Are Novel Allergen or Hydrolysed Diets an Effective Means of Reducing the Gastro-intestinal Signs in Dogs With Inflammatory Bowel Disease When Compared to Oral Prednisolone?

A Knowledge Summary by

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KNOWLEDGE SUMMARY

Clinical bottom line

Novel allergen or hydrolysed diets are a valid modality for the management of gastro-intestinal symptoms in dogs with chronic enteropathy, however bias in case selection in the literature means a direct comparison of dietary modification versus prednisolone was not able to be achieved. Further prospective trials would be needed to better answer this PICO.

Question

In (dogs with chronic enteropathy) is the (use of either a novel allergen or a hydrolysed diet) as effective as the (use of prednisolone) in (controlling the gastro-intestinal signs)?

Clinical Scenario

You have just obtained some histopathology results regarding Eric, a 4 year-old male neutered Staffordshire bull terrier. He has a 4 month history of intermittent, bilious vomiting twice a day and small intestinal diarrhea approximately once every 2-3 days although his stool always seems a bit soft. However, he remains bright and well in himself. He is a healthy weight, and in good body condition score (BCS 5/9). After a course of fenbendazole failed to improve the situation you performed routine haematology, biochemistry and urinalysis (which were unremarkable, including serum TLI, folate and cobalamin) in addition to abdominal ultrasonographic examination. You then elected to proceed to gastroduodenoscopy with mucosal biopsy. The biopsies documented the presence of a mild lymphoplasmacytic enteritis, confirming your suspicions of a chronic enteropathy. Normally, you would lean towards prescribing prednisolone at this time however Eric's owner is not keen on him having steroids unless absolutely necessary, having read about their side effects on the internet. The practice's new graduate recently said something about using hypoallergenic diets for cases like these and you are interested to know if this would be a suitable option for Eric instead of prednisolone.

Summary of the evidence

IBD: Inflammatory bowel disease

CIBDAI: Canine Inflammatory Bowel Disease Activity Index. Score 0-3= clinically insignificant disease. 4-5= mild IBD. 6-8= moderate IBD. >9= severe IBD.

CCECAI= Canine Chronic Enteropathy Clinical Activity Index. Score 0-3= clinically insignificant disease. 4-5= mild IBD. 6-8= moderate IBD. 9-11= severe IBD. >12= Very severe IBD.

Allenspach (2007)	
Population:	Dogs with signs of chronic enteropathy (vomiting or diarrhea 6+ weeks).
Sample size:	70 dogs (n=70).
Intervention details:	-Follow up information was available for 3 years (monthly updates) with repeat examinations should symptoms worsen. -All dogs had other causes of their symptoms eliminated and histological evidence of inflammatory intestinal infiltrates was documented. -No dog received antibiotics or corticosteroids or antacids for 2

	weeks prior to entering the trial. -Prior to referral, dogs received fenbendazole (50mg/kg SID 5 days) -All dogs received haematology, biochemistry (inc. TLI, folate and cobalamin), urinalysis, faecal analysis (smear, culture, zinc flotation), CRP measurement and abdominal ultrasound. -All dogs given a CIBDAI score. -An endoscopy score was given to each dog for the duodenum and colon (0 being normal- 3 severe changes to mucosa/ difficulty insufflating). -5 biopsy specimens were examined and graded with mild (infiltrative cells but normal architecture) to severe (infiltrates with extensive architectural distortion and epithelial immaturity/areas of epithelial necrosis). -Dogs given elimination diet for 10 days; improvement = assigned "food responsive". No improvement means assigned to "steroid-treatment group".2mg/kg/d PO for 210 days, tapered over 10 weeks. -Dogs in food responsive group re-evaluated after 4 weeks with repeat CIBDAI score and endoscopy/ histopathology scores assigned. -The steroid responsive group was re-evaluated in the same way after 10 weeks. Steroids had been stopped 2 weeks prior to this. -All dogs received elimination diet exclusively for 14 weeks. -Dogs not responding to prednisolone underwent a second 10 week course. These dogs received ciclosporine 5mg/kg PO for 10 weeks before repeat endoscopy.
Study design:	• Prospective clinical trial.
Outcome studied:	• To establish predictors of a negative outcome (euthanasia due to refractory symptoms).
Main findings: (relevant to PICO question):	• 39 dogs were in the food responsive group. • 21 dogs required prednisolone in addition to the elimination diet. • 10 dogs classified as having protein-losing enteropathy (PLE) as they had panhypoproteinaemia with severe hypoalbuminaemia (mean albumin 11.3g/L SD 3.19 range 10-18g/L ref 24-35g/L and ascites +/- pleural effusion/peripheral oedema). • Variety of breeds represented. • No statistically significant difference in the sex distribution between groups. 34 females overall (22 spayed) and 36 males (15 neutered). • Mean age 5.3yrs (range 6m- 13yrs). Mean age of food responsive group 3.5yrs (range 0.6-7.6) which was significantly less than the steroid responsive group; mean age 6.52yrs, range 2.1- 13yrs. • Only 1 dog died in the food responsive group in a 3 year follow up period. • On a provocation diet, 31/39 dogs did not re-develop clinical signs and remained symptom free. In the other 8 dogs signs did recur so food intolerence was suspected.

