The role of diet in managing inflamatory bowel disease affected dogs: a retrospective cohort study on 76 cases

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Inflammatory bowel disease,
Hydrolyzed protein,
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Summary
The term inflammatory bowel diseases (IBD) refers to a group of idiopathic, chronic intestinal diseases characterized by a diffuse infiltration of inflammatory cells into the *lamina propria* of the intestine. The pathogenesis of IBD is unknown. The most common signs described are diarrhoea, vomit, and progressive weight loss. In order to make a definitive diagnosis, though, the presence of inflammatory cells infiltration must be evident on histopathologic analysis. The therapeutic approach has 2 main goals: decrease the inflammatory response and remove possible antigenic sources, such as food components or intestinal microflora. Therefore, the most common therapy is the association of Prednisone with a single protein diet, especially when the inflammatory cells infiltration is severe. Another way to reduce the antigenic stimulation is to control the intestinal microflora, so antibiotics and pre/probiotics may be used. This retrospective study tested and compared the therapeutic value of Prednisone and specific diets, used as a single therapy or combined together. The results show a significative clinical improvement in dogs fed with hydrolized protein diets rather than novel protein diets. Finally, fish is the more reliable source of protein to use during therapy, because of its low ability to trigger an antigenic reaction.

Il ruolo della dieta nella gestione di cani affetti da malattie infiammatorie croniche intestinali: studio retrospettivo su 76 casi

Parole chiave
Malattia infiammatoria cronica intestinale,
Proteine idrolisate,
Nuova fonte proteica.

Riassunto
Il termine IBD indica un gruppo di patologie enteriche croniche caratterizzate da infiltrazione di cellule infiammatorie a livello della lamina propria dell'epitelio intestinale. La patogenesi della malattia infiammatoria intestinale è sconosciuta ma, in base alle conoscenze relative alla corrispondente patologia umana (Morbo di Chron), si ritiene che l'evento preponderante sia rappresentato dalla "rottura" della tolleranza immunologica nei confronti di antigeni normalmente innocui, flora batterica commensale e componenti alimentari. Il quadro clinico correlato all'IBD è variabile in funzione della gravità dell'infiltrato e della porzione ed estensione di tratto gastroenterico colpito. I segni più frequenti sono diarrea, vomito e dimagramento progressivo. La diagnosi definitiva può essere emessa soltanto sulla base del riscontro istopatologico di cellule infiammatorie a livello della lamina propria. I protocolli terapeutici utilizzati ad oggi nel cane variano a seconda della gravità della patologia e hanno due scopi principali: limitare la risposta infiammatoria cellulo-mediata ed eliminare gli stimoli antigenici che possono scatenare la flogosi. Pertanto, sono ampiamente diffusi l'uso di farmaci immunosoppressori e l'adozione di diete specifiche è ampiamente diffuso, pertanto. Inoltre, si può agire anche a livello di flora microbica intestinale attraverso antibiotici e prodotti pre o probiotici. In questo studio retrospettivo è stata valutata e confrontata l'efficacia terapeutica di glucocorticoidi e diete specifiche, sottolineando come l'impiego di alimenti dedicati sia imprescindibile per avere buoni risultati e remissione della sintomatologia a lungo termine. Nello specifico, sono state contrapposte diete contenenti proteine, idrolisate e non idrolisate, evidenziando una maggiore percentuale di risposta a trattamenti che includessero il primo tipo di fonti proteiche. Infine, tra le diverse proteine di origine animale, le più efficaci nell'ausilio alla terapia per l'IBD sono state pesce, pollo e tacchino.

Introduction

The term Inflammatory Bowel Diseases (IBD) refers to a group of idiopathic, chronic intestinal diseases characterized by a diffuse infiltration of inflammatory cells into the *lamina propria* of the intestine (Nelson *et al.* 1988).

The pathogenesis of canine IBD is not completely understood, but there are some indications and theories in both human and veterinary research studies. The intestinal inflammatory response is thought to arise from an altered interaction among the mucosal immune system, gut microbes, and/or food components (Washabau *et al.* 2010). The reason for this impaired immunoregulation is not fully known, but there is evidence of genetic predisposition in several breeds, including German Shepherds, Boxer dogs, Shar-Peis, Soft Coated Wheaten Terriers, and Basenjiis (Simpson and Jergens 2011).

Dogs affected by IBD show chronic intestinal signs such as vomit, diarrhoea and progressive weight loss. In order to classify the condition severity, 2 clinical scoring systems are available: the Canine Inflammatory Bowel Disease Activity Index (CIBDAI) and the Canine Chronic Enteropathy Clinical Activity Index (CCECAI) (Allenspach *et al.* 2007). However, a complete classification should also include characteristics and severity of histopathological findings.

