Pitfalls and Progress in the Diagnosis and Management of Canine Inflammatory Bowel Disease

Kenneth W. Simpson, BVM&S, PhD[a,*],
Albert E. Jergens, DVM, MS, PhD[b]

KEYWORDS

• Inflammatory bowel disease • Enteropathy • Bacteria • Diet

Inflammatory bowel disease (IBD) is the collective term for a group of chronic enteropathies characterized by persistent or recurrent gastrointestinal (GI) signs and inflammation of the GI tract. It is widely accepted that IBD involves a complex interplay among host genetics, the intestinal microenvironment (principally bacteria and dietary constituents), the immune system, and the environmental triggers of intestinal inflammation.[1] However, the specific steps that lead to IBD and the basis for phenotypic variation and unpredictable responses to treatment are not known.

This article examines IBD in dogs, focusing on the interaction between genetic susceptibility and the enteric microenvironment (bacteria, diet), the utility of recently developed histologic criteria, the prognostic indicators, and the standardized approaches to treatment.

GENETIC SUSCEPTIBILITY

The predisposition of certain breeds to IBD strongly supports a role for host genetics (**Table 1**). However, causal genetic defects have not been identified to date.

The genetic basis of human IBD, principally Crohn disease (typified by granulomatous inflammation of the ileum and/or colon), ulcerative colitis (diffuse colonic

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[a] Veterinary Clinical Sciences, College of Veterinary Medicine, Cornell University, VMC2001, Ithaca, NY 14853, USA
[b] Veterinary Clinical Sciences, 2446 Lloyd Veterinary Medical Center, College of Veterinary Medicine, Iowa State University, Ames, IA, USA
* Corresponding author.
E-mail address: kws5@cornell.edu

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Table 1
Breed predisposition and canine IBD

Breed	Phenotype	Possible Genetic Basis
Irish setter[13]	Gluten-sensitive enteropathy	Autosomal recessive
German shepherd dog[3,10,11]	Antibiotic-responsive enteropathy	? IgA deficiency SNPs: TLR5, NOD2
Basenji[21]	Immunoproliferative small intestinal disease	—
Lundehund[23]	Protein-losing enteropathy, lymphangiectasia, atrophic gastritis, gastric carcinoma	—
Yorkshire terrier[22,37]	—	—
Rottweilers (Europe)[56,57]	Protein-losing enteropathy, lymphangiectasia, crypt lesions	—
Soft-coated wheaten terrier[14,15]	Protein-losing enteropathy, nephropathy	Common male ancestor
Shar-pei[20]	Cobalamin deficiency	Autosomal recessive, chromosome 13
Boxer dog[5,9,25]/French bulldog[58]	Granulomatous colitis (HUC)	SNPs: NCF2

Abbreviations: HUC, histiocytic ulcerative colitis; SNP, single nucleotide polymorphism.

inflammation), and celiac disease (inflammation and villous atrophy of the small intestine), is much better established. In Crohn disease, genetic susceptibility is increasingly linked to defects in innate immunity exemplified by mutations in the innate immune receptor NOD2/CARD15, which in the presence of enteric microflora may lead to upregulated mucosal cytokine production and delayed bacterial clearance or killing, thereby promoting and perpetuating intestinal inflammation.[1,2] The predisposition of certain dog breeds (see **Table 1**), along with clinical response to antibiotics, for example, in boxers and German shepherds, points to a similar interaction of host susceptibility and microflora in dogs.[3–6] In boxers with granulomatous colitis (GC), lasting remission correlates with the eradication of mucosally invasive *Escherichia coli* that have a novel adherent and invasive pathotype associated with Crohn disease,[5,7,8] and genome-wide analysis has identified disease-associated single nucleotide polymorphisms (SNPs) in a gene (*NCF2*) that is involved with killing intracellular bacteria.[9] Studies in German shepherds have identified polymorphisms in innate immunity factor TLR5, which segregates with disease, and have shown that German shepherds have increased *TLR2* and decreased *TLR5* expressions relative to healthy greyhounds.[10] In addition, 4 nonsynonymous SNPs were identified in exon 4 of the canine NOD2 gene. The heterozygote genotype for all 4 NOD2 SNPs was significantly more frequently found in the IBD population ($P = .04$; odds ratio [OR], 2.34; confidence interval [CI], 1.03–5.28) than in controls. These results were also mirrored in non–German shepherd breeds: the heterozygote genotype for all 4 SNPs was significantly more frequently found in a population of 96 dogs of different breeds with IBD than the non–German shepherd control population ($P = .0009$; OR, 3.06; CI, 1.55–6.05).[11] These results suggest that genetic abnormalities in innate immune sensing or killing enteric bacteria underlie the antibiotic responsiveness of German shepherds and boxer dogs.

In human beings, celiac disease is an inflammatory disorder of the small intestine with an autoimmune component and strong heritability. Genetic studies indicate

a strong association with HLA and have identified more than 30 non-HLA risk genes, mostly immune-related.[12] Most of the celiac disease–associated regions are shared with other immune-related diseases, as well as with metabolic, hematologic, or neurologic traits, or cancer. In dogs, the interaction of genetics and diet is supported by the finding that gluten-sensitive enteropathy in Irish setters is an autosomal recessive trait, but the casual mutation has not been identifed.[13] Adverse reactions to food are also described in soft-coated wheaton terriers (SCWT) affected with protein-losing enteropathy and protein-losing nephropathy.[14] Pedigree analysis from 188 dogs demonstrated a common male ancestor, although the mode of inheritance is unknown.[15] Autoantibodies to perinuclear antineutrophil cytoplasmic antibodies (pANCA), associated with ulcerative colitis in humans,[16] have been demonstrated in 20 of 21 SCWT, and their occurrence preceded hypoalbuminemia by an average of 2.4 years.[17] Elevated pANCA levels are also described in 61% of 90 dogs of various breeds with food-responsive enteropathy versus 31% to 34% dogs with non–food-responsive IBD.[18,19] These findings suggest that immune dysregulation as evidenced by autoantibody formation is a relatively common and early feature of food-responsive enteropathies in dogs.

