Inflammatory bowel disease in dogs and cats

Introduction and definition

The term inflammatory bowel disease (IBD) describes an idiopathic gastrointestinal (GI) disorder characterized by persistent or recurrent GI signs and histological evidence of GI inflammation in animals for which no underlying cause can be found. It is typically quoted as being the most common cause of chronic intestinal disease in dogs and cats. However, accurate data on its prevalence is lacking, partly because many cases are not characterised fully, and partly because those histological criteria necessary for its definitive diagnosis remain controversial. A histological template, published by the WSAVA GI Standardization Group in 2008, may allow determination of which histological criteria are most important in the diagnosis and offers the opportunity to compare prospective, objective, therapeutic trials.

It seems likely that IBD is not simply one disease. The disease varies greatly, not only in severity, but also in its anatomical distribution (i.e. gastritis, enteritis, colitis, gastro-enteritis, enterocolitis, gastro-entero-colitis) and the type of inflammatory reaction; lymphocytic-plasmacytic enteritis (LPE) is the most common form reported; eosinophilic gastro-enteritis (EGE) is less common; and granulomatous enteritis is rare; neutrophilic infiltration is sometimes seen in feline and rarely in canine IBD but is an early feature of human IBD (Crohn’s disease and ulcerative colitis). However, the canine and feline diseases bear little resemblance clinically or histologically to these human forms of IBD.

As the definition of IBD requires there to be no underlying cause of intestinal inflammation, it is superfluous to call it idiopathic IBD. However, the indiscriminate use of the term IBD is unhelpful as a number of other diseases are associated with chronic intestinal inflammation (Table 1) and should be ruled out before true IBD can be diagnosed.

<table>
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<th>Table 1 Causes of Chronic Small Bowel Inflammation</th>
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Presentation

Inflammatory bowel disease is undoubtedly a common cause of chronic vomiting and diarrhoea in dogs and cats, but in reality it is probably overdiagnosed because of difficulties in interpretation of histopathologic specimens and failure to eliminate other causes of mucosal inflammation.

No apparent gender predisposition has been reported and, in both dogs and cats, IBD is most common in middle-aged animals, although intermittent signs at an earlier age are sometimes noted. There are reports of intestinal inflammation in much younger animals (≤6 months). However, these may
Clinical signs

The most common clinical signs in IBD are vomiting and diarrhoea, but an individual case may show some or all of the signs in Table 2. Clinical disease activity indices, which give a numerical score to specific signs, aid quantification of the severity of IBD and provide objectivity in comparing published studies. Only by using such objective criteria will it be possible to assess the response to treatment and to make a prognosis.

In some patients, clinical signs of IBD appear to start with an obvious precipitating event (e.g., stress, dietary change) although signs may spontaneously wax and wane. Postprandial pain and/or eating grass can be significant signs even in the absence of other signs. Rarely, weight loss may occur in the absence of overt diarrhoea and, if appetite is normal, is a reflection of SI malabsorption with compensatory colonic reabsorption preventing obvious diarrhoea.

There is a rough correlation between the region of the GI tract affected and the nature of the signs: vomiting is more common if gastric or upper SI inflammation is present; SI-type diarrhoea and weight loss are typical of SI inflammation; LI-type diarrhoea may be the result of primary colonic inflammation or secondary to prolonged SI diarrhoea.

**Table 2 Clinical Signs Associated with Inflammatory Bowel Disease**

- Abdominal discomfort/pain
- Altered appetite
  - Decreased appetite/anorexia
  - Eating grass
- Polyphagia
- Excessive barborvomosis and flatus
- Diarrhoea
  - Small intestinal-type diarrhoea
    - Large volume
    - Watery
    - Melena
  - Large intestinal-type diarrhoea
    - Haematochezia
    - Mucoid stool
    - Frequency and tenesmus
- Hypoproteinaemia
- Ascites
- Subcutaneous oedema
- Hydrothorax
- Lethargy
- Thickened bowel loops
- Vomiting
  - Bile
  - Food
  - Hair in cats
  - Grass in dogs
  - Blood (haematemesis)
- Weight loss

**Aetiology**

The aetiology of IBD in dogs and cats is unknown, but comparisons have been made with human IBD where the breakdown of immunological tolerance to luminal bacterial antigens is thought to be critical. Breakdown may result from disruption of the mucosal barrier, dysregulation of the gut-associated lymphoid tissue (GALT), or disturbances in the microbial flora, or any combination of these factors.