Given these hypotheses on IBD pathogenesis, its therapy has 2 main goals: to reduce the host's inflammatory response and to minimize antigen exposure. To achieve those goals, treatment protocols may include immunosuppressive drugs, a specific diet, and antibiotics.

Over the past few years, it has become clear that not every IBD patient needs the protocol mentioned above (Guilford *et al.* 2003). In fact, the use of immune-suppressants is recommended only in moderate or severe cases (CIBDAI 6-9), where the inflammatory cells infiltrate needs to be reduced in order to permit a proper intestinal absorption. Otherwise, when the condition is mild (CIBDAI lower than 6), a restriction diet may be sufficient to grant remission of signs.

This diet consists in a novel protein diet, which does not trigger a hypersensitivity response to food antigens. Recently, also hydrolyzed protein diets have been successfully used in canine IBD treatment (Marks *et al.* 2002, Mandigers *et al.* 2010).

In this report we describe the results of a cohort study conducted on about 76 IBD affected dogs. Two treatment protocols are considered in this report, the animals underwent one or the other depending on the clinical severity of the symptoms that they showed. If the CIBDAI score was 6 or more, we evaluated the association between drugs (immunosuppressive and antibiotics) and a restricted diet; if the CIBDAI score was below 6 we used only a specific diet, based either on novel protein sources or on hydrolyzed proteins from sources to which dogs had already been exposed before.

Materials and methods

We analysed medical charts of dogs referred to the University of Perugia Veterinary Teaching Hospital (VTH) (Perugia, Italy) between 2006 and 2013.

In 2013, there were 12,699, 6,832 (53.8%) males and 5,867 (46.2%) females. Of these 120, 74 (61.7%) males and 46 (38.3%) females, and 120 dogs showed only chronic intestinal signs.

All these dogs underwent endoscopy in order to confirm the suspicion of IBD. Endoscopy was performed in general anaesthesia with a Pentax EG-1840 scope, and several biopsy samples were taken from the small and/or large intestine: the choice between a colonoscopy and an esophagogastroduodenoscopy was based on clinical signs.

Biopsy samples were analysed at the University of Perugia (Perugia, Italy) - Veterinary Pathology Section. The histopathological evaluation was subjective until 2008, when standardization for small animal IBD was introduced (Day *et al.* 2008). The histopathological findings confirmed IBD diagnosis in 86 dogs out of 120, 57 (66.3%) males and 29 (43.7%) females.

Therapy was based only on IBD clinical severity, according to the CIBDAI scoring system. Specifically, we considered as severe all dogs with a CIBDAI > 8; as moderate all dogs with CIBDAI 6-8; as mild all dogs with a CIBDAI < 6.

For dogs with moderate or severe IBD (CIBDAI 6-9), we prescribed both drugs (Prednisone 1-2 mg/kg for 45 days and metronidazole + spiramicin 5 mg/kg for 21 days) and a specific diet. However some owners did not follow the specific diet, as we discovered in the follow-up at 6 months. Animals diagnosed with mild IBD (CIBDAI < 6) received only the specific diet, and we let the owners decide between a novel protein and a hydrolyzed protein diet.

We asked the owners to come back for a follow-up endoscopy and reassessment of the CIBDAI 45 days after the beginning of treatment. Seventy-six owners came back, and only 23 of them allowed us to perform a second endoscopy. We considered responsive to therapy all animals that showed remission of signs proved by a lower CIBDAI and an improvement in histopathological findings; those dogs started to taper prednisone.

After 6 months from the diagnosis of IBD we were able to reach all the 76 owners in order to collect information about follow-up by a phone questionnaire, and we classified as unresponsive dogs that showed relapses.

Due to the therapy differences, these 76 dogs ended up into 3 groups:

Group 1 - Drugs and diet: 44 dogs with moderate or severe disease;

Group 2 - Diet: 14 dogs with mild disease;

Group 3 - Drugs: 18 dogs with moderate or severe IBD who received only antibiotics and prednisone, because the owners refused to give the diet.

Statistical analysis aimed at finding differences in outcome among these 3 groups.

We also investigated the effect of following (Group 1) or not following (Group 3) the specific diet in dogs with moderate or severe disease IBD, and the effect of protein source in those dogs that followed the diet (Group 1 + Group 2).

Data were analysed using the Chi-Squared test, or Fisher's Exact Test if Chi-Squared test conditions were not satisfied (Campbell *et al.* 2007); we considered significant a *P value* < 0.05.

Results

Dogs with only chronic intestinal signs represented 0.9% of the medical records. The percentage of males in this group was 61.7% and did not differ from the percentage of males in the overall population, 53.8%. Among the 86 dogs diagnosed with IBD (Table I), the percentage of males was 66.3%, which was significantly greater (P = 0.022) than those present in the overall population. Most of the dogs (69.70%) checked for relapses after 6 months were also males.

