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Inflammatory bowel disease in veterinary medicine

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1. ABSTRACT

Canine and feline inflammatory bowel disease (IBD) denotes a heterogeneous group of idiopathic, chronic, relapsing inflammatory disorders of the gastrointestinal tract that are immunologically-mediated. While their exact etiologies remain unknown, results from basic science and clinical studies suggest that interplay between genetic factors and enteric bacteria are crucial for disease development, owing to abnormal host responses directed against the commensal microbiota. Key clinical signs include vomiting, diarrhea and weight loss, and histopathologic lesions of inflammation may involve the stomach, small intestine, or colon. Recent advances in molecular tools, disease activity indices, and biomarker development now permit objective assessment of IBD severity at diagnosis and in response to various therapies. Treatment of IBD involves both dietary and pharamacologic interventions as well as therapeutic manipulation of the enteric microbiota through the use of antibiotics and soluble fiber (prebiotic) supplements. Here we provide a comprehensive overview on the etiopathogenesis, clinical features, diagnosis strategies, current treatment recommendations, and outcomes from veterinary studies in dogs and cats with IBD. We also offer scientific comparison between human and canine IBD.

2. INTRODUCTION

Inflammatory bowel disease (IBD) is a collective term applied to a group of chronic enteropathies characterized by persistent or recurrent gastrointestinal (GI) signs, inflammatory infiltrate, and response to treatment with diet, antibiotics, or immunosuppressive drugs, whereby the basis for different response or lack of responses is not known (1-8). The cause for IBD is unknown and this disorder is distinct from other causes of chronic intestinal inflammation (Table 1). IBD is arguably the most common histopathologic diagnosis in dogs and cats with chronic GI signs although its true prevalence is unknown (7). Signs of vomiting, diarrhea, alterations in appetite, and weight loss generally predominate and IBD may cause mucosal inflammation in any portion of the GI tract (but especially the small intestine). Lymphocytic-plasmacytic enteritis is the most common reported form although eosinophilic, granulomatous, and suppurative intestinal inflammation may also occur (1, 2, 7, 9, 10). Treatment of IBD involves both dietary and anti-inflammatory interventions as well as therapeutic manipulation of the enteric microbiota through the use of antibiotics and soluble fiber (prebiotic) supplements.

This review will examine IBD in companion animals, focusing on the genetic, immunologic,

Table 1. Causes for chronic intestinal inflammation in dogs and cats

Causes for Chronic Intestinal Inflammation
Chronic infection
• *Giardia* spp
• *Tritrichomonas foetus*
• *Cryptosporidium* spp
• *Histoplasma* spp
• *Toxoplasma* spp
• *Mycobacteria* spp
• Protothecosis
• Pythiosis
• Pathogenic bacteria (*Campylobacter jejuni,*
• *Salmonella* spp, adherent/invasive *E. coli*
Antibiotic-responsive enteropathy
Food allergy
Other primary gastrointestinal diseases
• Intestinal lymphangiectasia
• Lymphoma
• Adenocarcinoma
• Other neoplasms
Idiopathic causes
• Lymphocytic-plasmacytic enteritis/colitis
• Eosinophilic gastroenterocolitis
• Non-AIEC granulomatous enteritis

Important IBD mimics include antibiotic-responsive enteropathy and adverse food reactions which include food allergy and food intolerance. AIEC = adherent/invasive *E. coli.*

clinicopathologic, and microbiologic features of these disorders as compared to human IBD (i.e., Crohn's disease and ulcerative colitis). Included will be a discussion on the proposed etiopathogenesis followed by the clinical features of IBD, including the presenting signs, differential diagnoses, endoscopic appearance, histopathological features, and indices for assessment of disease severity. An overview of treatment strategies and parameters which provide long-term prognostic information will also be covered. Finally, the potential value of the dog as a spontaneous model for studying mechanisms of inflammation in human IBD will conclude the discussion.

3. ETIOPATHOGENESIS OF IBD

The etiology for IBD in most dogs and cats remains unknown similar to human IBD. The current paradigm of Crohn's disease (CD) and ulcerative colitis (UC) involves complex interactions between environmental factors, such as the intestinal microbiota, and dysregulated host responses in a genetically-susceptible individual (11, 12). Advances in understanding the genetics of human IBD have occurred from single nucleotide polymorphism (SNP) and candidate gene approaches, as well as from studies utilizing transgenic mouse models of intestinal inflammation. Collectively, this work has identified several genes (e.g., NOD2/CARD15, IBD5, IL23R, SLC22A4/5 (OCTN1 and OCTN2), ATG16L1, and IRGM that contribute to disease susceptibility through their effects on barrier function, innate, and adaptive immunity. These genetic variants with functions associated with human IBD and the pathogenesis of experimental colitis have been reviewed elsewhere (13-17).

The study of canine IBD also suggests that interplay between genetic factors and enteric bacteria are crucial for disease development, owing to abnormal host responses directed against the commensal microbiota. In support of this notion, several dog breeds are recognized as being predisposed to specific forms of IBD including immunoproliferative enteropathy in Basenjis, protein-losing enteropathy (PLE) in Soft-Coated Wheaton Terriers, and granulomatous colitis (GC) in Boxers (9, 18-21). Genome wide association analysis has identified disease associated SNPs in Boxer dogs with GC that may impact bacterial killing (Craven M and Simpson KW, unpublished observations). This could explain the presence of *E. coli* within mucosal macrophages of GC affected dogs and remission of signs after their eradication with antibiotics (22). In dogs with GC and people with Crohn's ileitis, *E. coli* is a predominant member of the Proteobacteriaceae colonizing the colonic and ileal mucosa, respectively (23, 24). *E. coli* associated with GC in Boxer dogs displays pathogen-like behavior in cultured cells (24) and belongs to a putative new pathogroup of adherent and invasive *E. coli* (AIEC) which have been repeatedly isolated from patients with Crohn's disease (CD) in France, Spain, the UK, and USA (23, 25-28). A direct role for AIEC in CD is supported by their ability to induce granulomatous lesions *in vitro* ((23, 25, 26, 28-33) and to exploit host defects in bacterial killing and autophagy conferred by CD related polymorphisms in ATG16L, IRGM, and NOD2 (31, 33).