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A key mechanism down-regulating any response to commensals is relocation of TL2 and TL8 to intracellular and basolateral membrane locations in response to stimulation by bacterial PAMPs. Furthermore TLRs is only ever found on the basolateral membrane. This localisation prevents immune activation by commensal bacteria within the lumen, whilst still allowing a response to pathogens expressing LPS, flagellin etc., whenever they break through the epithelial barrier. In addition, luminal bacteria can stimulate intracellular TLR antagonists, such as toll-interacting protein (TOLLIP) and peroxisome proliferator-activated receptor-γ (PPARγ) in enterocytes. Therefore they tend to inhibit any TLR stimulation, whilst TOLLIP prevents the activation of the key, pro-inflammatory nuclear transcription factor NF-κB, which is also directly inhibited by PPARγ. The best current hypothesis for explaining when a response occurs is the “danger theory” 26. Invading pathogens cause cell damage leading to the release of chemokines, e.g., interleukin (IL)-8, pro-inflammatory cytokines (e.g., IL-1, IL-6, and tumour necrosis factor (TNF)-α), and inflammatory mediators, e.g., prostaglandins, leukotrienes) which act as “danger signals”.

Consequent stimulation of intracellularly located TLRs leads to activation of NF-κB and expression of TNF-α. In this altered environment, the immune system changes from tolerance to an active immune response, which can be either Th1 dominated (i.e., cytotoxicity and IgG responses) or Th2 dominated (i.e., IgE responses) depending on the nature and dose of the antigen. This Th1-Th2 paradigm is a gross simplification of the actual mucosal immune response; for example, regulatory cytokines (e.g., IL-10, IL-17 and transforming growth factor (TGF)-β) all modify the response. Results of studies measuring cytokine mRNA in dogs have been conflicting, and in feline IBD the response could not be classified as Th1 or Th2 27–29.

The hypothesis is that the type of response depends on the context in which the antigen is presented, and how the antigen and the mucosa interact.

Up-regulation of class II major histocompatibility (MHC) molecule expression has been documented in feline IBD, suggesting antigen processing and presentation by enterocytes 27. Yet, what prompts tolerance to break down in IBD is unresolved.

Ultimately, the mucosal immune response is aimed at eliminating the pathogen completely. Unfortunately, bystander damage of host cells is almost inevitable, although if the antigenic challenge is contained, the danger signals will diminish, and so the mucosa will be repaired and normal function will be restored. However, if the danger persists, either because the mucosal barrier remains breached and the pathogenic insult continues, or because of an inherent abnormality in the GALT, a state of chronic inflammation ensues. This may also lead to a breakdown in tolerance to harmless environmental antigens (food components and/or commensal bacteria) and consequent inflammation.

Genetic factors are likely to contribute to the pathogenesis of IBD, and in humans the strongest associations are with genes of the human major histocompatibility complex (MHC), a gene dense area containing the human leukocyte antigen (HLA). Furthermore, some human patients with Crohn’s disease have a mutation in the NOD2-CARD15 gene. The product of this gene detects bacterial LPS and can thereby activate the pro-inflammatory transcription factor NF-κB. Such a link may explain the development of aberrant immune responses to bacteria in certain individuals. Genetic polymorphisms in either NOD2 or TLRs may occur in certain dog breeds. There is some evidence of TLR polymorphisms in German shepherd dogs with anal furunculosis, a condition that is sometimes associated with concurrent colitis 28. A predictable up-regulation of TLRs has been demonstrated in canine IBD. This may be an epiphenomenon associated with inflammation, but could indicate hyper-responsiveness of TLRs to luminal bacteria or alterations in inhibition by TOLLIP.

Chronic inflammation ultimately leads to histopathologic changes, which are likely to be similar regardless of the inciting cause. Undiagnosed infection remains a possibility for intestinal biopsy is performed. Such tests cannot prove IBD, but the diagnosis is largely one of exclusion. They do help eliminate the possibility of gross intestinal disease (e.g., tumour, intussusception), extraintestinal disease (e.g., pancreatitis), and known causes of intestinal inflammation. Furthermore, by determining whether focal or diffuse intestinal disease is present, the clinician can choose the most appropriate method of intestinal biopsy.

Haematology

Haematological examination in IBD is often unhelpful, although sometimes a neutrophilia, with or without a left shift, is noted; a mature neutrophilia was reported in 22% of 133 cats reported by both anorexia and intestinal malabsorption. Therefore, IBD can result in subacute failure (chronic inflammation) or cobalamin (distal inflammation) concentrations or both (diffuse inflammation). Low serum cobalamin can cause abnormal intestinal histology as well as reduced appetite, and poor hair coat 27.

