**IDIOPATHIC INFLAMMATORY BOWEL DISEASE**

Tonya E. Boyle, DVM  
*Resident, Internal Medicine*

Sally A. Bissett, BVSc, MVSc, DACVIM  
*Assistant Professor, Internal Medicine*

Department of Clinical Sciences  
College of Veterinary Medicine  
North Carolina State University

IDIOPATHIC INFLAMMATORY BOWEL DISEASE (IBD) is an umbrella term used to describe several small and large intestinal disorders characterized by chronic gastrointestinal (GI) signs and histologic evidence of mucosal inflammation when a specific etiology cannot be found. Idiopathic IBD in veterinary medicine should not be confused with IBD in human medicine, which represents terminology specific for Crohn’s disease, ulcerative colitis, and indeterminate colitis and is assessed with an activity index for classification of disease severity. Criteria for canine IBD activity index has been described and may make future classification of disease severity in dogs more straightforward but has yet to be widely implemented. Although similarities to human IBD exist in some veterinary patients, IBD in small animals is classified according to the predominant type of cellular infiltrate and the area of intestine affected.

Hallmark GI signs of IBD in dogs and cats are recurrent or persistent vomiting or diarrhea, weight loss, protein loss, and inappetence or polyphagia that may be responsive to immunotherapeutic medications. Idiopathic IBD is an important and prevalent disease in small animal medicine with a prognosis that ranges from good to grave.

**DIAGNOSTIC CRITERIA**

**Historical Information**

**Gender Predisposition**

- None known.

**Age Predisposition**

- Middle-aged to older animals are predisposed, but animals of any age can be represented.

**Breed Predisposition**

IBD can occur in any breed of dog and cat, but known and suspected breed associations include:

- **Soft-coated wheaten terriers**: Protein-losing enteropathy (PLE) with or without protein-losing nephropathy (PLN).
- **Yorkshire terriers**: Lymphangiectasia and lymphocytic-plasmacytic enteritis (LPE).
- **Basenjis**: Immunoproliferative enteropathy.
- **German shepherds**: LPE, antibiotic-responsive diarrhea.
- **Chinese shar-peis**: LPE with or without PLN (most often secondary to renal amyloidosis).
- **Norwegian Lundehunds**: PLE.
- **Siamese cats**: LPE anecdotally reported.

**Owner Observations**

Chronic or recurrent GI signs such as:

- Vomiting.
- Diarrhea: Small bowel, large bowel, or a combination of both.
- Weight loss.
- Inappetence or increased appetite.
- Occasionally, dogs present with abdominal enlargement or respiratory distress associated with ascites or pleural effusion secondary to hypoproteinemia.

**Other Historical Considerations/Predispositions**

- Genetic predisposition is likely.
- Numerous environmental triggers leading to the breakdown of mucosal immunologic tolerance to luminal antigens (bacterial, dietary, or endogenous) are thought to predispose patients to IBD.

**Physical Examination Findings**

The physical examination is often unremarkable in dogs and cats with IBD. Abnormal findings may include:

- Weight loss or poor body condition.
- Diarrhea or pain on rectal examination.
- Increased borborygmi and flatus (more common in dogs).
- Thickened bowel loops or enlarged mesenteric lymph nodes on abdominal palpation (more common in cats).
- Abdominal pain or discomfort.
- Ascites secondary to PLE.
Laboratory Findings
No pathognomonic changes in the hematologic profile and serum biochemistries are observed. Baseline laboratory tests should always be performed to evaluate the patient for other systemic or metabolic disease entities, protein loss, and iron deficiency anemia. Common but nonspecific abnormalities observed with IBD include:

Complete Blood Count (CBC) $ 
- Anemia secondary to chronic blood loss or chronic inflammation.
- Mild to moderate neutrophilia (typically without a left shift).
- Eosinophilia.
- Thrombocytopenia and thrombocytosis have also been reported.

Biochemical Panel $ 
- Hypoalbuminemia, hypoglobulinemia, or panhypoproteinemia.
- Hyperglobulinemia secondary to chronic inflammation (more common in cats).
- In dogs, mild alkaline phosphatase (ALP) and alanine aminotransferase (ALT) enzyme elevations secondary to intestinal inflammation.
- In cats, hepatic enzyme elevations are more likely to be hepatocellular (e.g., predominantly ALT) in origin.
- Hypcholesterolemia with PLE.
- Hypokalemia secondary to anorexia (in cats).
- Hypocalcemia (despite correction for hypoalbuminemia) secondary to malabsorption.
- Hypomagnesemia secondary to malabsorption or chronic diarrhea.