	• 10 dogs in ST group responded to the initial therapy and did not relapse for 3 years. A further 3 patients in the steroid group were euthanased after the steroid trial and the remaining 8 dogs received ciclosporine, which saved 2 dogs from euthanasia. • Dogs with large intestinal signs were more likely to be food responsive. • The CIBDAI was significantly lower in the food responsive group than in the steroid-responsive group. • Dogs in the food responsive group improved significantly more than the steroid responsive group. • CIBDAI was median score 6.3, range 2-12 initially, which decreased to 1.2, range 0-7 afterwards. In the steroid group the median starting score was 8.3, range 2-15 versus 5.5, range 0-16 after intervention.
Limitations:	• Only 10 days allowed for dogs to be food responsive (this can take 4 weeks). • The data collected here was part of a larger trial with the University of Bern. • Small Intestinal Bacterial Overgrowth was not excluded first. • The diet used was salmon and rice, not a hydrolysed diet and so it is possible that some dogs who did not respond favourably to this diet may have responded better to a hydrolysed protein diet. • The overall severity of disease in a patient may have affected their likelihood of responding to dietary manipulation.

Craven (2004)	
Population:	Dogs with idiopathic inflammatory bowel disease (histologically confirmed) between 1995 and 2002.
Sample size:	80 dogs (n=80).
Intervention details:	• Case records were reviewed and owners contacted by telephone to complete a questionnaire over the phone. • Referring vets were also contacted for additional information if required. • Dogs were classed as being in either remission (complete control of signs for 6m+), intermittent signs (every 14 days or more) or uncontrolled disease (signs seen more frequently than every 14 days). • Owner gave an assessment of quality of life. • Animals excluded if gastric mucosa inflammation present alone in presence of helicobacter.
Study design:	Retrospective observational study.
Outcome studied:	Control of clinical signs.

