected before therapy and therefore more likely to have a poor response. Further studies are needed to confirm the relative contributions from clinical disease severity and the use of concurrent antibiotic and/or glucocorticoid to the odds of a poor response.

Hypocobalaminaemia has also been shown to be a negative prognostic indicator in dogs with CE and may predict refractoriness to treatment (Allenspach *et al.* 2007). In cats, hypocobalaminaemia has been shown to be a negative prognostic indicator in alimentary lymphoma (Kiselow *et al.* 2008). In addition, cobalamin supplementation in cats with small intestinal disease and severe hypocobalaminaemia can help to improve clinical signs in most affected cats (Ruaux *et al.* 2005). Hypocobalaminaemia may also be associated with refractoriness to treatment in cats with CE (Jergens 2012). Although, in our study only a third of cats had serum cobalamin concentration measured, unfortunately we did not take into consideration the serum cobalamin concentration of these cats or the effect of additional supplementation on treatment response. Therefore, future studies will aim to determine the clinicopathological variables that help to predict treatment response to hydrolysed diets and the effects of concurrent cobalamin supplementation on this response in these cats. This will then help to confirm the relative contributions from hypocobalaminaemia and the use of prior or concurrent antibiotic and/or glucocorticoid to the odds of a poor response.

The majority of cats in our study were treated for suspected CE rather than definitive CE. Therefore, the cats first prescribed a hydrolysed diet with concurrent antibiotic and/or glucocorticoid may have had more severe clinical signs due to alimentary neoplasia rather than CE and therefore inherently a poorer response to treatment. Unfortunately, restricting our study to those cats that were definitively diagnosed with CE following intestinal histopathology would have eliminated almost 90% of the cats and would not have accurately reflected the overall population that commonly present to primary practices where these diets are empirically used before intestinal biopsy. In addition, to ensure our results were relevant to the majority of cats that are empirically treated with these diets in primary veterinary practice, there were no minimum required diagnostic tests for inclusion. However, further studies using defined population of cats with chronic vomiting and/or diarrhoea with standardised investigations performed, such as a minimum of retroviral testing, haematology, serum biochemistry, serum thyroxine for cats >6 years of age and faecal analysis or empirical deworming for cats with diarrhoea and ideally trans-abdominal ultrasound and further laboratory tests such as serum vitamin B12, folate, trypsin like immunoreactivity and pancreatic lipase immunoreactivity will help to inform primary care veterinary surgeons about cats that are the best candidates for treatment with these diets. Furthermore, defining the population of cats according to specific GI signs, such as vomiting alone or predominantly large intestinal diarrhoea will also help inform primary care veterinary surgeons about which specific GI signs may benefit from treatment with these diets.

Although the majority (71%) of the cats in our study were first prescribed a hydrolysed diet without concurrent antibiotic or glucocorticoid, these medications had been used for vomiting and/or diarrhoea before the initiation of the diet in over 50% of cases. In our study, the use of these medications before the use of the diet was associated with higher odds of a poor response. Although, this might have been due to the prescribing habits of primary care veterinary surgeons, for example clinicians more likely to use these medications before the diet are more likely to use them after the diet for vomiting/diarrhoea compared to those that did not use these medications before the diet. Another explanation for this finding includes the potential negative effect of antibiotics on the intestinal microbiota (Manchester *et al.* 2019). The possible resultant intestinal dysbiosis that may arise from the antibiotic may then subsequently affect the response to a hydrolysed diet. Similarly, glucocorticoids have an effect on the mucosal immune system by dampening inflammation (Coutinho & Chapman 2011), which may also subsequently affect the response to a hydrolysed diet. Further studies utilising randomised controlled trials rather than observational studies are needed to determine whether antibiotic or glucocorticoid use before a hydrolysed diet affects the outcome. Also, further studies are needed to support or refute the use of antibiotics in cats with chronic GI signs of undermined aetiology, due to the concerns regarding intestinal dysbiosis and antibiotic resistance with their use. Therefore, empirical use of antibiotics before, during or after multiple failed dietary trials utilising different

strategies should be cautioned against until more evidence for their efficacy is available in cats with chronic GI signs of undetermined aetiology.