Shar-peis with cobalamin deficiency may present with small bowel diarrhea and also frequently weight loss and GI protein loss.[20] Two microsatellite markers (DTR13.6 and REN13N11) on canine chromosome 13 show evidence of linkage disequilibrium and support an autosomal recessive trait for cobalamin deficiency in this breed.[20] The Lundehund, Basenji, and Yorkshire terrier breeds have characteristic breed-associated GI diseases, but the genetic basis for these conditions is unknown.[21–23]

THE INTESTINAL MICROENVIRONMENT

Bacteria

Although intestinal bacteria are implicated frequently as a pivotal factor in the development of IBD in humans and animals, the specific bacterial characteristics that drive the inflammatory response have remained elusive. Advances in molecular microbiology are beginning to enable the in-depth analysis of complex bacterial communities without bacterial culture. Culture-independent analyses of bacterial 16S ribosomal DNA (rDNA) libraries in humans reveal that more than 70% of fecal flora appears uncultivable, and in healthy individuals there is significant variation in the flora in different GI segments and luminal contents compared with the mucosa.[24]

The application of 16S rDNA sequence–based analysis in combination with fluorescence in situ hybridization (FISH) has enabled the discovery of invasive *E coli* in the colonic mucosa of boxers with GC that is similar in pathotype to adherent and invasive *E coli* associated with intestinal inflammation in humans.[5,7] Eradication of the invasive *E coli* in boxer dogs with GC correlates with remission from disease, inferring a causal relationship.[8,25] Increasingly, studies across species show that intestinal inflammation is associated with a shift in the microbiome from gram-positive Firmicutes (eg, Clostridiales) to gram-negative bacteria, predominantly Proteobacteria, including Enterobacteriaceae.[7,26–28] Mucosa-associated Enterobacteriaceae have been found to correlate with duodenal inflammation and clinical signs in cats with signs of GI disease.[26] Studies in German shepherds with antibiotic-responsive enteropathy indicate an increased prevalence of Lactobacillales relative to greyhound controls and a complex and variable dysbiosis in dogs with tylosin-responsive enteroapthy.[10,29] It remains to be determined whether these alterations in noninvasive mucosal and luminal bacteria in dogs and cats typically diagnosed with lymphoplasmacytic IBD

are a cause or a consequence of the inflammation, but their discovery has provided new opportunities for therapeutic intervention.

DIETARY CONSTITUENTS

Growing evidence supports the importance of diet in the development of canine and feline IBD. Irish setters develop an enteropathy that is related to the ingestion of gluten.[13] In SCWT, adverse reactions to corn, tofu, cottage cheese, milk, farina cream of wheat, and lamb have been described.[14] In these dogs, serum albumin concentrations decreased and fecal alpha1-protease inhibitor concentration increased when compared with baseline values 4 days after the provocative trial. Antigen-specific fecal IgE levels varied throughout the provocative trial, with peak levels after ingestion of test meals. The pANCA levels were elevated in 20 of 21 SCWT and 61% of 90 dogs of various breeds with food-responsive diarrhea (evaluated before treatment).[17,18] The underlying disease processes driving this autoantibody formation remains to be determined.

In controlled studies of 65 dogs with IBD and diarrhea of at least 6 weeks' duration, 39 responded to being fed an antigen-restricted diet of salmon and rice for 10 days.[18] The conditions relapsed in only 8 dogs when they were challenged with their original food, and none were sensitive to beef, lamb, chicken, or milk. In a recent study, 26 dogs with signs of chronic GI disease (6 had normal GI pathology) were fed either a soy and chicken hydrolysate (n = 18, Hypoallergenic diet, Royal Canin) or an intestinal diet (n = 8, Intestinal diet, Royal Canin).[30] The initial response to the diet was 88% in both groups; however, over a 3-year period, only 1 of 6 dogs on the intestinal diet was maintained in remission versus 13 of 14 on the hydrolysate. Approximately 66% of the dogs in either group relapsed in response to the original diet. In an ongoing prospective trial,[31] the authors have observed positive responses to a hydrolyzed soy diet in 59% of 27 dogs with IBD. In this study, a marked perturbation of the duodenal microbiome (dysbiosis) was detected in a majority of dogs with IBD, including those with a response to diet. From a comparative standpoint, of 55 cats with chronic GI disease 49% responded to dietary modification; signs recurred in 16 of 26 cats challenged with the original food. The dominant group of antigens eliciting a response in these cats was cereals, wheat, corn, or barley.[32]

Taken as a whole, these studies reveal responses to diet in approximately 50% of dogs with chronic GI signs and IBD.[18,30,31,33] The diagnostic terms food responsive, or dietary intolerant are more appropriate than food allergy where an immunologic basis for disease has not been identified. The observations that many patients do not relapse on rechallenge with the original diet, and that many react to cereal-based ingredients rather than animal proteins, has important implications for pathogenesis and treatment. The high response rates to diets that differ markedly in their composition (eg, hydrolyzed soy vs salmon), but are formulated from relatively few ingredients, raises the possibility that it is perhaps the absence of certain ingredients, rather than the modification or substitution of dietary protein, that has a beneficial effect. For instance, carrageenan, a common ingredient in canned pet foods, directly induces GI inflammation and inhibits apoptosis.[34]

DIAGNOSIS

A diagnosis of IBD usually involves careful integration of signalment, home environment, history, physical findings, clinicopathologic testing, diagnostic imaging, and histopathology of intestinal biopsies.