German Shepherd Dogs (GSD) show increased susceptibility to chronic enteropathy, typified by lymphocytic-plasmacytic inflammation and clinical responses to antibiotics, diet, or immunosuppression (1, 34, 35). Recent studies in GSD with IBD using contemporary culture independent techniques have identifed dysbiosis in association with differentially high and low expression of pattern recognition receptors TLR4 and TLR5, respectively, relative to healthy Greyhounds (36). The possibility that allelic variation of pattern recognition receptors TLR2, 4, and 5 could contribute to a functionally abnormal response to the intestinal microbiota in GSD was explored using a candidate gene approach to identify single nucleotide polymorphisms (SNPs). Three non-synonymous SNPs in the TLR5 gene and 2 non-synonymous SNPs in the TLR4 gene, respectively, were identified and evaluated further in a case-control study and found to be significantly associated with IBD (37). Additionally, multiple SNPs were identified in the canine NOD2 gene of both IBD-affected GSD and IBD-affected non-GSD breeds suggesting that NOD2 mutations contribute to chronic mucosal inflammation in heterogeneous canine populations.

Further evidence of deranged innate immunity in IBD includes the observation that bacteria-responsive TLR2, 4, and 9 were up-regulated in inflamed duodenal and colonic mucosa of IBD affected dogs relative to clinically healthy Beagles (38). Moreover, dogs with clinically severe, active IBD expressed higher levels of TLR2 receptors in the duodenum which correlated to clinical disease severity (39). In human IBD, activation of nuclear transcription factor NFκB is markedly up-regulated and strongly influences the course of mucosal inflammation through the production of IL-23 (40). It has been shown

Table 2. A summary of immunopathologic findings seen with canine and feline IBD

Parameter	Immunologic Abnormality	Clinical Study
A. Canine IBD Immunopathologic Summary		
Parameter	Immunologic Abnormality	Clinical Study
Mucosal B lymphocytes	↓ or ↑ IgG cells in small intestine	3, 44
Mucosal B lymphocytes	↑ IgA, IgG cells in colon	55
Mucosal B lymphocytes	↑ plasma cells in colon	48
Mucosal T lymphocytes	↓ $CD3^+$ cells in small intestine	3
Mucosal T lymphocytes	↑ $CD3^+$, $CD4^+$, $TCR\alpha\beta^+$ cells in small intestine	1
Mucosal T lymphocytes	↑ $CD3^+$, $CD8^+$ cells in colon	55
Mucosal T lymphocytes	↓ $TCR\gamma\delta^+$ IEL via flow cytometry	7
Mucosal mast cells	↓ or ↑ mass cells in small intestine	1
Mucosal macrophages	↑ in colon of HUC	9
Nitrate in lavage	↑ in colonic luminal nitrite and IgG	45
Mucosal iNOS	↑ iNOS in small intestine and colon	7
Mucosal MHC	↑ Class II^+ cells in colon (HUC)	9
Mucosal cytokines	Balanced Th1:Th2 mRNA expression in small intestine or colon	46, 47, 49
Mucosal cytokines	Predominant Th1 mRNA expression in colon	51
Mucosal TLR	↑ TLR2, 4, 9 in small intestine and colon	38
Mucosal NFκB	↑ macrophage expression	42
Mucosal apoptosis	↓ lymphocyte caspase 3	43
B. Feline IBD Immunopathologic Summary		
Commensal bacteria response	↑ Serum IgG responses	7
Mucosal MHC	↑ class II^+ expression in epithelia + macrophages	53
Mucosal cytokines via qRT-PCR	Balanced Th1:Th2 mRNA expression in small intestine	54
Mucosal cytokines via qRT-PCR versus histology	Balanced Th1:Th2 mRNA expression in small intestine	52

(A) Alterations in mucosal immune cells and mucosal markers are evident in canine IBD. (B) Cats with IBD show up-regulated mucosal MHC II expression while both dogs and cats have mixed Th1/Th2 cytokine activation relative to healthy animals. IEL = intra-epithelial lymphocytes; HUC = histiocytic ulcerative colitis; iNOS = inducible nitric oxide synthase; TLR = toll-like receptor.

that IL-23 promotes differentiation of novel $CD4^+$ effector T lymphocytes which produce IL-17 and cause subsequent activation of NFκB pro-inflammatory signals in CD (41). A recent study has shown that the presence of NFκB activation in lamina propria lymphocytes of intestinal biopsies of canine IBD was higher than in the control group (42).

The mucosal immunopathology of canine and feline IBD is derived from numerous studies (3, 7, 9, 38, 42-54) (Tables 2A and 2B). As previously documented in human IBD, specific subsets of immune cells, including lamina propria IgA^+ and IgG^+ plasma cells, $CD3^+$, $CD4^+$, and $CD8^+$ T cells, macrophages, and neutrophils are increased while mast cell numbers are decreased in canine IBD (1, 48, 55). However, gastric and colonic biopsies might be easiest to differentiate normal from IBD-affected tissues since duodenal biopsies have shown no differences in immune cell populations in healthy versus diseased cats (53) and dogs have similar numbers of $CD3^+$ T cells before and after clinical remission (56). More marked alterations in diverse immune cell populations occur in Boxer dogs with GC, which is typified by the infiltration of PAS positive macrophages and loss of goblet cells (9). Colonic lavage performed in dogs with IBD colitis yielded increased concentrations of nitrite and IgG in supernatant samples indicative of immune activation (45). Canine and feline IBD are characterized by altered mucosal cytokine profiles compared to healthy animals with both species showing mixed Th1/Th2 cytokine activation (47, 49, 52, 57). Feline studies have shown up-regulated expression of select pro-inflammatory (IL-6, IL-23) cytokines that correlate with other inflammatory indices (52). Other markers of IBD including serum concentrations of pANCA and acute phase proteins, mucosal NFκB activation, lymphocyte P-glycoprotein expression, and apoptotic mucosal markers are discussed in subsequent sections.