For those cats that were first prescribed diet without concurrent antibiotic or glucocorticoid, only 34% showed a poor response. This is similar to canine studies assessing the effect of diet alone on CE or chronic GI signs (Craven *et al*. 2004, Allenspach *et al*. 2007, 2016, Volkmann *et al*. 2017). Similarly, when using a commercial hydrolysed diet, 66.6% of dogs with CE were categorised as food-responsive (Marks *et al*. 2002, Mandigers *et al*. 2010b). Unfortunately, our study is unable to report on the effectiveness of hydrolysed diets in cats with chronic vomiting and/or diarrhoea, as a control group of cats not receiving these diets was not included. Comparison to a control group of cats receiving a non-hydrolysed diet is important, as elimination of any causative dietary trigger in susceptible cats by transitioning to a different diet, whether hydrolysed or not may be enough to resolve the clinical signs. Therefore, future studies assessing the effects of specific dietary strategies in cats with chronic GI signs should include a control group and should also take the full dietary history of each cat into consideration to determine the likelihood of a dietary trigger causing the chronic GI signs. Furthermore, unlike the canine studies above, our study did not assess reduction in clinical signs or disease activity score following initiation of treatment. The reason for not assessing clinical response in our study was this measure was deemed as subjective and not a measure that could be consistently assessed from all clinical records, especially as the cat may not have returned to the practice if their signs had improved or completely resolved. Therefore, in order to ensure the outcome measure was more objective and reliably assessed from all clinical records, subsequent prescription of antibiotic and/or glucocorticoid for on-going vomiting/diarrhoea at visits after the diet was prescribed was chosen. Further, our study does provide a benchmark for the number of cats returning with GI signs receiving treatment with antibiotic and/or glucocorticoid after initiation of hydrolysed diet in cats in primary practice. This will allow comparisons with other treatments, such as antibiotic alone, glucocorticoid alone, probiotic or other dietary strategies known to be effective for chronic idiopathic GI signs in cats, such as commercial therapeutic GI, limited-ingredient novel protein, modified fibre or low carbohydrate diets. This will then assist with decision-making on the best dietary strategy for these cases or define which cats are most likely to benefit from each of these diets, especially as dietary management of these cases currently involves trial and error to determine the best strategy for the individual patient.

Our study showed that cats above the age of 6 years had significantly higher odds of poor response compared to cats 6 years of age and younger. A previous study in dogs showed that food-responsive enteropathy cases were significantly younger compared to those dogs with CE that were treated with glucocorticoids in addition to diet (Allenspach *et al*. 2007). Another study, specifically in cats demonstrated that those with food-responsive enteropathy were younger (Gianella *et al*. 2017). Although, our study showed the same, another reason for this finding may be that older cats included in our study were more likely to have presented with undiagnosed conditions including alimentary neoplasia compared to the younger cats and therefore would be more likely to have a poor response to diet with or without concurrent antibiotic and/or glucocorticoid.