Dogs with IBD typically present for investigation of diarrhea, weight loss, or vomiting. The initial approach to chronic diarrhea or vomiting is based on determining its nature and severity and specific or localized clinical findings. The presence of additional clinical signs helps to refine the region of interest and probable cause, such as tenesmus and dyschezia, large bowel disease; melena, upper GI bleeding or ulceration; abdominal distention, difficulty breathing; or peripheral edema, enteric protein loss.

In cases in which diarrhea is present, this information is integrated to determine whether it is attributable to large bowel disease, as characterized by dyschezia, tenesmus, increased frequency of defecation, and small volume of feces with mucus and blood, or whether it is a consequence of small intestinal disease or exocrine pancreatic insufficiency, as characterized by a large volume of diarrhea, weight loss, and possible vomiting. In patients with abdominal pain, dehydration, frequent vomiting, or localized findings (eg, abdominal mass), these problems are pursued ahead of an in-depth workup for chronic diarrhea.

In patients with diarrhea and no obvious cause, it is best to adopt a systematic approach determined by the localization of diarrhea to the small or large bowel. Patients with signs of large and small bowel involvement are usually evaluated for diffuse GI disease.

Chronic small bowel diarrhea is a common presenting sign in dogs with IBD, and the diagnostic approach is summarized in **Table 2**. After exclusion of infectious and parasitic agents, non-GI disorders, exocrine pancreatic insufficiency, and intestinal structural abnormalities requiring surgery, the most common groups of intestinal diseases associated with chronic small bowel diarrhea are idiopathic IBD, diet-responsive enteropathy, antibiotic-responsive enteropathy, and lymphangiectasia.

Table 2
Initial diagnostic approach to chronic diarrhea

Integrate signalment, history, and physical examination	Breed predisposition, environment, diet, other clinical signs, localizing findings
Detect endoparasites and enteric pathogens	Fecal analysis (eg, Giardia)
Perform clinicopathologic testing	
Detect non-GI disease	CBC, biochemistry profile, UA, ± TLI, ACTH stimulation test, freeT_4/TSH levels, bile acid levels
Detect/characterize GI disease	Hypoproteinemia, hypocalcemia, hypocholesterolemia, leukopenia, leukocytosis, low cobalamin or folate levels[4]
Perform diagnostic imaging	
Detect non-GI disease	Radiography, ultrasonography of liver, spleen, pancreas, lymph nodes, masses, and effusions
Detect and characterize GI disease	Radiography, ultrasonography[59] to detect obstruction, intussusception, focal masses, thickening, loss of layering, hypoechoic appearance, hyperechoic striations

Abbreviations: ACTH, adrenocorticotropic hormone; CBC, complete blood cell count; T4, levorotatory thyroxine, TSH; thyroid-stimulating hormone, TLI, trypsin like immunoreactivity; UA, urinalysis.

The approach to this group of patients is usually determined by the severity of the clinical signs (ie, frequent severe diarrhea, excessive weight loss, decreased activity or appetite), along with the presence of hypoalbuminemia or hypocobalaminemia and intestinal thickening or mesenteric lymphadenopathy. In patients with these abnormalities, intestinal biopsy is required to define the cause (eg, lymphangiectasia, lymphoma) and to optimize therapy.

The clinical severity of intestinal disease can be quantified by determining the clinical disease activity index (eg, attitude, activity, appetite, vomiting, stool consistency, stool frequency, weight loss).[35] Measurement of serum C-reactive protein (CRP) levels has been shown to correlate with clinical disease activity (canine IBD activity index [CIBDAI]), and this implies that severe clinical disease is accompanied by a systemic inflammatory response.[35] Initial measurement of clinical disease activity or CRP levels may also be useful as a baseline for determining the response to treatment.

Controlled studies have shown that hypoalbuminemia is associated with a poor outcome in dogs with chronic enteropathy.[36,37] Serum concentrations of cobalamin and folate can be measured to determine whether supplementation is required, and low serum cobalamin concentration (<200 ng/L) is associated with a negative prognosis.[36]

Evaluation of hemostatic function is recommended to ascertain if hypo or hypercoagulability has developed as a consequence of enteric protein loss.

In stable patients with chronic diarrhea (ie, good attitude, appetite, mild weight loss, normal serum proteins, no intestinal thickening, or lymphadenopathy), and in those with undefined weight loss, measurement of serum cobalamin and folate concentrations can help determine the need for intestinal biopsy, localize the site of intestinal disease (eg, cobalamin is absorbed in the ileum), determine the need for cobalamin supplementation, and establish a prognosis. Stable patients with chronic diarrhea and normal cobalamin concentrations can be given the option of empirical treatment trials with diet, followed by antibiotics if there is no response to diet (see section on Minimal Change Enteropathy). Failure to respond to empirical therapy or worsening of disease is an indication for endoscopy and intestinal biopsy. In stable patients with chronic diarrhea and subnormal serum cobalamin levels, the authors pursue endoscopic evaluation and intestinal biopsy rather than empirical treatment trials.