The degree of hypocobalaminemia in canine IBD correlates with the degree of histological damage and a poorer prognosis 29. Although cobalamin deficiency is not diagnostic for IBD, it does require therapeutic correction as it has systemic metabolic consequences 30. Anecdotally, cobalamin-deficient cats with IBD require parenteral supplementation to respond optimally to immunosuppressive treatment.

Diagnostic imaging

Imaging is used to determine whether focal or diffuse disease is present and/or whether other organs are affected. Such information, together with specific clinical signs, aids the choice of the most appropriate biopsy method.

Plain radiographs may be useful for detecting gross disease;
It has been shown that the experience of the endoscopist, as well as the numbers and quality of biopsies can influence the reliability of the histological interpretation. Predictably, fewer biopsies are needed to reliably detect architectural changes when the biopsy quality is better (i.e., size, depth and integrity). There is also emerging evidence that ideal biopsies are more likely to show abnormalities than duodenal biopsies. Agreement between histopathologists often is poor, especially when examining endoscopic biopsies. In one study, AL was diagnosed by some pathologists in tissues from healthy dogs, and there was only reasonable agreement between four independent pathologists in about half of the samples examined. Indeed results may differ between ante-mortem endoscopic biopsies and post-mortem specimens from the same patient. Such discrepancies may occur because the two conditions may be present concurrently, because previous IBD has transformed into AL, because AL is more likely to be distal, or because low-grade AL was initially misdiagnosed.

Stanfordized histopathologic criteria and scoring schemes have been suggested by the WSAVA GI Standardization Group as a means of improving agreement. These recognize that intestinal inflammation cannot be diagnosed simply on increased cellularity, but that architectural changes must also be present. Increased cellularity may be merely a reactive response, and only evidence of mucosal damage can define IBD.

Therefore the clinician should always interpret endoscopic biopsy results cautiously, and in some cases, repeat biopsy (e.g., by exploratory laparotomy) may be required.

Other diagnostic investigations

Given the limitations of histopathology, other diagnostic tests for reliably diagnosing IBD and distinguishing it from AL would be helpful. Cytological examination of FNAs or squash preparations of biopsies are likely to be less sensitive and specific. Immunohistochemistry or flow cytometry can be used to analyze immune cell classes, and RT-PCR can measure cytokine mRNA expression. The presence of increased serum acute phase proteins, perinuclear antineutrophil cytoplasmic antibodies (pANCA), increased intestinal permeability, and faecal excretion of calprotectin may be useful markers of intestinal inflammation. Cytology testing can be used to distinguish AL from severe BID.

Types of IBD

The different forms of IBD recognised are based on their histological description (e.g., lymphoplasmacytic enteritis) but even then, it is often a mixed inflammatory response in which certain cells predominate and appear to be increased. The presence of architectural changes confirms that changes in cell numbers and distribution are related to true inflammation and are not merely a reactive response.

Lymphocytic-Plasmacytic Enteritis

Lymphocytic-plasmacytic enteritis (LPE) is the most common histological type of IBD. The clinical signs of LPE are indistinguishable from those of other histological types of IBD. A PLE associated with LPE and a concurrent protein-losing nephropathy has been described in Soft-coated Wheaten terriers. The treatment of and prognosis for LPE is the same as for any form of IBD, as outlined below.

Histologically, LPE is characterized by mucosal architectural changes associated with an infiltrate of lymphocytes and plasma cells. Complete or partial villus atrophy may be present, with villus fusion and crypt abscessation in severe cases. The degree of inflammation is variable, but the interpretation of what constitutes "mild"-moderate-"severe" has historically been subjective. Furthermore, inflammation may be patchy, and the presence of oedema may make true cell density difficult to assess. The relative proportion of lymphocytes and plasma cells varies between cases, but the significance of any difference or any variation in the pattern of lymphocyte distribution (e.g., villus, crypt, intraepithelial) is unknown.

In canine LPE increases in lamina propria T cells (especially CD4 cells), IgG plasma cells, macrophages, and granulocytes are reported and range in severity from mild to severe infiltration. Marked alterations in cytokine patterns also occur, with increased expression of Th1 (IL-2, IL-12, and interferon-γ), Th2 (IL-5, pro-inflammatory TNF-α, and immunoregulatory IL-10, TGF-β) cytokines. Increased concentrations of acute-phase proteins (e.g., C-reactive protein), reflect the inflammatory response and normalize after treatment. However, there are other causes of lymphocytic-plasmacytic infiltration of the SI (Table 1), including enteropathogens, bacteria, and Toxoplasma. All such underlying causes must be excluded before a diagnosis of idiopathic LPE is confirmed.