Our study had the additional following limitations: data entry was primarily recorded for clinical use and not for research purposes and may have therefore included some errors. Cats with concurrent dermatological signs at the time the diet was prescribed were excluded because these cats may have received dietary and/or medical therapy primarily for these signs rather than for the GI disease. Therefore, our study did not assess those cats with concurrent GI and dermatological signs that may have been food-responsive. Our study included only those cats that had diarrhoea, vomiting or both. Therefore cats with GI disease that had clinical signs recorded solely as weight loss or hyporexia were excluded. Our study did not take into account the dose and duration of medications or severity of clinical signs, which may have all contributed to treatment response. Our study assumed that diets that were not returned were fed, especially in light of the manufacturers money-refund guarantee with therapeutic diets. The indoor/outside status of the cat and access to additional foods was not taken into consideration. However, a recent study suggested that dogs with food-responsive enteropathy did not need to receive these diets exclusively for effectiveness at controlling clinical signs (Allenspach *et al*. 2016). Also, as the medical records for each cat only goes as far back as their first presentation to that practice, the use of antibiotic or glucocorticoid for vomiting/diarrhoea before this first visit can not be completely excluded in those cats that were reported not to receive these medications before initiation of the diet. However, cases that mentioned prior GI signs or treatment at previous practices when the GI signs were first described in the record were excluded if their prior notes were unavailable for review. Finally, data were reviewed and extracted by a single operator, which may have resulted in more errors than if two independent operators had performed data extraction (Buscemi *et al*. 2006). Therefore, future similar studies will aim to include two independent operators for data review and extraction.

In conclusion, 42% of cats prescribed a hydrolysed diet with or without concurrent antibiotic and/or glucocorticoid for chronic vomiting and/or diarrhoea of undetermined aetiology had a poor response for a follow-up period of at least 6 months. Cats that received antibiotic and/or glucocorticoid before or concurrently with the diet had higher odds of a poor response. However, further studies utilising randomised controlled trials rather than observational studies are needed to determine whether antibiotic or glucocorticoid use before or concurrently with a hydrolysed diet affects the outcome. Nevertheless, our results suggest that there is merit in trialling a hydrolysed diet first as a sole therapy in cats with chronic vomiting and/or diarrhoea of undetermined aetiology before resorting to antibiotic and/or glucocorticoid therapy for cases that respond poorly.

Conflict of Interest

No conflicts of interest have been declared.

References

Allenspach, K., Wieland, B., Grone, A., *et al*. (2007) Chronic enteropathies in dogs: evaluation of risk factors for negative outcome. *Journal of Veterinary Internal Medicine* **21**, 700-708

Allenspach, K., Culverwell, C. & Chan, D. (2016) Long-term outcome in dogs with chronic enteropathies: 203 cases. *The Veterinary Record* **178**, 368

Buscemi, N., Hartling, L., Vandermeer, B., *et al*. (2006) Single data extraction generated more errors than double data extraction in systematic reviews. *Journal of Clinical Epidemiology* **59**, 697-703

Coutinho, A. E. & Chapman, K. E. (2011) The anti-inflammatory and immunosuppressive effects of glucocorticoids, recent developments and mechanistic insights. *Molecular and Cellular Endocrinology* **335**, 2-13

Craven, M., Simpson, J. W., Ridyard, A. E., *et al*. (2004) Canine inflammatory bowel disease: retrospective analysis of diagnosis and outcome in 80 cases (1995-2002). *The Journal of Small Animal Practice* **45**, 336-342

Dennis, J. S., Kruger, J. M. & Mullaney, T. P. (1992) Lymphocytic/plasmacytic gastroenteritis in cats: 14 cases (1985-1990). *Journal of the American Veterinary Medical Association* **200**, 1712-1718

Dennis, J. S., Kruger, J. M. & Mullaney, T. P. (1993) Lymphocytic/plasmacytic colitis in cats: 14 cases (1985-1990). *Journal of the American Veterinary Medical Association* **202**, 313-318

Gianella, P., Pietra, M., Crisi, P. E., *et al*. (2017) Evaluation of clinicopathological features in cats with chronic gastrointestinal signs. *Polish Journal of Veterinary Sciences* **20**, 403-410

Guilford, W. G., Jones, B. R., Markwell, P. J., *et al*. (2001) Food sensitivity in cats with chronic idiopathic gastrointestinal problems. *Journal of Veterinary Internal Medicine* **15**, 7-13

Hart, J. R., Shaker, E., Patnaik, A. K., *et al*. (1993) Lymphocytic-plasmacytic enterocolitis in cats — 60 cases. *Journal of the American Animal Hospital Association* **30**, 505-514