Urinalysis $ 
- No pathognomonic changes in urinalysis are observed, but this important test should always be performed to evaluate for renal abnormalities.

Fecal Analysis $ 
- Fecal flotation or centrifugation and direct (wet mount) examination should be performed two or more times and be negative for intestinal parasites.
- Fecal *Giardia* antigen testing, *Trichomonas* (cats) culture or PCR, and *Cryptosporidium* (cats) acid-fast staining or antigen testing should be considered.
- Fecal or rectal cytology should be considered, and results should be negative for known pathogenic microorganisms (e.g., *Histoplasma* spp, *Prototheca* spp).
- Fecal cultures for enteropathogenic bacteria (e.g., *Salmonella* spp, *Campylobacter* spp) are rarely helpful in elucidating the cause of chronic diarrhea.
- Fecal α1-proteinase inhibitor concentrations are often elevated in patients with IBD and indicate protein loss before it may be clinically detectable.

Serum Trypsinlike Immunoreactivity (TLI), Pancreatic Lipase Immunoreactivity (PLI), Folate, and Cobalamin Concentrations $ 
- Serum TLI concentrations should be determined to rule out exocrine pancreatic insufficiency.
- Serum PLI concentrations should be considered to evaluate for pancreatitis.
- Serum folate concentrations may be decreased with proximal small intestinal inflammation and decreased absorption.
- Serum cobalamin concentrations may be decreased with distal small intestinal inflammation and decreased absorption (common in cats).

C-Reactive Protein $ 
- C-reactive protein, an acute phase protein of dogs, may be elevated in canine IBD, and concentrations may decrease with successful therapy.

Other Diagnostic Findings

Radiography $ 
- Survey abdominal radiographs are usually normal in IBD but are still useful to look for obstructive, neoplastic, and extra-GI causes of chronic GI signs.
- Contrast intestinal studies are not likely to contribute to the diagnosis of IBD.
- Thoracic radiography may be performed to rule out the presence of metastatic disease in middle-aged to elderly animals.

Ultrasonography $–$$ 
- Abdominal ultrasonography may reveal intestinal thickening and mesenteric lymphadenopathy. It may localize the intestinal lesion as segmental or diffuse and help to determine if the diseased intestine can be reached endoscopically or if surgical biopsies must be obtained for diagnosis. However, pathognomonic ultrasonographic changes of IBD do not exist.
- Ultrasound-guided fine-needle aspiration of en-
larged mesenteric lymph nodes and thickened intestinal wall can be attempted but may not yield diagnostically significant results.

**Intestinal Biopsy $–$$$$**

- Intestinal biopsy is always necessary to obtain a diagnosis of IBD and to rule out other causes for mucosal infiltrative disease. Biopsy samples may be obtained via endoscopy if the proximal (duodenal) intestine, colon, or distal ileum is affected. A gastric feeding tube may be placed at the time of endoscopy if the patient is anorectic or if there is evidence of hepatic lipidosis in a cat.
- Full-thickness surgical biopsies of the gut may need to be obtained via exploratory laparotomy or laparoscopy-assisted surgery if the most affected region of the gut is the mid to lower small intestine, if mesenteric lymph nodes or other abdominal organs (e.g., liver, pancreas) need to be biopsied, or if previous endoscopic biopsies are not diagnostic. In older cats, full-thickness Gl biopsies are often preferred to help differentiate severe LPE from small-cell lymphoma, which can be a diagnostic challenge for pathologists. Furthermore, immunophenotyping of endoscopic or full-thickness biopsies may help to differentiate severe IBD from well-differentiated lymphoma in cats.

**Summary of Diagnostic Criteria**

- Persistent or recurrent Gl signs.
- Unremarkable physical examination or abnormal abdominal palpation or rectal examination findings (discomfort, thickened intestines, enlarged lymph nodes, diarrhea).
- Failure to identify an infectious, obstructive, or extra-GI cause of the chronic signs despite appropriate laboratory tests and abdominal imaging.
- Unremarkable abdominal imaging (ultrasonography with or without radiography) or ultrasonographic evidence of thickened intestines (segmental or diffuse) or mesenteric lymphadenopathy.
- Histologic evidence of intestinal inflammation with the exclusion of other causes for mucosal infiltrative disease.