The most represented breeds were German Shepherds (10/86, 11.6%; 8/76, 10.5%) and Boxer dogs (8/86, 9.3%; 7/76, 9.2%). We also noticed that Mixed Breed dogs were 15 out of 86 (17.4%), and 14 out of 76 (18.4%). In the whole population of dogs registered at the Veterinary Teaching Hospital (Perugia, Italy), the percentage of these breeds were 9.1%, 3.5%, and 26.6%, respectively.

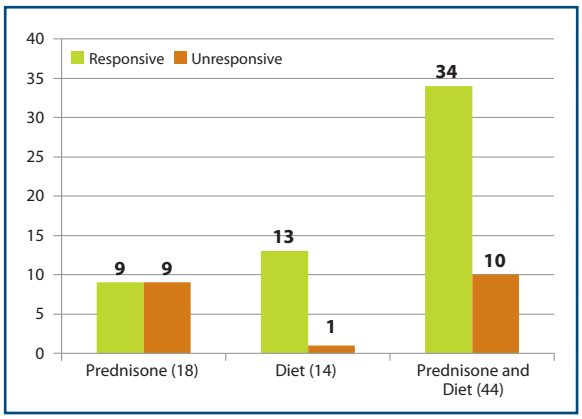

Figure 1. *Therapy Groups (n = 76).*

The age of the 86 IBD diagnosed dogs (mean ± s.d.) was 4.9 ± 3.6 years, and 5.0 ± 3.7 years in the 76 dogs of the follow-up group.

As far as clinical signs are concerned, diarrhoea has been the most common one (27/86, 31.4%; 25/76, 32.9%). Other reported symptoms were vomit (22/86, 25.6%; 18/76, 23.7%), anorexia (9/86, 10.5%; 9/76, 11.8%), vomit and diarrhoea (10/86, 11.6%; 9/76, 11.8%), vomit and anorexia (8/86, 9.3%; 7/76, 9.2%), vomit, diarrhoea, and anorexia (5/86, 5.8%; 5/76, 6.6%), and constipation (5/86, 5.8%; 3/76, 3.9%).

The distribution of the CIBDAI in the IBD diagnosed dogs and in the follow-up group is shown in Table II.

At day 45 of treatment we reassessed the CIBDAI and got the following results. Seven dogs showed an improvement of 2 points or more, 19 dogs an improvement of 1 point, 30 dogs were unchanged, 15 dogs showed a worsening of 1 point, and 5 a worsening of 2 or more points. The CIBDAI trend in the first 45 days was significantly associated with relapses after 6 months (P = 0.03) (Table III). Therefore the

Table I. *Frequencies of sex, breed, age class, and clinical signs in the IBD group (dogs with IBD confirmed by histopathological exam) and follow-up (after 6 months from the diagnosis of IBD; the owners were contacted by phone to collect information about follow-up).*

	Categories	IBD group (n)	Follow-up (n)
Sex	Male	57 (66.3%)	53 (69.7%)
	Females	29 (33.7%)	23 (30.3%)
Breed	German Shepherd	10 (11.6%)	8 (10.5%)
	Boxer	8 (9.3%)	7 (9.2%)
	Other breeds	53 (61.6%)	47 (61.8%)
	Mixed breed	15 (17.4%)	14 (18.4%)
Age	< 1 years	19 (22.1 %)	18 (23.7%)
	1- 6 years	32 (37.2%)	29 (38.2%)
	> 6 years	35 (40.7%)	29 (38.2%)
Signs	Diarrhea	27 (31.4%)	25 (32.9%)
	Vomit	22 (25.6%)	18 (23.7%)
	Anorexia	9 (10.5%)	9 (11.8%)
	Vomit and diarrhea	10 (11.6%)	9 (11.8%)
	Vomit and anorexia	8 (9.3%)	7 (9.2%)
	Vomit, diarrhea and anorexia	5 (5.8%)	5 (6.6%)
	Constipation	5 (5.8%)	3 (3.9%)
Total		86	76

result of the endoscopy was significantly associated with relapses after 6 months (P = 0.007). Although the concordance between CIBDAI and histological trend was just fair (Cohen's k = 0.21), as a matter of fact the 5 dogs with an improvement of both CIBDAI and histopathological findings had no relapses, while the 2 dogs with a worsening of both parameters had relapses. Finally, 3 of the other 16 dogs showed inconsistent trends and had relapses (P = 0.013).

The frequencies of relapses by group are reported in Figure 1: the dogs whose owner reported relapses at follow-up were 10 in Group 1 [22.7%; 95% Confidence Interval (CI): 11.5-37.8%], 1 in Group 2 (7.1%; 95% C.I.: 0.2-33.9%), and 9 in Group 3 (50.5%; 95% C.I.: 26.0-74.0%).