Both clinical and research data indicate that altered composition of the intestinal microbiota (dysbiosis) is pivotal in driving the inflammatory process in small animal IBD. A role for luminal bacteria is strongly suggested by observations that therapeutic levels of metronidazole and tylosin attenuate clinical disease in cats and dogs, respectively (58, 59). In separate studies, increased lamina propria myeloid/histiocyte antigen-positive macrophages, up-regulated epithelial MHC class II molecule expression, and increased antibody reactivity to components of the commensal microbiota have been associated with chronic intestinal inflammation in cats with IBD (53, 60). Furthermore, the numbers of mucosa-associated *Enterobacteriaceae* (determined by fluorescent *in situ* hybridization (FISH) using 16S rRNA bacterial probes) correlated with abnormalities in duodenal histology, up-regulated mucosal cytokine mRNA, and clinical signs in cats with IBD (52). In separate molecular studies, the diseased intestines of dogs with IBD were shown to be enriched with members of the families Enterobacteriaceae and Clostridiaceae (61, 62). These studies illustrate the potential importance of mucosa-associated bacteria in canine and feline IBD. Granulomatous colitis in Boxer dogs is now recognized to be associated with E. coli and clinical remission correlates with eradication of invasive E. coli by fluoroquinolone antimicrobial therapy (20, 22). Detailed phenotypical and comparative genetic analysis have confirmed striking similarities between AIEC isolates obtained from Boxer dogs with GC and AIEC isolates derived from ileal tissues of humans with Crohn's disease (23).

Table 3. Diagnostic tests for intestinal inflammation

Test	Rule out
Elimination diet	Adverse food reaction
Fecal examination	Nematodes/protozoa
Fecal culture	Bacterial enteropathogens
Serum biochemistry	Metabolic and systemic disease
Specialized serology	Specific tests to include:
TLI	Exocrine pancreatic insufficiency
PLI	Active pancreatic inflammation
Total T_4	Feline hyperthyroidism
Cobalamin	Hypocobalaminemia
Cortisol	Hypoadrenocorticism
Imaging	Masses, GI obstruction
Endoscopic biopsy	IBD, neoplasia, fungal
Celiotomy/biopsy	IBD, neoplasia, fungal
Laparoscopy/biopsy	IBD, neoplasia, fungal

IBD is a diagnosis of exclusion and requires elimination of IBD mimics through sequential diagnostic evaluation. TLI = trypsin-like immunoreactivity; PLI = pancreatic lipase immunoreactivity.

Thus, there appears to be considerable similarity in the pathogenesis of intestinal inflammation between human and small animal IBD. The mixed Th1/Th2 cytokine response seen with canine IBD is not dissimilar from the predominant Th2 response in UC (63, 64). Granulomatous colitis in Boxer dogs shares a variety of etiologic and immunopathologic features with CD (9, 24). Moreover, both human and small animal IBD are characterized by various genetic disorders that lead to aberrant host responses directed against the enteric microbiota.

4. CLINICAL FINDINGS AND DIAGNOSIS OF IBD

4.1. Clinical presentation

The clinical manifestations of IBD are diverse and are influenced by the organ (s) of involvement, presence of active versus inactive disease, and the occurrence of physiologic complications seen with enteric plasma protein loss and/or micronutrient (cobalamin) deficiency (1, 2, 4, 5, 7, 65-67). Canine and feline IBD are diseases which predominantly affect middle-aged animals. Vomiting and diarrhea are most commonly observed and are often accompanied by decreased appetite and weight loss. Gastric and duodenal inflammation is associated with vomiting and small bowel diarrhea while colonic involvement causes large bowel diarrhea with blood, mucus, and straining. Some cats might have intercurrent inflammatory disease involving the liver or pancreas which contributes to clinical findings (67, 68). Disease affecting both the small and large intestines will result in mixed GI signs. Severe enteritis may result in progressive enteric plasma protein loss (i.e., panhypoproteinemia) causing ascites, especially in dogs. The clinical course of IBD is generally cyclical and is characterized by spontaneous exacerbations and remissions. Triggers for recurring signs are rarely identified but may include dietary indiscretion, transient exposure to intestinal pathogens, or drug (e.g., steroids, NSAIDs) administration (7).

4.2. Differential diagnoses

A diagnosis of IBD is one of exclusion and requires elimination of IBD mimics. Other possible causes for chronic intestinal inflammation may be excluded by complete clinical examination, laboratory testing, and specialized instrumentation (Table 3). After the exclusion of infectious/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 minimal change enteropathy (defined by normal endoscopic and histological apearance) that may respond to diet or antibiotics, and inflammatory bowel disease (diet-responsive, antibiotic-responsive, steroid-responsive, or unresponsive) and lymphangiectasia. Differentiation of severe IBD from well-differentiated lymphoma may be especially problematic in cats (69, 70). Therefore, a clinical diagnosis of IBD is based on: (1) the presence of persistent (>3 weeks) GI signs; (2) inability to identify known enteropathogens or other causes of signs of gastrointestinal disease; and (3) histopathologic confirmation of intestinal inflammation ((2, 4, 71, 72).

4.3. Fecal examination

Fecal examination by direct wet mount or flotation techniques is important to rule out parasitic causes (protozoa, nematodes) for mucosal inflammation. Giardia and cryptosporidium infections are best detected using indirect-fluorescent antibody (IFA) tests. Cats having chronic large bowel diarrhea should be screened for *Tritrichomonas foetus* infection by polymerase chain reaction (PCR) (73). Young animals with bloody mucoid stools and cytologic evidence of mucosal inflammation should have fecal cultures performed to rule-out infection with pathogenic (*Campylobacter jejuni*, Salmonella) bacteria.