Hosmer, D. & Lemeshow, S. (2000) *Assessing the Fit of the Model*. John Wiley & Sons, New York, NY, USA

Jergens, A. E. (2012) Feline idiopathic inflammatory bowel disease: what we know and what remains to be unraveled. *Journal of Feline Medicine and Surgery* **14**, 445-458

Kathrani, A., Sanchez-Vizcaino, F. & Hall, E. J. (2019) Association of chronic enteropathy activity index, blood urea concentration, and risk of death in dogs with protein-losing enteropathy. *Journal of Veterinary Internal Medicine* **33**, 536-543

Kiselow, M. A., Rassnick, K. M., Mcdonough, S. P., *et al*. (2008) Outcome of cats with low-grade lymphocytic lymphoma: 41 cases (1995-2005). *Journal of the American Veterinary Medical Association* **232**, 405-410

Laflamme, D. P., Xu, H., Cupp, C. J., *et al*. (2012) Evaluation of canned therapeutic diets for the management of cats with naturally occurring chronic diarrhea. *Journal of Feline Medicine and Surgery* **14**, 669-677

Manchester, A. C., Webb, C. B., Blake, A. B., *et al*. (2019) Long-term impact of tylosin on fecal microbiota and fecal bile acids of healthy dogs. *Journal of Veterinary Internal Medicine* **33**, 2605-2617

Mandigers, P. J., Biourge, V. & German, A. J. (2010a) Efficacy of a commercial hydrolysate diet in eight cats suffering from inflammatory bowel disease or adverse reaction to food. *Tijdschrift voor Diergeneeskunde* **135**, 668-672

Mandigers, P. J., Biourge, V., Van Den Ingh, T. S., *et al*. (2010b) A randomized, open-label, positively-controlled field trial of a hydrolyzed protein diet in dogs with chronic small bowel enteropathy. *Journal of Veterinary Internal Medicine* **24**, 1350-1357

Marks, S. L., Laflamme, D. P. & Mcaloose, D. (2002) Dietary trial using a commercial hypoallergenic diet containing hydrolyzed protein for dogs with inflammatory bowel disease. *Veterinary Therapeutics* **3**, 109-118

Menard, S. (1995) Applied Logistic Regression Analysis, SAGE publications Inc, CA, USA

Ed Myers, R. (1990) Classical and Modern Regression with Application. 2nd edn. PWS-KENT, Boston, MA, USA

Nelson, R. W., Dimperio, M. E. & Long, G. G. (1984) Lymphocytic-plasmacytic colitis in the cat. *Journal of the American Veterinary Medical Association* **184**, 1133-1135

Paiva, S. (2013) A fuzzy algorithm for optimizing semantic documental searches. *Procedia Technology* **9**, 1-10

Perea, S. C., Marks, S. L., Daristotle, L., *et al*. (2017) Evaluation of two dry commercial therapeutic diets for the management of feline chronic gastroenteropathy. *Frontiers in Veterinary Science* **4**, 69

Ruaux, C. G., Steiner, J. M. & Williams, D. A. (2005) Early biochemical and clinical responses to cobalamin supplementation in cats with signs of gastrointestinal disease and severe hypocobalaminemia. *Journal of Veterinary Internal Medicine* **19**, 155-160

The Venom Coding Group. (2019) VeNom veterinary nomenclature [Online]. VeNom Coding Group. http://venomcoding.org. Accessed January 28, 2019

Vetcompass. (2019) VetCompass™ programme [Online]. London: RVC Electronic Media Unit. http://www.rvc.ac.uk/VetCOMPASS/. Accessed March 5, 2019

Volkmann, M., Steiner, J. M., Fosgate, G. T., *et al*. (2017) Chronic diarrhea in dogs – retrospective study in 136 cases. *Journal of Veterinary Internal Medicine* **31**, 1043-1055

Willard, M. D. (1999) Feline inflammatory bowel disease: a review. *Journal of Feline Medicine and Surgery* **1**, 155-164