INTESTINAL BIOPSY

Intestinal biopsies can be acquired endoscopically or surgically. In patients without an indication for surgery (eg, intestinal masses, anatomic or structural disease, perforation), the authors prefer to perform diagnostic endoscopy to visually inspect the esophageal, gastric, and intestinal mucosa and to procure endoscopic biopsy samples. It is noteworthy that in some, but not all, studies the endoscopic appearance of the small intestine correlates better with outcome than the histopathologic appearance.[30,36] If there is a suspicion of ileal involvement (eg, low cobalamin levels, ultrasonographic evidence of disease), transcolonic ileoscopy is performed in addition to the standard upper GI tract endoscopic examination.

Guidelines for biopsy acquisition have recently been published.[38] Operator experience and biopsy sample quality and number are of key importance in facilitating histopathologic evaluation. Surgical biopsy is usually preferred if involvement of the submucosa or muscularis is suspected or when endoscopic biopsy findings do not adequately explain the clinical picture.

HISTOPATHOLOGIC EVALUATION

The most common histopathologic diagnoses in dogs with chronic diarrhea are IBD, lymphangiectasia, and lymphoma. The most common histopathologic lesion found in the intestines of dogs involves increased cellularity of the lamina propria and is usually referred to as IBD. The extent of inflammation varies and ranges from focal to diffuse involvement of the small and large intestines. The type and degree of cellular accumulation is also variable and is subjectively categorized as normal, mild, moderate, or severe. The emphasis on cellularity has meant that abnormalities in mucosal architecture have been somewhat overlooked, but their correlation with proinflammatory cytokines and clinical severity of disease highlights the importance of evaluating these features.[26,39] It should be emphasized from the outset that whereas histopathologic changes can be helpful, they frequently represent a common end point of many different diseases.

Cellular Infiltrates

Intestinal infiltration with macrophages or neutrophils raises the possibility of an infectious process, and culture, special staining, and FISH are indicated.[5,26]

The presence of moderate to large numbers of eosinophils in intestinal biopsy samples, often accompanied by circulating eosinophilis, suggests possible parasitic infestation or dietary intolerance.[40]

Increased numbers of lymphocytes and plasma cells, so-called lymphoplasmacytic enteritis, is the most frequently reported form of IBD. Moderate to severe lymphoplasmacytic enteritis is often described in association with a protein-losing enteropathy.[41] Predisposed breeds include the Basenji, Lundehund, and Shar-Pei.[20,21,23] However, the appropriateness and clinical relevance of the term lymphoplasmacytic enteritis is a contentious issue, particularly in the small intestine. Dogs have similar numbers of duodenal CD3-positive T cells before and after clinical remission induced by diet or steroids,[42] and cats with and without signs of intestinal disease have similar numbers of lymphocytes and plasma cells.[43]

Mucosal Architecture

Several studies indicate that changes in mucosal architecture, such as villous morphology, lymphatic dilatation, goblet cell mucus content, and crypt lesions, are related to the presence and severity of GI disease.[8,13,26,41,44] Recent studies using quantitative observer-independent variables (eg, inflammatory cytokines) to identify histopathologic correlates of disease have shown that in cats with signs of GI disease, villus atrophy and fusion correlate with the severity of clinical signs and degree of proinflammatory cytokine upregulation in the duodenal mucosa.[26] Architectural changes in the gastric mucosa also correlate with cytokine upregulation in dogs with lymphocytic gastritis.[39]

In the colon, loss of mucus and goblet cells has been correlated with the presence of GC and severity of lymphoplasmacytic colitis.[8,44,45]

Dilation of lymphatics and the presence of crypt abscesses and cysts are most frequently encountered in dogs with protein-losing enteropathies and are often accompanied by lymphoplasmacytic inflammation of varying severity.[22,41,46,47]

Standardized Grading

The interpretation of GI histopathologic findings varies considerably among pathologists.[48] To address this problem, a working group established by the World Small Animal Veterinary Association (WSAVA) formulated a scheme to standardize

the evaluation of intestinal histopathologic findings.[49] A potentially useful feature proposed in this scheme is the summing of scores in 8 predetermined categories to give an indication of disease severity, by which a score of 1 to 8 is mild, 9 to 16 is moderate, and 17 to 24 is marked. To investigate the utility of this approach, the authors have applied the WSAVA criteria to colonic biopsies from boxer dogs with GC[8] and have directly compared the WSAVA scheme to a previous one (the Roth scheme) developed for evaluating canine colitis (**Table 3**).[44] Both schemes assign an overall grade of normal, mild, moderate, or severe/marked and a final diagnosis that describes the dominant abnormalities. However, the schemes differ markedly in other respects. The Roth scheme, which was developed specifically for colitis, accounts for changes in goblet cells, which are considered of particular importance in colitis,[5,45] whereas the WSAVA scheme does not. It is evident that the final diagnosis using both schemes was concordant in 5 of 7 dogs (see **Table 3**). One of the discordant cases differed only in the degree of granulomatous inflammation assigned (Roth moderate vs WSAVA marked). However, in the other case, the Roth score assigns a final diagnosis of moderate GC, whereas the WSAVA scheme assigned a grade of no GC. This difference is because the standardized reporting form used in the WSAVA scheme only considers inflammation in the lamina propria, and not the submucosa or muscularis.[49] The WSAVA scores are readily summed and yield scores ranging from 4 to 16 in GC, with pretreatment scores decreasing in all dogs after enrofloxacin treatment (scores range from 2–8). However, because GC is a very severe form of canine colitis, it is concerning that the total scores in dogs with severe/marked GC range from 11 to 16 of 24, which corresponds to an overall severity grading of moderate. Thus it appears that the simple summing method proposed in the WSAVA scheme underestimates the severity of GC. This limitation is likely a consequence of assigning equal value to each of the 8 categories being evaluated, with the result that abnormalities

Table 3
Application of standardized grading to GC in boxer dogs

	Roth[44]		WSAVA[49]		Goblet Cell Depletion	
Dog	Pre	Post	Pre	Post	Pre	Post
1	3	2 g (2 wk), 1 lp (7 mo)	11	8[c], 2[d]	3	2[c], 0[d]
2[a]	2	NA	4	NA	0	NA
3	3	1 g	16	5	3	0
4	2	1 g	10	6	3	1
5[b]	2	1 g	12	4	2	1
6	3	NA	12	NA	3	NA
7	3	3 g	14	9	2	3

0, normal; 1, mild; 2, moderate; 3, marked/severe.