4.4. Hematology

Routine hematology may reveal non-regenerative anemia reflective of chronic inflammation or enteric blood loss. Neutrophilia with or without a left shift is associated with erosive/ulcerative intestinal lesions. Eosinophilia is seen with some forms of IBD such as eosinophilic enteritis. Thrombocytopenia and thrombocytosis are uncommon hematologic manifestations observed in dogs with IBD (74).

4.5. Serum biochemistry and specialized serologies

Results from biochemical analysis rarely provide pathognomonic evidence for IBD but do facilitate the recognition of abnormalities in other organs which may cause GI signs. In cats with IBD, hyperproteinemia and mild elevation in liver enzymes (i.e., alanine aminotransferase (ALT) and alkaline phosphatase (ALP)) are often reported (2, 65, 66, 75). Dogs with PLE frequently have hypoalbuminemia and hypoglobulinemia which may be accompanied by hypocholesterolemia and hypocalcemia. The presence of hypoalbuminemuia correlates with negative outcome in dogs (4, 5). While cats with IBD might have increased serum fPLI concentrations (suggestive of pancreatitis) this association does not appear to influence clinical outome based on a recent report (76). On the other hand, increased serum PLI (i.e., cPLI) concentration in dogs with IBD has been associated with a worse clinical outcome (77). Dogs and cats with chronic small bowel disease may have decreased serum cobalamin concentration secondary to cobalamin malabsorption (67). Failure to recognize and correct hypocobalaminemia

associated with cobalamin deficiency can delay clinical recovery even with specific therapy for IBD (78). Low serum cobalamin has also been correlated with a poor prognosis in dogs with chronic enteropathy (4).

4.6. Diagnostic imaging

Abdominal radiology is most helpful in the assessment of extra-alimentary tract disorders causing gastroenteritis. Abdominal ultrasound is superior to radiology in defining focal versus diffuse mucosal disease, intestinal wall thickness, and mesenteric lymphadenopathy seen with IBD as well as other infiltrative (e.g., lymphoma) disorders (79). Older cats with ultrasonographic evidence of muscularis propria thickening are more likely to have lymphoma versus IBD (80). Ultrasonographic examination allows for fine needle aspiration of enlarged lymph nodes and focal wall thickening to provide samples for cytologic analysis.

4.7. Endoscopy and mucosal biopsy

Endoscopic examination with mucosal biopsy is essential to confirm a diagnosis of IBD and to determine the extent of disease. The most widely reported endoscopic abnormalities seen with canine and feline IBD include mucosal friability, increased granularity, and mucosal erosions (2, 4, 75, 81). The association between endoscopic lesions and disease activity in small animal IBD has been investigated only to a limited extent. In separate investigations, endoscopic abnormalities to the duodenum of dogs with IBD did or did not correlate to clinical indices of inflammation (4, 81). The presence of severe mucosal lesions in the duodenum, but not the colon, was associated with negative outcome in one study (4). In contrast to dogs, cats with IBD have endoscopic abnormalities which do correlate to both clinical disease activity and histopathologic lesions at diagnosis (52, 75). Standard mucosal biopsies of the stomach and duodenum alone may occasionally miss more distal sites (e.g., ileal mucosa) of cellular infiltration. Therefore, it is suggested that ileal biopsies should be obtained in cats to increase diagnostic yield whenever gastroduodenoscopy or colonoscopy is performed, especially since lymphoma is an important differential diagnosis in cats (69). The need to perform ileoscopy may be guided by the presence or absence of hypocobalaminemia since cobalamin is absorbed in the ileum.

4.8. Histopathology of IBD

Histopathologic evaluation of biopsy specimens is presently required for definitive diagnosis of intestinal inflammation. The microscopic findings in IBD consist of minimal to pronounced inflammatory cell infiltration of the gastric and/or intestinal mucosa accompanied by varying degrees of mucosal architectural disruption. Unfortunately, biopsy interpretation is notoriously subjective and suffers from extensive interobserver variability and the technical constraints of specimen size and procurement/processing artifacts inherent in evaluation of endoscopic specimens (82, 83). Several grading systems for evaluation of endoscopic specimens from dogs and cats with IBD have been proposed but controversy exists regarding definitive morphologic criteria for making a histopathologic diagnosis of IBD and no standard microscopic grading system of IBD has been validated with respect to disease severity or outcome (2, 9, 52, 65, 72, 84-86). One recent effort to standardize the assessment of gastrointestinal inflammation between pathologists has resulted in design of a histology monograph that defined numerous morphologic and inflammatory features in endoscopic biopsies (87). However, even with this standardized scheme there was very poor agreement between pathologists (86) and simply summing unweighted numerical severity scores did not reflect the severity of disease (e.g., the maximal score in Boxer dogs with fatal GC was 16 out of 24). Subsequent analysis of these parameters has resulted in development of a 'model system' for defining intestinal inflammation of IBD that is presently being tested in a separate clinical trial.

At present, IBD is subjectively classified based on the predominant cellular infiltrate within the lamina propria. Intestinal infiltration with macrophages or neutrophils raises the possibility of an infectious process, and culture, special stains and fluorescence *in situ* hybridization (FISH) are indicated. The presence of moderate to large numbers of eosinophils in intestinal biopsies, which is often accompanied by circulating eosinophilia, suggests possible parasitic infestation or dietary intolerance. 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 seen in Basenji, Lundehund, and Chinese Sharpei breeds. However, the appropriateness and clinical relevance of the term lymphocytic plasmacytic enteritis is a contentious issue. Dogs have similar numbers of $CD3^+$ T cells before and after clinical remission (56), and cats with and without signs of intestinal disease have similar numbers of lymphocytes and plasma cells (53).

Recent studies indicate that changes in mucosal architectures, such as villous morphology and goblet cell mucus content, are related to the presence and severity of gastrointestinal disease. These studies have used quantitative observer-independent variables (e.g., inflammatory cytokines, intestinal mucus) to identify histopathological correlates of disease. In cats with signs of GI disease, villus atrophy and fusion correlated with severity of clinical signs and degree of proinflammatory cytokine upregulation in the duodenal mucosa (52). Architectural changes in the gastric mucosa also correlated with cytokine upregulation in dogs with lymphocytic gastritis (88). In the colon, loss of mucus and goblet cells correlates with the severity of disease in dogs with "lymphoplasmacytic" and granulomatous colitis.

