Part 1: Presentation Aims
(1) To define IBD and provide a current perspective of its importance to practitioners
(2) To review relevant diagnostic criteria for accurate diagnosis and to eliminate IBD mimics
(3) To review the limitations of endoscopic specimens for diagnosis of IBD inflammation
(4) To correlate clinical signs and histopathologic lesions of IBD using evidence-based observations

Definition and Scope of the Problem
Inflammatory bowel disease (IBD) broadly refers to a group of idiopathic, chronic gastrointestinal disorders characterized by benign mucosal inflammation. While the exact prevalence of IBD is unknown, it is arguably the most common histopathologic diagnosis obtained in dogs and cats with chronic vomiting and/or diarrhea. It is likely that IBD represents one form of chronic enteropathy that is distinguished from food-responsive and antibiotic-associated causes for gastroenteritis by therapeutic responsiveness. While the etiology for IBD remains unknown, accumulating evidence in humans and animal models suggests that intestinal inflammation results from altered interaction between resident microbes and the mucosa in a susceptible host. Aggressive host immune responses directed against bacteria and/or their products play a central role in the pathogenesis of chronic mucosal inflammation. The concept of impaired immunoregulation in IBD is supported by observations of increased numbers of immunoglobulin cells and T cells in inflamed tissues; up-regulated mucosal/luminal expression of nitric oxide metabolites; and altered serum concentrations of select acute phase proteins, such as C-reactive protein, in diseased dogs. Genetic predispositions are recognized in several breeds, including Siamese cats, German shepherds, basenjis, soft-coated Wheaton terriers, shar-peis, and French bulldogs, which develop a histiocytic ulcerative colitis.

Diagnosis of IBD is defined by the following features: (1) the presence of persistent gastrointestinal signs, which are characterized by cyclic periods of active and inactive disease; (2) inadequate response to dietary trials and anthelmintic therapies alone; (3) failure to document other causes for gastrointestinal inflammation; and (4) histopathologic (e.g., morphologic) evidence of benign mucosal inflammation. Clinical signs (vomiting, small and/or large bowel diarrhea, weight loss, alterations in appetite) are attributed to mucosal cellular infiltrates, inflammatory mediators, and inflammation-associated dysmotility. Histopathologic evaluation of biopsy specimens is required for definitive diagnosis; however, no standard microscopic grading system of IBD lesions has been universally accepted. 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. 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.

Relevant Diagnostic Testing
A diagnosis of IBD is one of exclusion and requires ruling out many other diseases that may cause intestinal inflammation. Systemic diseases, chronic parasitism, adverse food reactions (e.g., food allergy or intolerance), infectious diseases, and alimentary lymphosarcoma are the major differential diagnoses for canine and feline IBD. The optimal diagnostic protocol for IBD has yet to be established. It is essential that clinical signs be correlated with histologic evidence of gastroenteritis, and that other causes for chronic mucosal inflammation are eliminated by appropriate diagnostic testing. Therapeutic trials using anthelmintics or hypoallergenic diets may be effective in animals having parasitic or dietary causes, respectively, for enterocolitis.

Histopathologic Evaluation of Intestinal Biopsy Specimens
Histologic evaluation of biopsy specimens is required for definitive diagnosis. No standard microscopic grading system of IBD lesions has been established. Several histologic grading systems for evaluation of endoscopic specimens from dogs and cats with IBD have been described. Endoscopically obtained GIT mucosal biopsy collection remains the gold standard but presents a variety of challenges for both the clinician and the pathologist. It is recognized that these specimens are small, prone to procurement and/or processing artifact, and are difficult to optimally orient for accurate morphologic characterization. Note that extensive interobserver variability in interpretation between pathologists can occur. Recent studies show that the diagnostic accuracy (i.e., accurate
microscopic evaluation by the pathologist) is influenced by differences in endoscopic training and the optimal number of biopsy specimens submitted by the endoscopist that might detect a morphologic abnormality.

There is a clear need for standardization of upper/lower GIT endoscopic procedures. A histopathologic template has been recently published by the WSAVA Gastrointestinal Standardization Subgroup, which provides both illustrative and narrative interpretation of endoscopic specimens. There would appear to also be a need for standardized protocols when submitting endoscopic samples to the pathology laboratory. These adjunct data might include the provision of clinical signs, laboratory and/or radiographic findings, and even recommendations as to how to best “package” biopsies (e.g., biopsy cassette, lens paper, or cucumber slice) for transportation.

Relationship Between Histopathologic and Clinical Findings

The clinical course of IBD is characterized by spontaneous exacerbations and remissions, which make assessment of disease burden difficult. Moreover, gastrointestinal signs are highly variable, and the severity of disease may differ appreciably between patients depending on localization and extent of affected regions of the gastrointestinal tract. Various indices have previously been used to assess IBD activity in dogs, including clinical signs, histopathologic grades of mucosal inflammation, phenotypic analysis of immune cells, and measurement of inflammatory mediators such as metabolites of nitric oxide and altered expression of cytokine mRNA transcripts. Comparative indices for use in the cat have only recently been described.