WSAVA total: 1 to 8, mild; 9 to 16, moderate; 17 to 24, marked.

Abbreviations: g, granulomatous infiltrate; lp, lymphocytic plasmacytic infiltrate; NA, not available.

[a] Submucosal macrophages.

[b] Muscularis macrophages.

[c] 2 weeks time point.

[d] 7 months time point.

Data from Mansfield CS, James FE, Craven M, et al. Remission of histiocytic ulcerative colitis in Boxer dogs correlates with eradication of invasive intramucosal *Escherichia coli*. J Vet Intern Med 2009;23(5):964–9.

such as ulceration (marked epithelial change), and granulomatous or neutrophilic inflammation, are weighted similarly to lymphoplasmacytic infiltrates, which vary widely in health and disease.[1] A further limitation of the WSAVA scheme with respect to GC is that it does not consider goblet cells, which are decreased in GC and other forms of colitis and show dramatic increases after treatment (see **Table 3**).[5,44,45]

The recent finding that the WSAVA scheme, like previous standardized photographic schemes,[39] has poor agreement among pathologists[50] questions further the ability of standardized grading in its current form to translate to improved diagnosis and management of patients with IBD. Clearly, the emphasis on histopathologic evaluation has to shift from the subjective reporting of cellularity to identifying and reporting features that correlate with the presence of disease and its outcome.

THERAPEUTIC APPROACHES FOR IBD

The therapeutic approach to IBD is influenced by suspicion of a breed-related problem; the severity of disease as characterized by clinical signs, serum albumin and cobalamin concentrations, and endoscopic appearance; the type of cellular infiltrate; the presence of bacteria or fungi; and the presence of architectural changes, such as atrophy, ulceration, lymphangiectasia and/or crypt cysts. Therapeutic intervention is directed at correcting nutritional deficiencies (eg, cobalamin deficiency) and counteracting inflammation and dysbiosis (**Fig. 1**).

MINIMAL CHANGE ENTEROPATHY

Minimal change enteropathy is characterized by low clinical disease activity, normal serum albumin and cobalamin levels, and normal intestinal histopathologic findings.

Empirical Treatment

Typically, the empirical treatment for *Giardia* and endoparasitic infection is the oral administration of fenbendazole, 50 mg/kg, for 5 days.

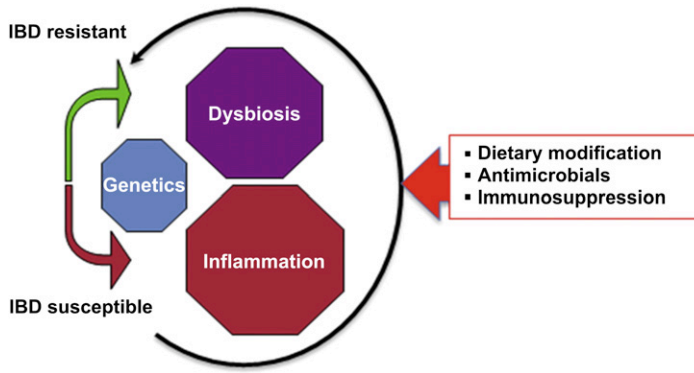

Fig. 1. Genetic susceptibility, intestinal inflammation, and the enteric microbiome are intimately related to IBD. Genetic susceptibility to IBD affects inflammation and dysbiosis. In an IBD-resistant individual, host genotype acts as a brake to limit the development and perpetuation of inflammation and dysbiosis. In an IBD-susceptible individual, disease-associated genetic polymorphisms may decrease the threshold for initiating and sustaining inflammation and dysbiosis. Therapeutic intervention is aimed at counteracting inflammation and dysbiosis.

Dietary Trial

Options for dietary trials are outlined in **Box 1**. A positive response suggests diet-responsive enteropathy, a term that includes both dietary allergy and intolerance. In dogs with GI signs related to diet, a clinical response is usually observed within 1 to 2 weeks of changing the diet.[18,30,31] If the response is good, the diet should be continued. Rechallenge with the original diet is required to confirm that clinical signs are related to the diet. However, few owners consent to rechallenge. Challenge with single dietary ingredients is necessary to define the specific components eliciting an adverse response. If dietary trials with 2 different diets are unsuccessful, the next step is usually an antibiotic trial.

Antibiotic Trial

An antibiotic trial typically involves oral administration of tylosin, 10 to 15 mg/kg, every 8 hours; oxytetracycline, 20 mg/kg, every 8 hours; or metronidazole, 10 mg/kg, every 12 hours.[3,4,6] A positive response suggests antibiotic-responsive enteropathy, which was called small intestinal bacterial overgrowth despite the absence of increase in total bacteria (for further explanation of this topic, see article by Hall elsewhere in this issue).[3,4,51] The dog is typically maintained on antibiotics for 28 days. If signs recur after stopping, long-term antibiotic therapy with tylosin, 5 mg/kg, administered orally once a day can be used to maintain dogs that are tylosin responsive (Elias Westermarck, personal communication, 2010). If the response is poor, the patient should be carefully reappraised before considering other treatment options.