Main findings: (relevant to PICO question):	• Median age 4.3yrs (range 6m-14yrs). 49 male dogs (11 neutered) and 31 female (23 neutered). • Median duration of clinical signs prior to diagnosis was 9.5 months (range 0.5-78) • Intestinal biopsies were diagnostic in 70/77 dogs. 2 dogs found to have infiltration in the sub-mucosa. • Prednisolone was the most commonly prescribed medication. 45/74 dogs receiving medication had this (61%). • 13/20 dogs with upper intestinal disease received immunosuppressive therapy. 17/32 dogs with lower intestinal disease received immunosuppressive treatment as did 17/22 dogs with diffuse disease. There was no significant difference between treatment and outcome in these groups. • 38 dogs received prescription diets. This was continued in 30 dogs and diet was not known for the remaining 6 dogs. Diet type was not associated with outcome. • Quality of life was available for 53/74 dogs at follow up. No dogs decreased in quality of life after treatment and quality of life was significantly associated with the outcome of treatment. • 21/80 dogs were in remission at follow-up. Of these, 19 were on no treatment and 2 received pulse therapy. Median duration of remission was 14 months (range 6-55). • 50% of dogs had “intermittent” signs for a median 17 months (range 7-64) and 26 dogs received treatment. 8 dogs received pulse therapy and 18 dogs received continuous treatment. Median relapse frequency was 3 months, range 14 days-5 months. • 3 dogs afterwards had uncontrolled IBD, of median duration 19 months (range 10-25 months). • 10 dogs were euthanised due to refractory IBD. 6 dogs died due to unrelated reasons. • The duration of clinical signs was not correlated with outcome. • There was no association between the outcome and the site, type or severity of disease, although hypoalbuminaemia was associated with a negative outcome more strongly.
Limitations:	• Retrospective study has inherent limitations associated with it, including a higher risk of bias. • Dogs not re-examined, merely owner responses to telephone questionnaire. - No direct comparison between the use of prednisolone and a hydrolysed diet is possible. • The authors merely state that a “prescription” diet was used. The exact details of the diet used are not known.

Kawano (2016)

Population:	Dogs diagnosed with chronic enteropathy (diagnosed by endoscopic biopsy), that did not respond to 2 weeks of antibiotics (metronidazole, ampicillin or fluoroquinolone) and did not receive any immunosuppressive agents in the 2 weeks prior to enrollment. Endoparasites were ruled out by faecal smear and zinc sulphate flotation.
Sample size:	n=32
Intervention details:	• All dogs received the elimination diet for at least 10 days. The diet was selected based on the Lymphocyte Proliferation Test (LPT). If a food resulted in a lymphocyte proliferation index >1.2% then the allergen was excluded in the diet trial. • A positive response to a diet trial (gastro-intestinal symptoms improved) meant they were classified as "food responsive" • If the dog failed to improve on the elimination diet, then glucocorticoids were prescribed (prednisolone 0.5-2mg/kg/day). • Improvements meant they were classified as "steroid responsive". • Serum albumin was measured in all cases, <20g/L defined hypoalbuminaemia.
Study design:	Prospective clinical trial.
Outcome studied:	Improvement in the gastro-intestinal symptoms.
Main findings: (relevant to PICO question):	• Average age of patients: 5.33 years (range 4 months-13 years) • 31/32 cases displayed a positive LPT to 2+ allergens. 1 dog showed 0 response to LPT. • After the elimination diet, 18/32 dogs were classified as food-responsive. • The remaining 14 were steroid responsive. • Successful diets used included Anallergenic (n=8), Select Protein (Royal Canin D&T; n=1), z/d ULTRA allergen-free (n=2) and w/d (n=1: Hills), home-made diets (n=2) and D Assist KO Select Protein (n=1: Eukanuba). • Histopathology documented 25 dogs suffered from lymphocytic-plasmacytic enteritis (13 dogs were in the steroid group, other 12 were food responsive), 3 dogs had eosinophilic enteritis and 4 dogs had "minimal change". • Dogs who were steroid responsive had a higher CCECAI score than dogs who were food responsive. 8.6 (mean; SD 3.3) versus mean 6.4 (SD 2.8) for food responsive. Overall mean was 7.4; range 1-13. This difference was not statistically significant. • 10 dogs had hypoalbuminaemia. 8 of these were steroid responsive and 2 food responsive. • Animals with minimal change are advised to undergo dietary management first.

Limitations:	• No dietary provocation tests performed. • Not all animals received a hydrolysed diet; some only received restricted antigen diet. • The LPT is not a definitive test and the presence of positive response to food allergens on immunology testing in dogs with suspected intolerances is controversial. • It is often recommended to allow 4 weeks to see an effect from dietary trials; some dogs were only provided with the diet for 10 days. • Not all dogs will have been through the same protocols so standardisation is an issue with this study. This may have introduced a selection bias that favored dogs with milder disease. • Not a large amount of patients, and there was no long term follow-up.