4.9. Clinical activity indices

Clinical indices remain the most widely used tools in assessing disease activity in human IBD, both as a measure of the initial response to individual treatments and to long-term prognosis (89-93). Similar scoring systems have now been designed for use in the dog. The canine inflammatory bowel disease activity index (i.e., CIBDAI) is a numerical clinical scoring index composed of six

Table 4. The canine IBD activity index (CIBDAI)

Attitude/activity	**Assessment:**
0	Normal
1	Slightly decreased
2	Moderately decreased
3	Severely decreased
Appetite	Assessment:
0	Normal
1	Slightly decreased
2	Moderately decreased
3	Severely decreased
Vomiting	Assessment:
0	None
1	Mild (one time/week)
2	Moderate (two to three times/week)
3	Severe (more than three time times/week)
Stool consistency	Assessment:
0	Normal
1	Slightly soft feces or fecal blood, mucus or both
2	Very soft feces
3	Watery diarrhea
Stool frequency	Assessment:
0	Normal
1	Slightly increased (two to three times/day)
2	Moderately increased (four to five times/day)
3	Severely increased (more than five times/day)
Weight loss	Assessment:
0	None
1	Mild (< 5% loss)
2	Moderate (5-10% loss)
3	Severe (> 10% loss)
Cumulative score	Disease
0-3	Clinically insignificant disease
4-5	Mild IBD
6-8	Moderate IBD
≥9	Severe IBD

This numerical scoring system defines clinical disease activity on the basis of six salient gastrointestinal signs. The composite CIBDAI score defines clinically insignificant disease or the presence of mild, moderate, or severe IBD.

parameters which has recently been evaluated in separate clinical trials (Table 4). In one study, CIBDAI scoring was used to assess disease activity in relationship to histopathologic findings and C-reactive protein (CRP) concentrations in IBD dogs pre- and post-treatment (71). Still others have utilized this index in treatment trials evaluating single versus combination drug protocols for IBD, long-term outcome measures for IBD, and in the assessment of biomarkers for gauging intestinal inflammation (4, 8, 56, 71, 81, 94, 95). While CIBDAI scoring provides important information during treatment it does not seem to correlate with histopathologic grade (4, 42, 56, 81). Iterations of this original index have recently evolved and may have utility in future trials (4, 81).

An index for assessment of inflammatory activity in cats with chronic enteropathy has also recently been designed (75). The feline chronic enteropathy activity index or FCEAI is comprised of five independent variables (along with histopathologic inflammation) which can be temporally assessed and compared when collected at different times (Table 5). Similar to human and canine indices, the magnitude of the numerical score is proportional to the degree of disease activity. This index may serve as the principal measure of response to a therapeutic trial and could also be used to tailor medical therapy for an individual patient's need. Importantly, clinical trial results indicate that the FCEAI may be used to assess disease activity in cats having either IBD or food-responsive enteropathy (75).

5. TREATMENT OF IBD

Treatment principles for canine and feline IBD are empirical and consist of combination therapy using both dietary and pharmacologic interventions. As compared to clinical trials evaluating the efficacy of therapy for CD and UC, only one randomized, controlled drug trial for canine IBD has been reported (94). There are, however, abundant evidence-based observations that feeding elimination diets and administering corticosteroids, immunosuppressive drugs, and/or select antibiotics are useful in the clinical management of canine and feline IBD. There is relatively sparse clinical data investigating prebiotic or probiotic therapy for IBD.

5.1. Nutritional therapy

The rationale for dietary therapy of IBD is that restricting exposure to antigens (i.e., dietary proteins) known to evoke sensitivity will reduce exaggerated host responses and attenuate intestinal inflammation. Other indications for specialized nutrition include the presence of decreased appetite, impaired nutrient absorption, or enteric plasma protein loss seen with moderate-to-severe mucosal inflammation. The benefits of dietary therapy alone (or in conjunction with pharmacological therapy) in the clinical management of canine and feline IBD are well documented (4, 6, 8, 65, 66, 71, 75, 94, 96) (Table 6). While evidence-based observations indicate that most dogs and cats respond favorably to dietary intervention, the superiority of one

Table 5. The feline chronic enteropathy activity index (FCEAI)

Variable	Assessment
GIT signs	No or yes
Attitude/activity	
Appetite	Scored
Vomiting	0-3*
Diarrhea	
Weight loss	
Endoscopic lesions	0=no; 1=yes
Total protein	0=normal; 1=increased
ALT/ALP	0=normal; 1=increased
hosphorous	0=normal; 1=decreased

Similar to the CIBDAI, this clinical scoring system incorporates multiple variables including gastrointestinal signs, endoscopic lesions, and select biochemical analytes. Clinical trials indicate that the FCEAI is useful for defining disease activity in cats having either IBD or food- responsive enteropathy. * Range of gastrointestinal signs from not present (0) to severe (3).

Table 6. Nutritional therapy for canine and feline IBD

Clinical Study	Species (No.)	Diet	Primary/Adjunct role	Response
66	Cat (28)	Controlled	Adjunct	50% respond
6	Cat (60)	Controlled	Adjunct	80% respond
96	Dog (6)	Elimination	Primary	70% respond
71	Dog (58)	Elimination	Adjunct	80% respond
8	Dog (65)	Elimination	Primary	50% respond
4	Dog (70)	Elimination	Adjunct	60% respond
94	Dog (54)	Elimination	Adjunct	80% respond
75	Cat (17)	Elimination	Adjunct	100% respond

Dietary therapy for chronic IBD is an important intervention and may be used as either a primary or adjunct treatment along with the administration of pharmacologic agents.