GRANULOMATOUS OR NEUTROPHILIC ENTEROPATHY

Enteropathies characterized by neutrophilic or granulomatous inflammation are described infrequently in dogs. Some may be associated either with bacterial infections, such as from *E coli* (GC in boxers), *Streptococcus*, *Campylobacter*, *Yersinia*, and *Mycobacteria*, or with fungal (eg, *Histoplasma*) or algal (eg, *Prototheca*) infections.

Box 1
Options for dietary trials

Global modification

- Switch to a different diet or a different manufacturer

Optimize assimilation

- Highly digestible (usually rice based)
- Fat restricted (<15% dry matter)
- Easy-to-digest fats (eg, medium-chain triglyceride oil)
- Restricted fiber

Antigenic modification

- Antigen-restricted /novel protein source
- Protein hydrolysate

Immunomodulation

- Altered fat composition (eg, ω-3 or ω-6 fatty acid, fish oil)
- Prebiotics (eg, inulin)

Culture of mucosal biopsies, intestinal lymph nodes, and other abdominal organs and imaging of chest and abdomen should be undertaken in cases of granulomatous or neutrophilic enteritis to detect infectious organisms and systemic involvement. Gomori methenamine silver, periodic acid–Schiff, Gram, and modified Steiner stains are the traditional cytochemical stains used to search for infectious agents in fixed tissues. FISH with a probe directed against eubacterial 16S ribosomal RNA is a more contemporary and sensitive method of detecting bacteria within formalin-fixed tissues.[26,42] It is imperative not to immunosuppress patients with granulomatous or neutrophilic infiltrates until infectious agents have been excluded.

Eradication of mucosally invasive *E coli* in boxers with GC is associated with clinical cure, but treatment failure associated with antibiotic resistance is increasing.[5,8,25] The prognosis for idiopathic granulomatous or neutrophilic enteropathies is regarded to be poor if an underlying cause is not identified.

LYMPHOCYTE AND PLASMA CELL PREDOMINANT ENTEROPATHY

Studies in dogs with chronic diarrhea diagnosed as lymphoplasmacytic enteritis provide reasonable evidence that various subsets of dogs will respond to treatment with diet, antibiotics, or immunosuppressive therapy (**Fig. 2**).[4,6,18,30,36] At present, because there is no reliable means for predicting which dogs will respond to which treatment, treatment consists of a series of therapeutic trials.

Response to Standardized Therapy

As mentioned earlier, in controlled studies of 65 dogs with IBD and diarrhea of at least 6 weeks' duration, 39 of 65 dogs responded to dietary modification (restricted antigen diet) and the remaining dogs were treated with corticosteroids (2 mg/kg every 24 hours for 10 days, followed by a tapering dose over 10 weeks).[18] The CIBDAI and histopathologic scores were similar (>70% moderate to severe in each group) in dogs that did and did not respond to diet. Dogs that responded to diet tended to

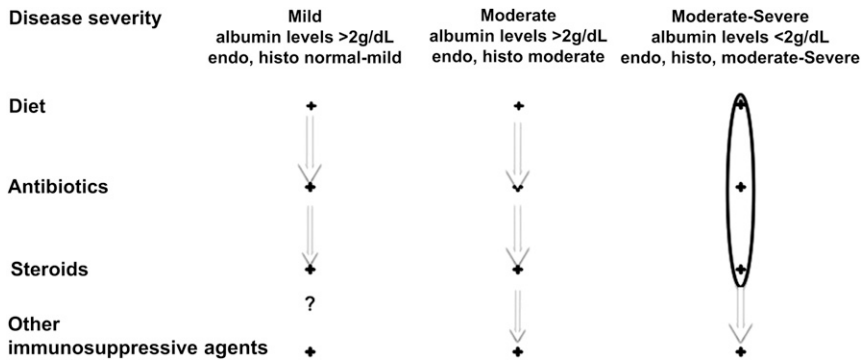

Fig. 2. Treatment by therapeutic trials in dogs with lymphocytic plasmacytic enteritis. A sequential step-up approach, starting with dietary modification is usually applied to patients with mild to moderate disease. The need and clinical confidence to step up between different treatment modalities (diet, antibiotics, steroids, other immunosuppressive therapy) is indicated by the size of the arrows. In dogs with severe disease, a step-down approach is used, with concurrent therapy with diet, antibiotics, and steroids/azathioprine given from the outset (indicated by the circle), and immunosuppressive therapy and antibiotics are withdrawn in patients with a favorable response. endo, endoscopy; histo, histopathology.

be younger and had higher serum albumin concentrations than dogs that did not respond to diet. Dogs that did not respond to diet were treated with steroids. The intestinal histopathologic findings did not differ in either diet-responsive or steroid-responsive dogs before and after treatment. Of the 21 diet-unresponsive dogs, 10 responded to prednisolone with no relapse after taper for up to 3 years. Of the 11 diet- and steroid-unresponsive dogs, 9 were euthanased after administration of steroids, with only 2of 8 steroid-refractory dogs responding to cyclosporine administered orally (5 mg/kg every 24 hours for 10 weeks).[18]

The approach outlined in **Box 2** incorporates an antibiotic trial (tylosin) into a diet (hydrolysate) and immunosuppression–based approach. In an ongoing study,[31] 26 of 27 (96%) dogs with IBD have responded to standardized treatment: 16 diet responsive, 3 steroid responsive, 3 partially responsive to food + antibiotics, 3 responsive to food + steroid + antibiotics, and 1 responsive to antibiotics alone. The response to diet in 21 dogs with normal serum protein levels was 67%, compared with 33% in 6 dogs with low serum protein levels. It is noteworthy that we observed clinical remission in response to dietary manipulation alone in 2 of 6 dogs with IBD accompanied by hypoproteinemia.