**Diagnostic Differentials**

- **Chronic Gl infections** (bacterial, parasitic, fungal, algal, viral) are diagnosed by fecal tests (flotation and centrifugation, direct examination, cytology, antigen tests, culture, polymerase chain reaction), serology (FeLV, FIV), and histologic examination of gut biopsy samples or are suspected after resolution with empiric therapy.
- **Extra-GI causes** of chronic Gl signs (e.g., hyperthyroidism, hypoadrenocorticism, pancreatitis, exocrine pancreatic insufficiency, renal disease, liver disease) are mostly ruled out via routine laboratory tests (hematology, serum chemistries) and, when indicated, more specialized laboratory tests (total T4, TLI, PLI, serum bile acids, basal cortisol or adrenocorticotropic hormone stimulation test) and abdominal imaging.
- **Obstructive causes** of chronic Gl signs (e.g., Gl neoplasia, gastric foreign material, pyloric stenosis, intussusception, hypomotility disorders) are diagnosed via abdominal imaging procedures (survey or contrast radiography, ultrasonography), exploratory laparotomy, and histologic examination of gut biopsies in some cases.
- **Adverse food reactions** (food intolerance or food allergy) are diagnosed via an elimination dietary trial (see dietary therapy).
- **Fiber-responsive diarrhea**, which is typically large-bowel diarrhea, may respond to a high-fiber diet or a fiber supplement added to the diet.
- **Antibiotic-responsive diarrhea** may be diagnosed based on the remission of signs with antibiotic therapy, recurrence when therapy is discontinued, and resolution when therapy is reintroduced.
- **LPE**, the most common form of IBD, is diagnosed based on histologic evaluation of gut biopsy samples and ruling out other causes of enteritis (see above).
- **Eosinophilic enteritis**, the second most common form of IBD, is diagnosed based on histologic evaluation of gut biopsy samples and ruling out other causes of enteritis (see above).
- **Histiocytic ulcerative colitis** has been most commonly reported in young boxers and is characterized by colonic ulceration on endoscopic evaluation and the histologic finding of periodic acid–Schiff–positive macrophages. Mounting evidence suggests that enteroinvasive *Escherichia coli* plays an important role in the pathogenesis of this “IBD variant.”
- **Granulomatous enteritis** is diagnosed based on histologic evaluation of gut biopsy samples and ruling out other causes of enteritis (see above). This is an extremely rare IBD variant.
- **Gl lymphangiectasia** is diagnosed based on histologic evaluation of gut biopsy samples.
- **Gl lymphoma** is diagnosed based on histologic evaluation of gut biopsy samples and immunotyping for monoclonal cells.
- **Irritable bowel syndrome** is a diagnosis of exclusion (Gl biopsies are unremarkable). Patients suspected to have this disorder may respond to environmental stress reduction, fiber supplementation, and drugs used to modify or normalize gut motility.
TREATMENT RECOMMENDATIONS

Initial Treatment

- **Dietary therapy** ideally includes a low-fat, highly digestible elimination diet. A strict elimination diet contains a single-source novel or hydrolyzed protein and a single-source carbohydrate that is gluten free. This diet should be fed for a minimum of 4 weeks to determine if the disease is diet responsive. $\dollar$

- **Antibiotic therapy** can be administered alone or in combination with dietary therapy to determine if the disease is antibiotic responsive. There is currently little evidence to support the use of antibiotics in combination with glucocorticoid therapy. The mechanism by which the antibiotics listed below exert their effect is poorly understood but may involve decreased bacterial adhesion, altered intestinal flora populations, and antiinflammatory effects.
  - **Metronidazole**: 10 mg/kg PO bid for 3–4 weeks to assess response. Lower doses can be used long term if resolution occurs. $\dollar$
  - **Tylosin**: 10–20 mg/kg PO bid for 3–4 weeks to assess response. Lower doses can be used long term if resolution occurs. $\dollar$