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 for long-term prognosis. Similar studies have now recently been reported in the dog. Jergens et al. (2003) reported the use of a clinical scoring index (i.e., Canine IBD Activity Index [CIBDAI]) to assess disease activity in relationship to histopathologic findings and serum C-reactive protein (CRP) concentrations. These data showed that clinical scores correlated best to a combination of histopathologic severity and CRP concentration at diagnosis; however post-treatment histopathologic assessment was not performed. In a separate investigation, Garcia-Sancho et al. (2007) showed that clinical signs and macroscopic endoscopic lesions improved over 120 days in non-hypoproteinemic dogs treated with prednisone and metronidazole; however, treatment did not lead to significant changes in the severity of the gastric and duodenal histopathologic lesions of the affected dogs. Similar findings of a disconnect between clinical signs and histopathologic lesions of IBD have been reported by others. Allenspach et al. (2006) showed that total lymphocyte numbers in the duodenal mucosa of IBD dogs did not change after treatment with cyclosporine. Munster et al. (2006) also failed to demonstrate a strong association between efficacy of therapy (reflected by CIBDAI score) and histologic lesion severity. More recently, a large prospective study evaluating 70 dogs with chronic enteropathy failed to show an association between severity of histologic changes (at diagnosis) and long-term outcome over 3 years (Allenspach et al. 2007).

In summary, a review of the evidence currently available indicates that there is not a strong association between clinical findings and histopathologic lesions in dogs with IBD. This is especially true when one evaluates post-treatment changes in disease activity and its correlation to post-treatment histopathologic findings. There is some evidence that dogs with moderate to severe IBD accompanied by elevated CRP levels are more likely to have significant histologic lesions than those dogs having only mild clinical signs. In contrast to IBD in dogs, a recent report on cats with IBD showed a positive correlation between morphologic changes (epithelial alterations, villus fusion, atrophy), gastrointestinal signs, and up-regulated expression of some pro-inflammatory cytokines (Janeczko et al. 2008).

References


**Part 2: Presentation Aims**

1. To demonstrate the utility of a clinical index of disease activity (CIBDAI) for canine IBD
2. To introduce the clinical role/utility of a feline IBD activity index
3. To define the role for biomarkers in the diagnosis, treatment, and prognosis of canine and feline IBD

**The Canine IBD Activity Index (CIBDAI)**

One study has reported the use of a simple scoring index (e.g., canine IBD activity index or CIBDAI) for assessment of disease activity at diagnosis, and following medical therapy. Using this system, 6 prominent gastrointestinal signs (attitude/activity, appetite, vomiting, stool consistency, stool frequency, and weight loss) are scored 0 to 3 based upon the magnitude of their alteration from normal in a given IBD patient. These scores are then summed, yielding a total cumulative CIBDAI score, which reflects the presence of mild, moderate, or severe IBD.

Published data have shown that both the CIBDAI score and the serum CRP concentration decreased in dogs following successful medical (e.g., immunosuppressive drug therapy and dietary management) therapy for their disease. These accumulated observations suggest that the CIBDAI is a useful and reliable measure of clinical signs of inflammation in dogs with IBD. Furthermore, others have used this index for other forms of chronic enteropathy, including food-responsive diarrheas. Other iterations of this original scoring tool have been designed, including additional parameters such as pruritus, ascites, and borborygmus, but they have not been as robustly investigated.

**Current Feline Indices of Disease Activity**

Clinical research investigations have also validated disturbances in mucosal immunity in cats with IBD. Unfortunately, only a few of these immunologic parameters have been correlated to severity of clinical disease activity. Furthermore, the lack of consistent endoscopic abnormalities and the absence of standardized histologic criteria for diagnosis of FIBD hinder use of these indices as reliable markers of intestinal inflammation. Recently, sonographic findings including focal bowel wall thickening, loss of organized layer definition, and mesenteric lymphadenopathy were shown to have relevance in staging FIBD. However, the means by which severity of clinical signs was assessed was not defined in this investigation. Given these limitations and previous experiences with human IBD indices, the use of gastrointestinal signs and simple parameters of inflammation (such as measurement of the acute phase response) would appear most robust for clinical assessment of feline IBD activity.

**Tools for Prognostic and Therapeutic Monitoring**

Currently, IBD diagnosis and even treatment selection is accomplished based on clinical signs and empirical clinician assessment, combined with select laboratory tests for pathology and phenotypic expression. The optimal marker or markers have yet to be defined; however, several biomarkers may provide relevant information regarding disease activity at diagnosis and in response to medical therapy.

**Lymphocyte P-glycoprotein (PGP) Expression.** This is a transmembrane protein that functions as a drug efflux pump in the intestinal epithelium. In human IBD, PGP shows up-regulated expression in patients that fail to respond to glucocorticoids. One study in canine IBD has shown that PGP expression (via a mouse anti-human monoclonal antibody) was higher in dogs after treatment with prednisolone than before therapy, and that there was an association between a positive response to treatment and low PGP expression post-therapy. Thus, PGP expression may serve as a marker of therapeutic success. This specific assay is not currently available.
Serum C-reactive Protein (CRP). The role of this acute phase protein has been previously discussed. Summarizing the data to date, Jergens et al. (2003) reported the use of a clinical scoring index (i.e., Canine IBD Activity Index [CIBDAI]) to assess disease activity in relationship to histopathologic findings and serum C-reactive protein (CRP) concentrations. These data showed that clinical scores correlated best to a combination of histopathologic severity and CRP concentration at diagnosis; however, post-treatment histopathologic assessment was not performed. A review of the evidence currently available indicates that dogs with moderate to severe IBD accompanied by elevated CRP levels are more likely to have significant histologic lesions than those dogs having mild clinical signs.

Serum Albumin. The utility of serum albumin concentration as a negative prognostic indicator has now been reported in 2 separate canine investigations. In these case studies, affected dogs had PLE with significant albumin loss into the alimentary tract lumen. Both reports noted that hypoalbuminemia is associated with decreased long-term survival; prompting consideration for more aggressive medical therapies in affected animals. The role of hypoalbuminemia in feline IBD has not been fully elucidated.

References