Eosinophilic Gastroenteritis (EGE)

Eosinophilic gastroenteritis (EGE) is reported to be the second most common form of idiopathic IBD in dogs and cats. Evidence of mucosal architectural disturbances (e.g., villus atrophy) is present in conjunction with a mixed infiltrate of inflammatory cells in which eosinophils predominate. However, diagnostic criteria vary among pathologists; some define EGE based purely on subjective increases in mucosal eosinophil numbers, whereas others apply stricter criteria, requiring that eosinophils predominate in the lamina propria. As the number of mucosal eosinophils can vary markedly in normal dogs, this condition may be overdiagnosed. EGE may also be associated with systemic hypersensitivity syndromes in both cats and dogs.

An eosinophilic infiltrate may reflect dietary sensitivity, endoparasite, visceral larva migrans, or idiopathic. The eosinophil infiltration is likely to be the result of local and systemic production of cytokines and chemokines, such as IL-5, and members of the eotaxin family. These mediators may be produced by the Th2 subset of CD4 T cells.

EGE may be seen in dogs and cats of any breed and age, although is most common in younger adult animals. An increased incidence in German shepherds has been suggested, and boxers and dobermans may be predisposed. The clinical signs (Table 1) depend on the area of GI tract involved. Mucosal erosion/luceration may occur more frequently in EGE than in other forms of IBD, and so haematemesis, melena, or haematochezia may result. Severe EGE has been associated with PLE and, rarely, spontaneous perforation of the GI tract.

The diagnosis of EGE is made by histopathologic assessment of intestinal biopsies in conjunction with exclusion of parasites and food allergy. Eosinophilia is not invariably present in EGE and neither is it pathognomonic, because it may also be seen in parasitism, allergic cutaneous or respiratory disease, and mast cell neoplasia.

Empirical treatment with fenbendazole and an exclusion diet trial should be instigated to eliminate the possibilities of parasitism and dietary sensitivity before immunosuppressive therapy is considered.

Granulomatous (Regional) Enteritis

Granulomatous enteritis is an unusual form of IBD characterized by mucosal infiltration with macrophages, in the formation of granulomas. The distribution of inflammation can be patchy. Granulomatous enteritis has some histological...
features in common with human Crohn’s disease, but in Crohn’s the granulomata tend to be larger, causing intestinal obstruction and enterocutaneous fistulation. In regional enteritis larger granulomata are reported, but this condition is likely to be a form of granulomatous enteroitis. The response to therapy is usually poor, but a combination of surgical resection and anti-inflammatory treatment was reported to be successful in one case.

**Histiocytic ulcerative colitis**

This rare and unusual form of colonic inflammation, characterised by infiltration of macrophages staining positive by Periodic-Acid-Schiff (PAS), is no longer thought to be a form of IBD. It is seen almost exclusively in young boxer dogs. It responds poorly to immunosuppressive therapy typically used in IBD, but can be successfully treated with prolonged courses of enrofloxacin. The response to fluoroquinolones suggests an infective aetiology, and it has been suggested that intracellular infection by ‘attaching and invading’ E. coli (AIEC) underlies this condition.

Eighteen cats had cholangiohepatitis, and the prevalence of concurrent IBD (15/18; 83%) and pancreatitis (9/18; 50%) was not significantly different from 24 cats with no inflammatory liver disease. Yet, the WSAVA Liver Standardization Group only defined two major forms of biliary inflammation in cats (neutrophilic and lymphocytic cholangitis). Six of 15 cats in the Weiss study actually had neutrophilic infiltrates. Thus using the Liver Group’s definitions, any association is less clear, and further studies are clearly needed, especially as this study did not directly address how many cats with a primary diagnosis of IBD had evidence of triaditis.

**Treatment**

Whatever the histological type of IBD, treatment usually involves immunosuppressive drugs with a combination of dietary modification and antibacterial therapy.

A staged approach to therapy, i.e., sequential trials of antiparasitics, exclusion diet and antibacterials, is tried before immunosuppressive medication whenever possible. However, if clinical signs or mucosal inflammation are severe, early intervention with immunosuppression is essential. Future use of disease activity indices will provide more objective comparisons of different treatment regimens.

Supplementation with oral folate and parenteral cobalamin is indicated if serum concentrations are subnormal. Modulation of the enteric flora with prebiotics or probiotics may have benefits in targeting the pathogenesis of IBD; both can reduce intestinal inflammation in mouse models of IBD.

**Antibacterial therapy**

Treatment with antimicrobials can be justified in IBD because of the importance of bacterial antigens in its pathogenesis. Metronidazole is the preferred antibacterial for small animals. Its efficacy, especially in mild feline IBD, may be related to its immunomodulatory effects on cell-mediated immunity. Other antibacterials (e.g., oxytetracycline, tylosin) may also have immunomodulatory effects.