Mandigers (2010)	
Population:	Dogs with chronic enteropathy.
Sample size:	26 dogs (n=26)
Intervention details:	• Dogs were assigned to receive either a hydrolysed diet (18 dogs) or a highly digestible diet (8 dogs) after diagnosis of a chronic enteropathy (histologically confirmed). • Dogs were re-evaluated 3 times: at 3, 6-12 and 36 months. • Outcome measures included response of clinical signs (complete, partial or none), change in severity of signs (CIBDAI), change in body weight and need for further therapy. • Only dogs with signs of small intestinal disease were enrolled. • Dogs were excluded if they had received corticosteroids in the preceding 3 weeks or if hypoproteinaemia was preset. • Dogs not responding at the time of first follow up then other treatments added as needed. If a dog had responded then the dog was challenged with the previous diet for 7 days to see if it was an adverse food reaction. • At second follow up, repeat endoscopy was performed if the owner consented and other therapies offered if they had relapsed. Other therapies were also available if relapse occurred at the final re-evaluation. • Complete response: all signs resolved/returned to normal for the animal. Partial response meant signs were at least 50% improved, but not entirely normal.
Study design:	Randomised, controlled clinical trial (non-blinded).
Outcome studied:	To determine if a hydrolysed diet was superior in managing the symptoms of chronic enteropathy compared to a highly digestible diet.

Main findings: (relevant to PICO question):	• Despite randomisation, the CIBDAI was higher in the test diet group. • Most dogs responded at first evaluation, with no significant difference between groups. However, significantly more dogs remained asymptomatic at the 2nd and 3rd re-evaluation, with a significantly greater decrease in CIBDAI. • There was no significant difference between groups in terms of duration of clinical signs or patient age/sex/breed/body weight. • At first re-evaluation 16/18 dogs had responded to a test diet. 12 complete, 4 partial. 7/8 dogs responded to a control diet; 6 fully 1 partially. CIBDAI decreased significantly in both groups, but the test diet group decreased significantly more. Bodyweight increased significantly in the test diet group (median increase 4%; range 3-22%) with 13 dogs increasing, 1 dog decreasing and 4 dogs being stable. The control group bodyweight did not change significantly. (median 0%, range -9-17%. 4 dogs increased, 2 dogs decreased and 2 dogs were stable. Body weight not significantly different between groups though. • 4 of 6 dogs in the test diet group relapsed on dietary challenge and 4 of 6 of dogs on the control diet relapsed on challenge. • 22/23 dogs came for 2nd evaluation (other dog died of unrelated causes). • 13 dogs on test diet remained asymptomatic, other 2 dogs were partial responders. 2 of 7 control dogs remained asymptomatic, with a higher CIBDAI for this group. • Dogs in control diet group were offered alternative therapies. • At the final follow up, 20/23 dogs were still on the trial. 14 were in the test group, 6 from the control group. 1 test group dog experienced occassional symptoms and 2 did so after dietary indiscretion. Only 1 dog in the control group was still in remission. Other dogs were given alternative therapy.
Limitations:	• Results were based on subjective interpretation of clinical signs; repeatability of results may be difficult to achieve. • There was no group receiving prednisolone therapy in this trial so cannot compare the 2 modalities of treatment. • Selection bias is present in that patients with potentially more severe disease were excluded from the trial. • There is a potential conflict of interest with the authors • Many dogs had eosinophilic infiltrates on histopathology, which is different to the findings outlined in the PICO.

Marks (2002)	
Population:	Dogs with confirmed inflammatory bowel disease. All dogs had chronic vomiting and diarrhea of more than 3 months duration.

Sample size:	6 dogs (n=6)
Intervention details:	• Dogs were fed Purina HA HypoAllergenic diet; enzymatically hydrolysed and defatted soy globulin diet. • Prior to starting the diet trial all dogs had a faecal flotation test that was negative for parasites, physical examination and endoscopic examination ruling out other gastro-intestinal pathology and histologically confirmed inflammation of the stomach or duodenum. • Owners completed a questionnaire every 2 weeks for 10 weeks and repeat endoscopic examination was performed at the end of 10 weeks. • Dogs were recruited over a 6 month period. • All dogs were fed twice a day with the test diet according to their calculated energy requirement (132 X $BW_{kg}^{0.75}$) • Owners assessed faecal consistency daily, with an average figure collected every 2 weeks. • "Moderate improvement" represented a 50% improvement in faecal consistency or a 50% reduction in the frequency of vomiting. "complete resolution" was also an option. • Biopsies were examined in a blinded and randomised fashion by a single pathologist and a semi-quantitative score was assigned to the samples (0-3 as previously described).
Study design:	Non-randomised clinical trial.
Outcome studied:	Whether or not dogs improved after a hydrolysed diet and whether or not there was a histological improvement in the degree of mucosal inflammation.
Main findings: (relevant to PICO question):	• Mean age was 3.3 years, range 1.5- 9 years. • Duration of vomiting and diarrhea was a mean of 9months, range 3- 18 months. • 5 dogs had previously failed to respond to a variety of other medical therapies (excluding corticosteroids) including novel protein diets. • Faecal scores improved from a mean of 91.7 to 42.5 after dietary therapy. • 4 dogs achieved an "adequate" level of clinical benefit in terms of faecal consistency and 2 of these 4 achieved complete resolution of the diarrhea within 3 days. The other 2 dogs experienced a marked improvement over 12 days. • For one dog, a complete improvement was not made despite an improvement in faecal consistency and intermittent bouts of diarrhea persisted. • 2 dogs required additional medical therapy, although 1 dog was subsequently diagnosed with inflammatory bowel disease with concurrent exocrine pancreatic insufficiency. • Another dog displayed a moderate improvement in the symptoms, which completely resolved after the addition of metoclopramide.

Limitations:	• There was no control diet used and no group receiving prednisolone to allow for direct comparison between the 2 treatment modalities. • There was no long term follow-up information available. • There was no mention of a trial of anti-parasitic medicine to definitively eliminate endoparasites. • Only 1 hydrolysed diet was used; sometimes multiple hypoallergenic diets are required so there is a chance that the non-responders may have responded to an alternative diet. • Only a small study population was used.

Appraisal, application and reflection

The evidence available generally consisted of prospective clinical trials. These generally followed a similar set of inclusion criteria and diagnostic protocol, which allows for greater consistency in the results between papers. However no papers directly compared the use of a hydrolysed diet to the use of prednisolone; prednisolone was often used after dietary manipulation had failed and so it has not been possible to directly compare the 2 treatment modalities. There is a definite paucity in studies looking at long term follow up in dogs after a successful response to a hypoallergenic diet in the short term and so this would be interesting to consider for the future.

Selection bias was probably the most significant issue with the studies appraised above. The inclusion criteria many authors used played a big role in determining which intervention an animal received and the method used meant that only animals who were seemingly more affected progressed onto prednisolone therapy. This is less ideal from an efficacy perspective as it would be ideal to know which intervention yielded a greater response when directly compared. This would also be worthy of consideration for the future.

Methodology Section

Search Strategy	
Databases searched and dates covered:	Pubmed (1900 – 2017); CAB Abstracts (1983 – 2016)
Search terms:	(Dog OR dogs OR canine) (prednisolone OR diet OR food OR hydrolysed OR hydrolyzed OR hypoallergenic) (inflammatory bowel disease OR IBD OR chronic enteropathy OR food responsive enteropathy)
Dates searches performed:	30th August 2016

Exclusion / Inclusion Criteria	
Exclusion:	Articles that were not relevant to the PICO, articles not available in the English language and articles where the full text was not available. Review articles and case reports were also excluded.
Inclusion:	Original prospective or retrospective studies relevant to the PICO where the full text was available to examine.

Search Outcome						
Database	Number of results	Excluded – not available in the English language	Excluded – case reports	Excluded – review article	Excluded – not relevant to the PICO	Total relevant papers
NCBI PubMed	140	2	4	15	114	5
CAB Direct	26	0	0	1	25	0
Total relevant papers when duplicates removed						5

CONFLICT OF INTEREST

The author declares no conflicts of interest.

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