The difference between Group 1 and Group 3 was significant (P = 0.03), so in severe IBD cases the combination between diet and drugs resulted into a better outcome than the use of drugs alone (Figure 1).

The 58 dogs that received a specific diet (Group 1 + Group 2) were divided in 2 subgroups depending on protein types: 18 animals followed the "novel protein" diet, while 40 animals followed the "hydrolyzed protein" one. No difference statistically significant were found between "novel protein" diet and "hydrolyzed protein" diet. The frequencies of relapses were 7 (38.9%; 95% C.I.: 17.3-64.3%) with the novel protein diet and 4 with the hydrolyzed diet (10.0%; 95% C.I.: 2.8-23.7%) therefore the hydrolyzed protein diet seems to be more effective (P = 0.03).

Discussion

Table II. *Frequencies of Canine Inflammatory Bowel Disease Activity Index (CIBDAI) class in the IBD diagnosed dogs and in the follow-up group.*

		CIBDAI		
	Dog group	**< 6 (mild IBD)**	**6-8 (moderate IBD)**	**> 8 (severe IBD)**
0 day	IBD diagnosed	16 (18.6%)	21 (24.4%)	49 (57.0%)
	Follow-up	14 (18.4%)	19 (25.0%)	43 (56.6%)

Table III. *Association between Canine Inflammatory Bowel Disease Activity Index (CIBDAI) trend at 45 days and relapses after 6 months.*

	CIBDAI trend				
	-2 or better	**-1**	**0**	**+1**	**+2 or worse**
Relapses	0 (0%)	3 (15.8%)	9 (30.0%)	4 (26.7%)	4 (80%)
No relapses	7	16	21	11	1
Total	7	19	30	15	5

We analysed 76 medical charts of dogs affected by IBD. Our findings about sex, age, breed, and clinical signs more commonly related to IBD are in agreement with previous studies on this disease (Craven *et al.* 2004, Allenspach *et al.* 2007).

Adult or elderly dogs are more frequently affected and the most common signs are: diarrhoea, vomit, and anorexia.

A genetic predisposition to IBD has already been described in the relevant literature, with mutations on NOD2 and Toll-Like receptors (Simpson and Jergens 2011, Allenspach *et al.* 2010), thus compromising the gut innate immune response and making mutated animals more susceptible to develop altered immune reactions.

German Shepherds and Boxer dogs (Craven *et al.* 2004, Allenspach *et al.* 2010, Kathrani *et al.* 2011), which are the 2 most recurrent breeds in this study, are also the breeds more frequently associated with these mutations.

Among the IBD affected dogs analysed in this study, the percentage of males was greater than in the overall population of dogs registered at Perugia Veterinary Teaching Hospital (Perugia, Italy). This sex prevalence is in agreement with another retrospective study on canine IBD, in which 49 out of 80 dogs were males (Craven *et al.* 2004). Many analogies between human and canine IBD are documented, especially about pathogenesis (Cerquetella *et al.* 2010). In human medicine, it is well accepted that both Crohn's Disease and Ulcerative Colitis, the 2 forms of IBD in humans, have a greater prevalence of females (Brant and Nguyen 2008). However, IBD in humans has a wide genetic heterogeneity: the IBD3 is associated to sex-specific loci of the major histocompatibility region on chromosome 6 (Fisher *et al.* 2002), and also linked to the X chromosome (Hampe *et al.* 1999).

Both the reassessment of CIBDAI and of histological lesions after 45 day had a predictive value for relapses after 6 months.

Results about therapy at the 6th months follow-up indicate the great importance of including a specific diet in the treatment protocol. In fact, the comparison between Groups 1 and 3 showed that moderate and severe IBD had a significant reduction in the frequency of relapses after a therapy with both drugs and diet, rather than a therapy based only on drugs. Moreover, the use of hydrolyzed protein diets seems to be more effective than a novel protein diets inreducting relapses.

These results underline the key role of hypersensitivity to food antigens in perpetuating IBD (Guilford *et al.* 2003). In mild IBD cases, nutrition therapy can be sufficient to reduce the inflammatory stimulation and response. In moderate or severe

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IBD cases, immune-suppressants are necessary to reduce the inflammatory cells infiltrate in order to allow for a proper intestinal function, mostly in terms of absorption. We associated a restricted nutrition therapy so that food antigens reaching the gut immune system are minimized. The importance of this association is demonstrated in Group 3, where cases treated only with drugs had more relapses than Group 1.

The primary role of an altered immune response in IBD pathogenesis is also supported by the difference in the frequency of relapses between "novel protein" and "hydrolyzed protein"diets, although not significant and more studies will needed to support these preliminary findings. In fact, even proteins already present in a patient diet can be effective during therapy, as long as their molecular weight is reduced to the point to which they are no longer recognized as antigens by the gut immune system. Therefore, hydrolyzed protein diets can be a great aid in IBD therapy.

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