In summary, the positive response to dietary modification in 60% to 88% of dogs with lymphocyte and plasma cell dominant enteritis IBD[18,30,31,33] suggests that a dietary trial with a restricted antigen or hydrolyzed diet is a good therapeutic starting point. An unexpected positive finding of these recent studies is how few dogs require continuous treatment with corticosteroids or other immunosuppressive agents.

EOSINOPHIL-PREDOMINANT ENTERITIS

Eosinophilic enteritis is characterized by excessive accumulation of eosinophils in the lamina propria. This condition is speculated to result from an immunologic reaction to parasites or diet.[40] The disease may also involve other areas of the GI tract.

Clinical Findings

The principal clinical signs are chronic small bowel diarrhea accompanied by vomiting or weight loss. Large bowel signs or vomiting predominate in some cases. Physical findings range from normal to focally or diffusely thickened intestines and marked weight loss.

Diagnosis

Eosinophilic enteritis is diagnosed by adopting an approach similar to that described for lymphoplasmacytic enteritis. Clinicopathologic abnormalities may include peripheral eosinophilia. Mast cell neoplasms, hypoadrenocorticism, and endoparasites can produce a similar spectrum of clinical signs and should be ruled out.

Histopathology is characterized by accumulation of large numbers of eosinophils in the intestinal mucosa.

Treatment

Prophylactic administration of an anthelmintic, such as oral fenbendazole, 50 mg/kg, every 24 hours for 5 days, is warranted to treat potential visceral larva migrans, which has been associated with eosinophilic gastroenteritis. Some patients may respond to antigen-restricted or protein hydrolysate diets, and those failing dietary therapy are usually administered oral prednisolone, 2 mg/kg, every 24 hours that is tapered over an 8-week period. The prognosis for eosinophilic enteritis is typically considered good, with few patients requiring continuous immunosuppression.

Box 2
Standardized treatment of dogs with lymphoplasmacytic IBD

Mild to moderate clinical disease activity, mild to moderate histopathology (lymphocytes and plasma cells are predominant cell type), serum albumin levels greater than 2 g/L

Empirical treatment

- Treatment for *Giardia* and helminths if not already initiated. Cobalamin and folate supplementation if these are subnormal

Sequential treatment

- Dietary trial with a hydrolyzed or antigen-restricted diet for 2 weeks; if the response is good, then maintain on diet. Consider rechallenge to confirm dietary intolerance and single-ingredient challenge to define offending substrates
- Antibiotic trial, for example, tylosin for 2 weeks; if the response is good, maintain on antibiotics for 28 days and then discontinue. Consider transition to probiotics, despite the lack of evidence to support their ability to maintain remission
- Immunosuppression with glucocorticoids; for example, oral prednisolone 2 mg/kg every 24 hours for 21 days, 1 mg/kg every 24 hours for 21 days, 0.5 mg/kg every 24 hours for 21 days, 0.5 mg/kg every 48 hours for 14 days is a typical protocol. It is the authors experience that side effects of glucocorticoids are usually more marked in large than small breed dogs (this may be because of relative overdosing on the basis of body weight rather than surface area). For this reason, the authors typically initiate immunosuppression in all dogs weighing more than 31.5 kg with azathioprine ± concurrent glucocorticoid treatment at a faster taper for example, for dogs weighing more than 31.5 kg: oral azathioprine 2 mg/kg every 24 hours for 5 days, then 2 mg/kg every other day and oral prednisolone 2 mg/kg every 24 hours for 10 days, 1 mg/kg every 24 hours for 10 days, 0.5 mg/kg every 24 hours for 10 days, and 0.5 mg/kg every 48 hours for 10 days)
- If there is a poor response, reappraise before considering escalating immunosuppression (eg, add azathioprine or substitute with oral cyclosporine, 5 mg/kg, every 24 hours for 10 weeks[52] if already on azathioprine)
- If the response is good, first taper immunosuppression and then stop antibiotics

Moderate to severe clinical disease activity, moderate to severe intestinal histopathology (atrophy, fusion, lymphocytes and plasma cells are the predominant cell type), serum albumin levels less than 2 g/L

- Empirical treatment for *Giardia* and helminths if not already initiated
- Cobalamin and folate supplementation if their levels are subnormal
- Dietary modification pending biopsy result; concurrent dietary modification (hydrolyzed or antigen-restricted diet), antibiotics (eg, tylosin), and immunosuppression (glucocorticoids and/or azathioprine)
- If the response is poor, reappraise all findings before considering escalating immunosuppression (eg, cyclosporine)
- Consider failure to absorb oral prednisolone and switch to injectable corticosteroids
- Dexamethasone may be preferable to prednisolone in patients with ascites to avoid increased fluid retention
- Concurrent therapy with ultralow-dose aspirin (0.5 mg/kg) and judicious use of diuretics (furosemide [Lasix] and spironolactone are often used in patients considered at risk for thromboembolic disease and in those severely distended with tense ascites, respectively)
- The use of elemental diets and partial parenteral nutrition may be indicated in some dogs that have severe protein-losing enteropathy
- If the response is good, first taper immunosuppressive agents and then stop antibiotics