**Immunosuppressive drugs**

The most important treatment in IBD is immunosuppression. Corticosteroids are the mainstay, but alternative, cytotoxic immunosuppressive drugs, such as azathioprine in dogs and chlorambucil in cats, can be used for their steroid-sparing effects. In dogs, glucocorticoids alone are used most frequently, and prednisolone is the drug of choice. An initial dosage of one to two mg/kg is given orally every twelve hours for two to four weeks and then tapered slowly over the subsequent months. Initially signs of iatrogenic hyperadrenocorticism will occur. However, in some cases therapy can be completely withdrawn or at least reduced to a low dose given every 48 hours, when side-effects will be reversed.

Budesonide is an enteric-coated, locally active steroid that is destroyed 90% first-pass through the liver, and so has minimal systemic side-effects. A preliminary study showed apparent efficacy in dogs and cats, but limited information is published and a very wide dose range has been suggested.

Cyclosporine may show promise for the future in treating canine IBD, given its T lymphocyte-specific effects and its efficacy in canine anal furunculosis. Unfortunately, it is expensive but response to cyclosporine in 11/14 dogs with steroid-resistant canine IBD was highly significant. Finally, anti-TNF-α monoclonal antibody therapy has been adopted in severe cases of human IBD. Species-specific monoclonal antibodies will be needed to treat canine and feline IBD.

**Cholangiohepatitis**

**Portal hepatitis**

**IBD**

**No liver disease**

**Triaditis**

**Triaditis in cats**

Venn diagrams showing apparent association of feline cholangiohepatitis with IBD and pancreatitis. Integers indicate number of cases in each category. A significantly increased number of patients with cholangiohepatitis have IBD or pancreatitis or both (17/18), compared with cats with lymphocytic portal hepatitis (13/23) or no disease (6/24). Data based on Weiss et al 1996.

**Triaditis**

An association between lymphocytic cholangiohepatitis and pancreatitis is well recognized. In 1996, Weiss et al. described a further association with IBD (specifically LPE) in a study of 78 cats. Eighteen cats had cholangiohepatitis, and the prevalence of concurrent IBD (15/18; 83%) and pancreatitis (9/18; 50%) were significantly higher compared with cats without cholangiohepatitis (Figure 3). This association has been termed ‘triaditis’ or ‘tri-itis’.

The existence of triaditis may suggest that the epithelium in these three organs (biliary and pancreatic duct epithelial cells, and enterocytes) share a common antigen leading to a lymphocytic inflammatory response in each. No such antigen has yet been identified. Alternatively, intestinal inflammation may release mediators that cause dysfunction of the sphincter of Oddi with subsequent biliary stasis causing accumulation of abnormal bile ‘sludge’ or calculi, as is often seen in cholangiohepatitis. Concurrent biliary and pancreatic disease could then reflect the unusual anatomical structure of the feline duodenal papilla where the common bile duct and pancreatic duct anastomose before entering the duodenum.

**Diagram showing the anatomy of the feline common bile duct and pancreatic duct before entering the duodenum.**

**Common Bile Duct**

**Major Duodenal Papilla**

**Pancratic Duct**

However, the validity of the triaditis association has been questioned as concurrent disease is not present in all cases of cholangiohepatitis. Weiss et al. also described 36 cats with ‘lymphocytic portal hepatitis’, where the association with IBD (10/36; 28%) and pancreatitis (5/36; 14%) was not significantly different from 24 cats with no inflammatory liver disease. Yet, the WSAVA Liver Standardization Group only defined two major forms of biliary inflammation in cats (neutrophilic and lymphocytic cholangitis). Six of 15 cats in the Weiss study actually had neutrophilic infiltrates. Thus using the Liver Group’s definitions, any association is less clear, and further studies are clearly needed, especially as this study did not directly address how many cats with a primary diagnosis of IBD had evidence of triaditis.
Response to treatment and prognosis

There is a perception that the treatment of IBD is routinely successful and that full remission usually occurs. The author’s clinical experience and critical evaluation of the literature suggest that some were not truly IBD.

Finally, one unexpected finding has been that clinical improvement is not necessarily accompanied by histological improvement. It may be that histological remission is slower than clinical remission, but it more likely reflects the difficulty in assessing intestinal inflammation histologically. This problem has bedeviled the diagnosis of IBD ever since its earliest description. Again, it should be noted that a standardized template for assessing histology will improve the reliability of the diagnosis and allow objective assessment of different therapies.

References: