2005 Report From: WSAVA Gastrointestinal Standardization Group

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Background

The WSAVA Gastrointestinal Standardization Group was initially developed to obtain a world-wide standard for the histological evaluation of gastrointestinal tract disease of cats and dogs. At the present time, a number of histological grading schemes have been proposed but none are universally accepted. Consequently, an intestinal biopsy sent to four different pathologists may result in four different biopsy reports. This is true of many gastrointestinal disorders (e.g., malignancy, toxicity, infection, lymphatic dilation, inflammation, villus atrophy), but it is particularly true of inflammatory bowel disease. The situation is further complicated by different nomenclatures for the same disease or disease severity in different parts of the world. With the support of the WSAVA, the Gastrointestinal Standardization Group has proposed to develop a standardized histologic evaluation system that will be applied to all companion animal gastroenterologic disorders. Standardization will yield several obvious benefits including uniform diagnosis of disease, staging of disease, and the subsequent development of controlled clinical trials for the treatment of canine and feline gastrointestinal disorders.

Membership of the Group

Study Group Participants: Name/Country + Affiliation/Discipline/E-Mail

- Bilzer, Thomas/Germany, University of Dusseldorf/Pathology Bilzer@uni-duesseldorf.de
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Goals of the Group

Gastrointestinal diagnosis in small animals (dogs and cats) has been fraught with many difficulties, particularly in the histologic interpretation of intestinal biopsies. What constitutes normal intestinal morphology is only now being determined, and the recognition of subtle abnormalities is quite challenging. Although a number of criteria can be applied in the examination of biopsy specimens, the interpretation by the histopathologist is often quite subjective. Discrepancies in biopsy reports between different pathologists is surprisingly common. Consequently, several groups (including the Comparative Gastroenterology Society, the European Society for Comparative Gastroenterology, and the American College of Veterinary Internal Medicine) have called for national and international efforts to standardize the histologic evaluation of the gastrointestinal tract of cats and dogs. The recent work of the WSAVA Liver Standardization Group has provided additional impetus and urgency to the need for standardization of the primary disorders of the gastrointestinal tract.

Specific Aims

(1) An international group of scholars was organized from the specialties of Veterinary Pathology and Internal Medicine to review gastrointestinal tract diseases of dogs and cats. Clinicians and pathologists have been reviewing major and minor diseases of the gastrointestinal tract with the aim of standardizing language and nomenclature that are applied to the histologic characterization and diagnosis of gastrointestinal disease. To accomplish these goals, the group will hold four or five meetings over a two- to three-year period. Histology slides are distributed among the pathologists for their interpretation three to four months in advance of each meeting, and the pathologists and clinicians review, discuss, revise, and re-classify gastrointestinal diseases during 1-2 day meetings over a multi-headed microscope.

(2) Members of the International Working Group were recruited from the ACVIM, ECVIM, and other international Specialty Colleges and universities.

(3) Meetings of the International Working Group are held at annual meetings of the ACVIM, ECVIM, and WSAVA for the purposes of elevating the visibility and stature of the Working Group in the eyes
of the relevant International Specialty Colleges. (Many members of the Working Group are also likely to attend their own professional meeting, e.g., ACVIM Forum and ECVIM Congress.)

(4) The Group will report findings to Gastroenterology specialists in attendance at the annual meetings of the ACVIM and ECVIM during the two-year timeframe of the Working Group.

(5) After final consultation with other Gastroenterology specialists at the ACVIM and ECVIM annual meetings, the Group will develop and publish one or more Consensus Statements and other manuscripts in the pathology and internal medicine journals.

First Meeting of the Group

The Group held its first meeting on June 8 & 9, 2004 in St. Paul, Minnesota on the occasion of the 2004 ACVIM Forum in Minneapolis. The agenda for that meeting included problems in the interpretation of G.I. biopsies; gastric, intestinal, and colonic histopathology and immunopathology; problems and pitfalls in the diagnosis of IBD; gastrointestinal disease distribution; and, endoscopic standards and biopsy techniques.

The Need for Standardization

Following that meeting, the Group concluded that there is a great need for three types of standardization: histologic descriptions of gastrointestinal disease, the functional disorders (i.e., those disorders for which there are prominent gastrointestinal clinical signs but for which there is minimal to no histologic change), and each of the steps of a medical investigation. The latter standardization could include history taking, physical examination, laboratory tests including intermediate endpoint biomarkers, imaging procedures and reports, endoscopic procedures and reports, biopsy procedure, histopathology and biopsy reports, immunohistochemistry, treatment trials, and patient response/outcome.