LYMPHANGIECTASIA AND CRYPT CYSTS/ABSCESSES

Intestinal lymphangiectasia is characterized by abnormal distention of lymphatic vessels within the mucosa. Lymphangiectasia is a consequence of a localized or generalized lymphatic abnormality or an increased portal pressure (eg, right-sided heart failure, caval obstruction, hepatic disease). Lymphatic abnormalities are often associated with lipogranulomatous inflammation that is visible as small white granules on the intestinal mesentery. Tumor infiltration of lymphatics or lymph nodes can also cause lymphangiectasia. In some cases, lymphangiography reveals a generalized lymphatic abnormality. Dilation of lymphatics is associated with the exudation of protein-rich lymph into the intestine and severe malabsorption of long-chain fats. Crypt cysts and abscesses may also be observed in intestinal biopsies.

The Yorkshire terrier (4.2- to 10-fold relative risk), SCWT (concurrent proteinuria), and Norwegian Lundehund seem to be overrepresented, supporting a familial cause in some dogs.[14,15,22,23,37]

Clinical Findings

Clinical findings are essentially a consequence of the intestinal loss of protein and range from weight loss to chronic diarrhea, vomiting, ascites, edema, and chylothorax. In a study of 12 Yorkshire terriers,[37] hypoalbuminemia (<3.1 g/dL) was present in all 12 dogs (median 1.6 g/dL), and hypoglobulinemia (<1.9 g/dL) in 7 dogs (median 1.7 g/dL). Additional biochemical abnormalities included hypocalcemia (n = 12), hypocholesterolemia (n = 11), hypomagnesemia (n = 9), hypokalemia (n = 5), and hypochloremia (n = 5). Hypocalcemia and hypomagnesemia have been attributed to hypovitaminosis D.[53,54] Hematologic abnormalities in 12 Yorkshire terriers included mild anemia (n = 5), thrombocytosis (n = 8), mature neutrophilia (n = 6), and neutrophilia with a left shift (n = 3).[37]

Diagnosis

Lymphangiectasia usually presents as a protein-losing enteropathy, with endoscopic appearance of white blebs on the mucosa (dilated lymphatics). Endoscopic biopsies are often adequate. Surgical biopsy should be undertaken carefully, with appropriate attention to potential for bleeding, exacerbation of hypoproteinemia by fluid therapy, and potential for dehiscence.

Treatment

The cause of lymphangiectasia is usually not determined. Treatment is supportive and symptomatic. Dietary recommendations are similar to those for other causes of small bowel diarrhea (highly digestible, restricted antigen, or hydrolysate). Fat restriction has been emphasized as a mainstay of treatment, but no controlled studies have evaluated this approach. Medium-chain triglyceride (MCT) oil, usually in the form of coconut oil, at 0.5 to 2 mL/kg body weight per day can be added to the diet, or a diet already containing MCT can be fed to provide a source of calories, that is in theory easy to assimilate. The use of MCT improves outcome in children with primary lymphangiectasia,[55] but there are no studies in dogs.

Prednisolone, 1 mg/kg, every 24 hours is often administered orally and may work by decreasing lipogranulomatous inflammation or concurrent mucosal inflammation. Prednisolone is tapered to the lowest effective dose once remission has been achieved. In patients with severe malabsorption, parenteral glucocorticoids may be required, and a switch to dexamethasone may be made in patients with ascites or edema. Escalation of immunosuppression (eg, by oral administration of cyclosporine,

5 mg/kg, every 24 hours[52]) may be tried if the patient is unresponsive. However, patients with lymphangiectasia appear more prone to sepsis than other forms of IBD. So it is imperative not to overimmunosuppress these patients, and concurrent therapy with metronidazole or tylosin is frequently initiated to decrease the risk of bacterial translocation through the markedly impaired gut. Aspirin, 0.5 mg/kg, every 24 hours is often given orally to dogs with low antithrombin III levels if they are considered at risk for thromboembolism. Diuretics are used if ascites is problematic.

Response to therapy is variable with some dogs staying in remission for several years and others pursuing a path toward fulminant hypoproteinemia or thromboembolic disease. The prognosis is always guarded. In a recent study of 12 Yorkshire terriers,[37] empirical therapy with corticosteroids (11 of 12), azathioprine (2 of 12), antibiotics (amoxicillin-clavulanate, n = 6; metronidazole, n = 6; tylosin n = 5; and enrofloxacin n = 2), plasma, and diuretics was associated with a poor outcome. Of the 12 cases, 7 died or were euthanased within 3 months of diagnosis (thromboembolism was suspected in 3). Long-term survival was achieved in 3 dogs, (36, 24, and 8 months), and 2 are alive at 3 and 4 months after diagnosis.

SUMMARY

This article has examined IBD in dogs, focusing on the interaction between genetic susceptibility and the enteric microenvironment (bacteria, diet), the utility of recently developed histologic criteria, the prognostic indicators, and the standardized approaches to treatment. It is evident that despite much effort, the histopathologic interpretation of intestinal biopsies is still a substantial pitfall in the diagnosis and management of IBD. Progress has been made in documenting the clinical determinants of outcome, such as hypoalbuminemia and hypocobalaminemia, by performing standardized therapeutic trials in dogs with lymphoplasmacytic enteritis (at least 50% respond to diet alone, without recourse to immunosuppression), by identifying and treating invasive bacteria in patients with granulomatous inflammation, and by starting to unravel the basis of host susceptibility to IBD.

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