Table 7. Drug therapy for canine and feline IBD

IBD Study	Trial Design	Drug Therapy	Outcome
A. Canine			
2	RS	Pred, MTZ, 5-ASA	> 80% response
71	PT	Pred, MTZ, 5-ASA	> 80% response
5	RS	Pred, MTZ, 5-ASA, tylosin	Confounding variables; ↓ albumin = negative outcome
59	PT	Tylosin	↓↓ diarrhea in all dogs
95	PT	Pred, MTZ, 5-ASA, AZA	↓↓ diarrhea with immunosuppressive drugs
98	PT	Pred	> 75% response
99	PT	Cyclosporine	> 80% response in steroid refractory IBD
8	PT	Pred	> 50% response
81	PT	Pred + MTZ	> 75% response
4	PT	Pred, cyclosporine	> 60% response
56	PT	Pred	↓ albumin = negative outcome
22	PT	Enrofloxacin	> 85% response in HUC
94	RCT	Pred vs Pred+MTZ	> 80% response in both groups
B. Feline			
2	RS	Pred, MTZ	> 80% response
65	RS	Pred	> 50% response
66	RS	Pred, tylosin, 5-ASA	70% response
75	PT	Pred	100% response

Cumulative data shown is derived from different study designs including retrospective studies (RS), case-controlled prospective trials (PT), and randomized-controlled trials (RCT). Outcome measures include attenuation of gastrointestinal signs +/- biomarker analysis. PRED = prednisone or prednisolone; MTZ = Metronidazole; 5-ASA = sulfasalazine; AZA = azathioprine.

novel protein source versus another or the advantage in feeding an intact protein elimination diet versus a hydrolyzed protein elimination diet has not been shown to date. Characteristics of an ideal diet for IBD include the presence of a novel intact (e.g., whitefish, duck, venison, etc.) or hydrolyzed protein source, highly digestible carbohydrate, gluten-free, low in lactose and fat, nutritionally balanced, and high palatability (6, 7). A variety of commercial diets fulfills these requirements and is readily available for use in dogs and cats. Modifying the dietary n3:n6 fatty-acid ratio may also modulate inflammatory responses by reducing production of pro-inflammatory metabolites (97). Supplementation with parenteral cobalamin is advised if serum concentrations are subnormal.

5.2. Drug therapy

Drug therapy for canine and feline IBD includes the use of corticosteroids, antibiotics, and various immunosuppressive agents (2, 4, 5, 8, 22, 56, 59, 65, 66, 71, 75, 81, 94, 95, 98, 99) (Table 7). Practical drug treatment recommendations for IBD are determined by disease severity and clinical course (e.g., presence of mild IBD versus PLE), the involved segments of the alimentary tract, clinician experience, size of the patient impacting drug costs, and the potential risks or side-effects associated with use of some medications. Some clinicians prefer a sequential approach to nutritional and drug therapy for IBD. The optimal drug or drug combination as well as duration of therapy for induction and maintenance of remission of clinical signs have not been determined for most protocols (7, 71).

Several different combinations of glucocorticoids and antimicrobials have been used for treatment of canine IBD in different trials. One retrospective analysis of 80 dogs with IBD reported that treatment with prednisolone, sulfasalazine, metronidazole, or tylosin was not associated with a favorable long-term outcome (5). The initial therapy chosen in this trial consisted of multiple drugs and various combinations were administered, which confounded interpretation of response rates. The remission status was characterized as full (26%), partial with cyclical signs (50%), or incomplete (4%) at follow-up examination, but scoring indices were not utilized. A separate study reported that treatment with prednisone and metronidazole for 21 days significantly decreased the CIBDAI and CRP from baseline values in 58 IBD dogs, although sulfasalazine also was administered to some dogs with colitis (71). Similarly, the combination of prednisone and metronidazole administered at tapering doses over 90 days was associated with both clinical (CIBDAI) and endoscopic improvement in dogs with non-hypoproteinemic lymphocytic-plasmacytic enteritis (81). Still another study evaluated the association among drug treatment, clinical response, and histologic severity of inflammation at the time of diagnosis (95). Dogs with IBD were treated with multiple drugs (metronidazole, prednisolone, azathioprine, sulfasalazine or some combination of these) with efficacy assessed 3 times over a 12-week treatment period. Overall, 15 of 21 dogs with IBD of varying severity showed good therapeutic responses based on clinical (CIBDAI) scores. However, the effect of metronidazole treatment in a subset (n=5) of IBD dogs with low disease activity was questionable. Moreover, there was no significant association between efficacy of therapy and age, CIBDAI score, or serum albumin concentration. Finally, Allenspach *et al* showed that 10 of 21 dogs with chronic enteropathies that received oral prednisone responded to the initial treatment and failed to show any relapses for the next 3 years (4).

Other single and combination drug regimens have been reported to treat canine IBD effectively. Budesonide is widely used in dogs and is considered effective anecdotally; however, controlled trials attesting to its anti-inflammatory activity in IBD have not been performed (100). Cyclosporine was a useful rescue agent in 11 of 14 IBD dogs that were previously refractory to prednisolone and intermittent antibiotic therapy (99). Another investigation reported that a 10-week trial of prednisolone reduced clinical (CIBDAI) scores in IBD dogs post-therapy (8). Of interest, 54% of IBD dogs in this study were hypoalbuminemic at diagnosis, but the glucocorticoid responsiveness of these dogs in comparison to the non-hypoproteinemic IBD dogs was not reported. A small case series also suggested that tylosin may have a role in treating canine chronic diarrhea based on improved fecal consistency scores after antibiotic and dietary therapy (59). Antimicrobials, such as tylosin or metronidazole, may exert their anti-inflammatory actions in IBD through one of several mechanisms. One theory is that changing the intestinal microbiota prevents colonization by pathogenic bacteria (101). Another potential mechanism is that in genetically-susceptible hosts there is a lack of tolerance to commensal bacteria in the intestines, leading to activation of the gut immune system (11, 12, 101, 102). Suppression of the microbiota might lead to down-regulation of aberrant host responses directed against microbial antigens that trigger and perpetuate chronic mucosal injury. A 3 week course of metronidazole (15 mg/kg q12h) along with feeding an elimination diet was successful in treating chronic diarrhea in GSD having a distinctly different microbiome as compared to healthy dogs (39). Antibiotics such as amoxicillin-clavulinic acid and metronidazole also might have direct anti-inflammatory effects independent of their antimicrobial activity, including suppression of cell-mediated immunity (58, 103). Lastly, clinical remission in Boxers with GC correlated with eradication of mucosally invasive *E. coli* during treatment with enrofloxacin (22).