- **5-Aminosalicylic acid (5-ASA) therapy**: Numerous anecdotal reports as well as the authors’ clinical experience show that this class of drug may be used instead of corticosteroids (and combined with dietary therapy) in dogs with inflammation confined to the colon. The 5-ASA moiety acts locally as a potent prostaglandin synthetase inhibitor after large bowel microflora cleave the linkage between the 5-ASA groups (mesalamine, olsalazine) or the 5-ASA and the sulfa group (sulfasalazine). Keratoconjunctivitis sicca is the most commonly reported side effect, so all dog owners should be made aware of the potential for this side effect. Patients receiving this class of medications should be monitored routinely for adequate tear production.
  - **Sulfasalazine**: 10–25 mg/kg PO tid for 4–6 weeks to assess response in dogs and cats. Dose may then be decreased by 25% every 2 weeks if resolution occurs. $\dollar$
  - **Mesalamine**: 10 mg/kg PO tid for 4–6 weeks in dogs. Gradual dose reduction may be used if resolution occurs. $\dollar$
  - **Olsalazine**: 5–10 mg/kg PO tid for 4–6 weeks in dogs. Gradual dose reduction may be used if resolution occurs. $\dollar$

- **Immunosuppressive therapy** is recommended in combination with dietary therapy for patients with moderate to severe IBD and for patients with mild to moderate IBD that fail to respond to dietary and antibiotic therapy (or 5-ASA therapy for those with colitis).

Critical Care of Patients with Severe Hypoproteinemia or Cachexia

- **Colloid therapy**: Plasma or hetastarch, 10–20 ml/kg IV once and then as needed, may be necessary for initial oncocytic support if hypoalbuminemia is severe (<1.6 mg/dl). $\dollar$

- **Antithrombotic therapy**: Heparin, 300–900 IU/kg SC tid or as a daily continuous-rate infusion until the risk of thrombosis is reduced, should be considered if the albumin is <1.6 mg/dl and loss of antithrombin III is likely or documented. The benefits of heparin remain undocumented and controversial at this time. $\dollar$

- **Enteral feeding** via nasoesophageal, esophageal, gastric, or jejunal feeding tube may be required if the animal is anorectic. See above for dietary recommendations. The short-term use of a human elemental liquid diet and glutamine supplementation should also be considered for severe cases. $\dollar$$\dollar$$\dollar$

- **Total parenteral nutrition** or **partial parenteral nutrition** may be required if the animal is severely cachexic or anorexic and enteral feeding cannot be tolerated. $\dollar$$\dollar$$\dollar$$\dollar$

ON THE NEWS FRONT

- The recommendations and results of a 2-year investigational study by the World Small Animal Veterinary Association Gastrointestinal Standardization Group on Idiopathic IBD in dogs and cats will be presented at the ACVIM Forum in 2007.

- **Prednisone** (prednisolone in cats): 1–2 mg/kg PO bid for 2–4 weeks until remission is achieved; then taper to effect. $\dollar$

- **Azathioprine**: 2 mg/kg PO sid in dogs until clinical remission occurs (but not longer than 4–6 weeks), and then maintenance therapy every other day. This regimen is often used in combination with glucocorticoids in dogs with more severe IBD and in patients that respond poorly to glucocorticoids alone. CBCs and hepatic biochemical panels should be initially performed every 2 weeks to monitor for bone marrow suppression and liver toxicity. $\dollar$$\dollar$$\dollar$

- **Chlorambucil**: 2–6 mg/m² PO sid in cats until remission is achieved, and then maintenance therapy every other day. This regimen is often used in combination with glucocorticoids in cats with more severe IBD or in patients that respond poorly to glucocorticoids alone. CBCs should be performed every 2 weeks initially to monitor for bone marrow suppression. $\dollar$

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Alternative/Optional Treatments/Therapy
Alternate immunosuppressive therapy includes:

- **Budesonide:** 3 mg/m² PO sid for as long as required. Budesonide is a potent topical corticosteroid that may be used instead of the more traditional glucocorticoids (e.g., prednisone) in animals intolerant to their side effects or suffering from concurrent endocrinopathies, such as diabetes mellitus. Human enteric-coated formulations should be compounded before administration for maximal efficacy in cats and dogs with small intestinal IBD. Although systemic absorption of budesonide is limited, pituitary–adrenal axis suppression still occurs. Therefore, a tapering dose is recommended if budesonide therapy is to be discontinued.

- **Cyclosporine:** 2.5 mg/kg PO bid until remission is achieved; then taper to effect. Cyclosporine can be given to animals that have failed glucocorticoid therapy, either in conjunction with steroids or as a single therapy agent. Cyclosporine trough concentrations can be measured to evaluate for drug interactions or malabsorption with a suggested whole blood assay range of 200 to 400 ng/ml. The use of cyclosporine concentrations in companion animals remains controversial.