Initial Working Groups (chair in bold)

Inflammatory Bowel Disease:

- Al Jergens
- Ed Hall
- Michael Day
- Joanne Mansell
- Thomas Bilzer

Endoscopic Examination:
Second Meeting of the Group

The Standardization Group will hold its second meeting in Baltimore on May 31, 2005 on the occasion of the 2005 ACVIM Forum. The agenda for this meeting will include reviewing the progress of the subgroups working on endoscopic standardization, food sensitivity reactions, and gastrointestinal neoplasia; re-visiting plans for inflammatory bowel disease; and, entertaining a new proposal for validation of diagnostic tests.

New agendae

The Group is considering a specific proposal to derive guidelines for the validation of specialized gastrointestinal assays available to veterinary practices and veterinary laboratories. The Group would hope to establish criteria to define whether tests are certainly valid, probably valid, or if there is insufficient evidence to support their validity. Details of reference standards
would be published for various analytes used in gastrointestinal diagnosis. Reference laboratories and assay companies would be able to cite the guidelines as standards to which they adhere.

Area of Interest - Canine Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) may be defined using clinical, histologic, immunologic, pathophysiologic, and genetic criteria.

Clinical Criteria

IBD has been defined clinically as a spectrum of gastrointestinal disorders associated with chronic inflammation of the stomach, intestine and/or colon of unknown etiology.1 A clinical diagnosis of IBD is considered only if affected animals have: (1) persistent (>3 weeks in duration) gastrointestinal signs (anorexia, vomiting, weight loss, diarrhea, hematochezia, mucousy feces), (2) failure to respond to symptomatic therapies (parasiticides, antibiotics, gastrointestinal protectants) alone, (3) failure to document other causes of gastroenterocolitis by thorough diagnostic evaluation, and (4) histologic diagnosis of benign intestinal inflammation.2 Small bowel and large bowel forms of IBD have been reported in both dogs and cats, although large bowel IBD appears to be more prevalent in the dog.

Histologic Criteria

IBD has been defined histologically by the type of inflammatory infiltrate (neutrophilic, eosinophilic, lymphocytic, plasmacytic, granulomatous), associated mucosal pathology (villus atrophy, fusion, crypt collapse), distribution of the lesion (focal or generalized, superficial or deep), severity (mild, moderate, severe), mucosal thickness (mild, moderate, severe), and topography (gastric fundus, gastric antrum, duodenum, jejunum, ileum, cecum, ascending colon, descending colon).3 As with small intestinal IBD, subjective interpretation of large intestinal IBD lesions has made it difficult to compare tissue findings between pathologists. Subjectivity in histologic assessments has led to the development of several IBD grading systems.3-10

Immunologic Criteria

IBD has been defined immunologically by the innate and adaptive response of the mucosa to gastrointestinal antigens. Although the precise immunologic events of canine and feline IBD remain to be determined, a prevailing hypothesis for the development of IBD is the loss of immunologic tolerance to the normal bacterial flora or food antigens, leading to abnormal T cell immune reactivity in the gut microenvironment.11 Genetically engineered animal models (e.g., IL-2, IL-10, and T cell receptor knockouts) that develop IBD involve alterations in T cell development and/or function suggesting that T cell populations are responsible for the homeostatic regulation of mucosal immune responses.12 Immunohistochemical studies of canine IBD have demonstrated an increase in
the T cell population of the lamina propria, including CD3+ cells and CD4+ cells, as well as macrophages, neutrophils, and IgA-containing plasma cells. Many of the immunologic features of canine IBD can be explained as an indirect consequence of mucosal T cell activation. Enterocytes are also likely involved in the immunopathogenesis of IBD. Enterocytes are capable of behaving as antigen-presenting cells, and interleukins (e.g., IL-7 and IL-15) produced by enterocytes during acute inflammation activate mucosal lymphocytes. Up-regulation of Toll-like receptor 4 (TLR4) and Toll-like receptor 2 (TLR2) expression contribute to the innate immune response of the colon. Thus, the pathogenesis and pathophysiology of IBD appears to involve the activation of a subset of CD4+ T cells within the intestinal epithelium that overproduce inflammatory cytokines with concomitant loss of a subset of CD4+ T cells, and their associated cytokines, which normally regulate the inflammatory response and protect the gut from injury. Enterocytes, behaving as antigen-presenting cells, contribute to the pathogenesis of this disease.