Comparative data evaluating the efficacy of drug therapy for feline IBD is derived from only a few large case-based investigations (2, 65, 66, 75). In separate studies, it was shown that prednisolone alone (n=14 cats) or used in combination with tylosin or sulfasalazine (n=14 cats) resulted in resolution of clinical signs in cats with gastroenteritis or IBD colitis (65, 66). Prednisone used alone or in combination with another drug resulted in partial or complete resolution of clinical signs in 39 of 47 (80%) of diseased cats in a different study. A more recent trial reported excellent clinical responses with attenuation of gastrointestinal signs and disease activity scores in cats with IBD treated with prednisolone as a single drug induction agent (75). Taken together, these observations would suggest that corticosteroids such as prednisone and prednisolone are effective pharmacologic agents for treating cats with IBD.

It is clear that there are many aspects of IBD drug therapy in companion animals for which the data are lacking or inadequate, similar to human IBD (104). Additional prospective data (i.e., randomized controlled clinical trials) are needed to resolve these areas of controversy and to provide optimal drug treatment choices to the patient with IBD.

5.3. Probiotics and prebiotics

Increasing evidence supports a potential therapeutic role for probiotics and prebiotics in ameliorating chronic intestinal inflammation in humans (105-107). There have only been two studies involving the use of prebiotics on the intestinal microbiota in healthy dogs and cats. In one study, FOS supplemented at 0.75% dry matter produced qualitative and quantitative changes in the fecal flora of healthy cats (108). Compared with samples from cats fed a basal diet, increased numbers of lactobacilli and *Bacteroides* spp and decreased numbers of *E. coli* were associated with the FOS diet. However, bacteriologic examination of the duodenal juice in these same cats showed wide variation in the composition of the duodenal flora, across sampling periods, which was not affected by FOS supplementation (109). Moreover, healthy Beagle dogs fed a 1% FOS diet over a 3 month trial showed inconsistent fecal excretion of *Lactobacillus* spp and *Bifidobacterium* spp (110).

Very little has been reported on the use of probiotics to treat IBD in dogs and cats. Recent *in vitro*

studies have confirmed the capacity of a lyophilized probiotic cocktail (e.g., three different *Lactobacillus* spp strains) to modulate the expression of regulatory versus pro-inflammatory cytokines in dogs with chronic enteropathies (111). However, a clinical trial using this same probiotic cocktail fed to dogs with food-responsive diarrhea failed to induce consistent patterns of regulatory (e.g., beneficial) cytokine expression in spite of obvious clinical improvement (112). Conversely, a different probiotic strain (i.e., Prostora max® - consisting of *B. animalis* strain AHC7) was shown to provide more rapid resolution of acute diarrhea than dogs that received placebo (113). Importantly, results from clinical trials evaluating the efficacy of any probiotic therapy in idiopathic IBD have not been reported. The link between the intestinal microbiota and gastrointestinal health is now obvious and maintenance of microbial homeostasis holds promise as a therapeutic strategy for preventing/treating chronic intestinal inflammation. Future developments must include performance of randomized controlled trials to determine the role of probiotics and prebiotics in the management of canine and feline chronic enteropathies, including IBD.

6. BIOMARKERS AND OUTCOMES ASSESSMENT IN IBD

There is a need for biologic markers that can assess the natural progression and predict the course of clinical disease including response to treatments in humans and animals with IBD. The ideal laboratory marker might be serologic or tissue based and should have a variety of useful characteristics including: (1) be able to accurately identify individuals at risk; (2) be disease-specific; (3) be able to detect disease activity and monitor the effect of treatment; (4) be easy to perform; (5) be cost-effective such that serial evaluation may be performed; and (6) it should have predictive value towards predicting relapse or recurrence of the disease (71, 75, 114). A variety of **serologic immune markers** (e.g., perinuclear anti-neutrophil antibody (pANCA), anti-*Saccharomyces cerevisiae* antibody (ASCA), *E. coli* outer membrane porin C (Omp C), anti-CD related bacterial sequence (I2), CBir1 flagellin), **tissue markers** (e.g., mucosal cytokines and chemokines (TNF-α, IL-6, IL18), adhesion molecules (RANTES), markers of activation (NFκB), immune cells (IL-17 positive T cells, neutrophils, $CD11c^+$ dendritic cells), and non-immune cells (TLR2, TLR4), tissue expression of matrix metalloproteinases (MMPs)), and **other laboratory markers (**e.g., ESR, serum CRP, fecal calprotectin, other S100 A proteins) used in monitoring human IBD are discussed elsewhere (11, 12, 101, 102, 114-116).

Titers for pANCA have been evaluated as diagnostic markers in canine IBD. In one study, 31 dogs with chronic intestinal inflammation were compared with 29 dogs with acute or chronic diarrhea of known origin and with 42 healthy dogs (117). Results indicated that pANCA was a highly specific marker for IBD although the sensitivity of the assay was too low to be of value as a routine screening test. More recently, pANCA was shown to be a highly specific marker versus anti-nuclear antibody (ANA) for differentiating dogs with IBD from other gastrointestinal disorders (118). Still others have shown the pANCA might have value as a diagnostic marker of familial PLE in Soft Coated Wheaton Terriers, and may help guide treatment decisions concerning dietary management of canine food-responsive enteropathy (FRE) (8, 119). Taken together, these data indicate that serum pANCA may be a sensitive biomarker for canine IBD although the association between pANCA and clinical disease activity has not been demonstrated.