- **Mycophenolate mofetil** is an immunosuppressive drug that is increasingly used in dogs. It is metabolized to mycophenolic acid, which inhibits inosine monophosphate dehydrogenase for purine synthesis and ultimately suppresses lymphocyte proliferation and decreases antibody production. Mycophenolate should be used in patients with IBD with caution (and ideally avoided until more information is available) because it is known to cause inflammatory diarrhea in some people and dogs.

- **Anti–tumor necrosis factor–α monoclonal antibodies** have been used successfully in human IBD management and may hold promise if species-specific antibodies for feline and canine patients are developed. This therapy is not presently available for companion animals.

**Supportive Treatment**

- **Empiric deworming:** Fenbendazole, 50 mg/kg PO sid for 3–5 days, is recommended.

- **Cyanocobalamin:** If serum cobalamin levels are low, 250–1000 µg (Table 1) SC once weekly for 6 weeks and then every 1–2 months should be given as needed according to serum concentrations.

- **Prebiotic and probiotic supplements** are naturally occurring fermentable substrates and live microorganisms with beneficial physiologic or therapeutic activities, respectively. They increase beneficial and inhibit harmful microbes within the gut when administered orally. These substances have demonstrated efficacy in rodent models of IBD, but their effects in dogs and cats have not yet been determined.

**Patient Monitoring**

- Weekly to monthly rechecks are initially recommended depending on disease severity.

- Patients should be monitored for changes in appetite, body weight and body condition score, vomiting, and stool frequency and consistency. CBCs and serum proteins should also be monitored intermittently for patients with anemia, inflammation, or hypoproteinemia.

- Patients receiving myelotoxic and hepatotoxic drugs should have CBCs and serum biochemistries monitored every 2 weeks initially.

- Patients receiving 5-ASA therapeutics should be evaluated routinely for the development of keratoconjunctivitis sicca with regular (every 1–3 months) Schirmer tear testing.

**Home Management**

- Strict adherence to dietary recommendations (especially during diet trials).

- Compliance with prescribed medications is imperative for successful therapy.

- Close observation of the pet’s attitude, appetite, and bowel functions is extremely helpful.

- Commitment to regular follow-up appointments and maintaining good communication between the client and veterinarian helps to monitor therapy and avoid complications.

**Milestones/Recovery Time Frames**

- If improvement is seen with dietary therapy, it usually occurs within 2 to 4 weeks of starting the diet trial, but it may take up to 6 to 8 weeks in cats.

- If improvement is seen with antibiotic therapy, it is typically rapid (within days), but it may take up to 3 weeks in some animals.

- For 5-ASA therapy, improvement is typically seen within 2 to 4 weeks of starting therapy.

- For immunosuppressive therapy, improvement in clinical signs and biochemical parameters should be expected within 1 to 3 weeks.

**TABLE 1 Dose Ranges for Cyanocobalamin**

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<thead>
<tr>
<th>Animal Body Weight</th>
<th>SC Dose (µg)</th>
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<tbody>
<tr>
<td>Domestic cats; dogs ≤5 kg (≤10 lb)</td>
<td>250</td>
</tr>
<tr>
<td>Dogs, 5–15 kg (10–30 lb)</td>
<td>500</td>
</tr>
<tr>
<td>Dogs &gt;15 kg (&gt;30 lb)</td>
<td>1,000</td>
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</tbody>
</table>

- 5-ASA: 5-aminosalicylic acid; CBC: complete blood count; IBD: inflammatory bowel disease; SC: subcutaneous.
Treatment Contraindications

• Poorly digestible, low-quality diets.
• Although not a contraindication, it should be noted that patients with severe PLE and abdominal effusion are more prone to fluid shifts and delayed wound healing (especially if they are malnourished), making them higher-risk surgical candidates.

PROGNOSIS

The overall prognosis of IBD in small animals varies from good to grave and greatly depends on the extent and severity of the disease process and the individual’s response to therapy. The prognosis for most animals is good to excellent, but lifelong therapy may be required.

Favorable Criteria

• Early disease recognition, histologic classification, and therapeutic intervention.
• Resolution of GI signs without the use of immunosuppressive drugs.
• Rapid resolution of GI signs with appropriate therapy.
• Rapidly improved plasma proteins and effusion with therapy for animals with PLE.

Unfavorable Criteria

• Severity and extent of disease based on clinical signs, laboratory abnormalities, and histologic evaluation.
• Continued intestinal protein loss.
• Refractory disease: Persistence of GI signs despite dietary and medical management.
• Thromboembolic complications.

RECOMMENDED READING