Pathophysiologic Criteria

IBD may be defined pathophysiologically in terms of changes in transport, blood flow, and motility. The clinical signs of IBD, whether small or large bowel, have long been attributed to the pathophysiology of malabsorption and hypersecretion, but experimental models of canine IBD have instead related clinical signs to the emergence of abnormality motility patterns.

The pathophysiology of IBD is explained by at least two interdependent mechanisms: the mucosal immune response, and accompanying changes in motility.

Immune Responses - A generic inflammatory response involving cellular elements (B and T lymphocytes, plasma cells, macrophages, and dendritic cells), secretomotor neurons (e.g., VIP, substance P, and cholinergic neurons), cytokines and interleukins, and inflammatory mediators (e.g., leukotrienes, prostanoids, reactive oxygen metabolites, nitric oxide, 5-HT, IFN-\(\gamma\), TNF-\(\alpha\), and platelet-activating factor) is typical of canine and feline inflammatory bowel disease. There are many similarities between the inflammatory response of the small and large intestine, but recent immunologic studies suggest that IBD of the canine small intestine is a mixed Th1/Th2 response whereas IBD of the canine colon may be more of a Th1 type response with elaboration of IL-2, IL-12, INF-\(\gamma\), and TNF-alpha. Other studies of canine colonic IBD have demonstrated increased numbers of mucosal IgA- and IgG-containing cells, nitric oxide (NO), and inducible nitric oxide synthase (iNOS) in the inflamed colonic mucosa. Increases in the CD3+ positive T cell population of the inflamed colon are consistent with changes reported in the inflamed canine intestine. Thus, there are important similarities and differences between small and large bowel IBD.

Motility Changes - Experimental studies of canine large intestinal IBD have shown that many of the clinical signs (diarrhea, passage of mucus and blood, abdominal pain, tenesmus, and urgency of defecation) are related to motor abnormalities of the colon. Ethanol and acetic acid perfusion of the canine colon induces a large bowel form of IBD syndrome indistinguishable from the natural...
Inflammation in this model suppresses the normal phasic contractions of the colon, including the migrating motility complex, and triggers the emergence of giant migrating contractions (GMCs). The appearance of these GMCs in association with inflammation is a major factor in producing diarrhea, abdominal cramping, and urgency of defecation. GMCs are powerful lumen-occluding contractions that rapidly propel pancreatic, biliary, and intestinal secretions in the fasting state, and undigested food in the fed state, to the colon to increase its osmotic load. Malabsorption results from direct injury to the epithelial cells and from ultrarapid propulsion of intestinal contents by giant migrating contractions (GMCs) so that sufficient mucosal contact time is not allowed for digestion and absorption to take place.

Inflammation impairs the regulation of the colonic motility patterns at several levels, i.e., enteric neurons, interstitial cells of Cajal, and circular smooth muscle cells. Inflammation suppresses the generation of tone and phasic contractions in the circular smooth muscle cells through multiple molecular mechanisms. Inflammation shifts muscarinic receptor expression in circular smooth muscles from the M3 to the M2 subtype. This shift has the effect of reducing the overall contractility of the smooth muscle cell. Inflammation also impairs calcium influx and down-regulates the expression of the L-type calcium channel, which may be important in suppressing phasic contractions and tone while concurrently stimulating GMCs in the inflamed colon. Changes in the open-state probability of the large conductance calcium-activated potassium channels (KCa) partially attenuate this effect. Inflammation also modifies the signal transduction pathways of circular smooth muscle cells. Phospholipase A2 and protein kinase C (PKC) expression and activation are significantly altered by colonic inflammation and this may partially account for the suppression of tone and phasic contractions. PKC isoenzyme expression is down-regulated, PKC and isoenzyme expression is up-regulated, and the cytosol-to-membrane translocation of PKC is impaired. The L-type calcium channel, already reduced in its expression, is one of the molecular targets of PKC. Inflammation also activates the transcription factor NF-κB which further suppresses cell contractility.

Genetic Criteria

IBD may be defined by genetic criteria in several animal species. Crohn’s disease and ulcerative colitis are more common in certain human genotypes, and a mutation in the NOD2 gene (nucleotide-binding oligomerization domain) has been found in a sub-group of patients with Crohn’s disease. Genetic influences have not yet been identified in canine or feline IBD, but certain breeds (e.g., German shepherds, Boxers) appear to be at increased risk for the disease.

References