Other serologic markers including cytokines and acute phase proteins have been investigated in canine and feline IBD. In a recent paper, serum microalbumin, TNF-α, and CRP were prospectively evaluated in 16 dogs diagnosed with IBD (120). Unfortunately, serum TNF-α levels were normal in all IBD dogs in this study although CRP was increased in the majority of dogs. The role of CRP as a marker of intestinal inflammation in dogs with IBD has been more extensively evaluated. Jergens *et al* showed that dogs diagnosed with moderate-to-severe histologic IBD (n=28) had increased baseline CRP concentrations which decreased following successful medical therapy for intestinal inflammation (71). In a follow up drug study, this same group showed that CRP concentrations were increased in 23 of 54 (43%) IBD dogs on initial presentation and that serum CRP decreased with drug therapy to within reference intervals in most dogs (94). These observations suggest that CRP may be normal or increased in dogs with IBD and may be most useful in assessing the response of individual dogs to treatment along with changes in clinical indices (121). These findings are in broad agreement with reports in human IBD where patients may have CRP concentrations within the normal range at diagnosis with wide overlap observed between values for patients with CD and UC (121, 122).

Tissue markers of inflammation (besides mucosal cytokine mRNA expression) have also been investigated in canine IBD. The expression of caspase 3 was reduced in dogs with IBD versus healthy controls suggesting that impaired lymphocyte apoptosis might contribute to the pathogenesis of chronic intestinal inflammation (43). Activation of mucosal nuclear factor NFκB expression was shown to be linked with intestinal pathology of IBD in another study (42). Resolution of disease, as indicated by improvement in CIBDAI scores, was associated with decreased NFκB expression in macrophages of the lamina propria and in epithelial cells in this study. The expression of p-glycoprotein (i.e., p-gp) in mucosal lymphocytes has also been investigated and shown to be up-regulated in IBD dogs treated with prednisolone (98). Moreover, this earlier study showed that in dogs with steroid-responsive chronic enteropathy, low p-gp expression was associated with a good therapeutic response. Several other clinicopathologic markers have been useful to predict response to treatment and outcome in dogs with chronic enteropathy. In separate investigations, hypoalbuminemia or hypoalbuminemia and hypocobalaminemia were identified as risk factors for negative long-term outcome in dogs with IBD (4, 5).

Table 8. Comparative features of IBD in humans and dogs

Feature	Human IBD	Canine IBD
Genetic basis	Yes	Likely
Etiology	Unknown but likely multifactorial	Unknown but likely multifactorial
Commensal bacteria role	Yes	Yes
Hematochezia	Yes	Yes
Diarrhea	Yes	Yes
Definitive diagnosis	GI biopsy	GI biopsy
Disease activity assessment	Clinical indices; biomarkers (ASCA, pANCA, CRP, calprotectin)	Clinical indices; biomarkers (pANCA, CRP, calprotectin?)
Response to anti-inflammatory drugs	Yes	Yes
Response to antibiotics	Yes	Yes
Spontaneous "flares" in GIT signs	Yes	Yes

Idiopathic canine IBD shows numerous similarities to human IBD, including host defects in innate immunity contributing to disease susceptibility, prominent role for the commensal microbiota, biopsy confirmation for definitive diagnosis, use of clinical indices and biomarkers for disease assessment, and similar treatment interventions. These characteristics and others make the dog a useful animal model to study human IBD. GIT = Gastrointestinal tract

Little information is available regarding biomarkers of chronic intestinal inflammation in cats. Low serum cobalamin concentration is one variable that has been associated with refractoriness to treatment in cats with chronic enteropathy (67, 78). Both the FCEAI and serum acid glycoprotein (AGP) concentration decreased in cats successfully treated for IBD or FRE, suggesting that AGP may be suitable for laboratory evaluation of the effect of therapy in these patients.

In conclusion, it is obvious that no single biomarker, be it serologic or mucosal, can be considered as a predictor of disease progression or response to therapy in clinical practice. It would appear that these markers are most useful as adjunct tools for the clinician, along with clinical grading of disease severity, for assessment of therapeutic response in dogs and cats with IBD.

7. CONCLUSION AND FUTURE DIRECTIONS

Idiopathic IBD in dogs and cats represents a common and frustrating gastrointestinal disorder in veterinary medicine. More research is needed to unravel the mechanisms responsible for disease development and to translate these findings directly to human IBD. The primary features of IBD in humans and animals are remarkably similar (Table 8). Recent advances in clinical indices, histopathologic standards, and the development of species-specific immunologic reagents and innovative molecular tools have made the dog as an excellent 'spontaneous' animal model to study chronic immunologically-mediated intestinal inflammation including human IBD (22, 61, 62, 71, 72, 75, 87). In addition, the dog has higher genomic sequence similarity to human than the mouse, a species traditionally used for comparative disease genetics (123). However, clinical manifestations of complex disease in the mouse do not compare to the human form as closely as they do in the dog. Furthermore, the lifespan of the dog is much shorter than in humans; thus, clinical trials aimed at treatment of IBD can be carried out much quicker and yield results that should have relevant application to human trials (94). A new study has now demonstrated the contribution of dysregulated mucosal genes, including MMP1, S100G, CEACAM1, and PPARG, to the pathogenesis of chronic intestinal inflammation in dogs with IBD.

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Abbreviations: IBD = Inflammatory bowel disease, PLE = Protein-losing enteropathy, GC = Granulomatous colitis, AIEC = Adherent and invasive E. coli, GSD = German Shepherd Dogs, TLR = Toll-like receptor, SNP = Single nucleotide polymorphism, CD = Crohn's disease, FISH = Fluorescent *in situ* hybridization, PCR = Polymerase chain reaction, PLI = Pancreatic lipase immunoreactivity, CIBDAI = Canine inflammatory bowel disease activity index, CRP = C-reactive protein, FCEAI = Feline chronic enteropathy activity index, UC = Ulcerative colitis, FRE - Food-responsive enteropathy

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