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Inflammatory Bowel Disease

BASIC INFORMATION

DEFINITION
Inflammatory bowel disease (IBD) is a poorly defined and often incorrectly used term in ferrets and other small animals for a systemic inflammatory disease primarily involving the gastrointestinal tract. Clinical disease results from dysregulation of the mucosal immune response. The umbrella term *IBD* used in ferrets and other small animals for a variety of gastrointestinal diseases is not the same disease that is seen in humans. Clinical signs, origin, endoscopic features, and histopathologic features are very different from those seen in humans. Continued use of the term *IBD* for these diseases in small animals is a source of frustration and confusion to clinicians and pathologists alike.

SYNONYMS
- Crohn's disease, ulcerative colitis
- Incorrectly used synonyms: antibiotic responsive enteritis, eosinophilic enteritis or eosinophilic gastroenteritis, epizootic catarhal enteritis, food allergy, gluten hypersensitivity, lymphoplasmacytic enteritis, proliferative bowel disease or colitis

SPECIAL SPECIES CONSIDERATIONS
- Ferrets have been reported incorrectly to be susceptible to IBD.
- True IBD is rare in small animals.
- Cotton-top tamarins are natural animal models of human IBD.

EPIDEMIOLOGY

SPECIES, AGE, SEX
- Ferrets are susceptible to several gastrointestinal inflammatory conditions that have erroneously been placed under the umbrella term of IBD.
Inflammatory Bowel Disease

- The true incidence of IBD (Crohn’s disease and ulcerative colitis) in ferrets is unknown.

GENETICS AND BREED PREDISPOSITION
- In contrast to human and canine IBD, no genetic predisposition to IBD in ferrets is known.
- Recent research on Crohn’s disease in humans and mouse models of IBD has led to the idea that genetically susceptible individuals develop a dysregulated response of the mucosal immune system to commensal enteric flora. Many genetically susceptible humans, mice, and dogs have defects in intracellular pattern-recognition receptors (PRRs) (e.g., toll-like receptors [TLRs] and nuclear organization domain receptors [NODs]) that are responsible for clearing virulent and commensal bacteria. It is thought that this inability to clear commensal bacteria leads to chronic immune stimulation and harmful cytokine release, resulting in disease.

ASSOCIATED CONDITIONS AND DISORDERS
- IBD often results in extraintestinal disease.
  - Uveitis, cholangitis, and autoimmune liver, pancreatic, and joint disease is commonly seen in humans with IBD.
  - Soft-coated wheaten terriers with IBD often have concurrent protein-losing nephropathy.
  - IBD in cats is frequently associated with cholangiohepatitis and pancreatitis.
  - IBD in ferrets may be seen in association with splenomegaly and/or cholangiohepatitis.

CLINICAL PRESENTATION

DISEASE FORMS/SUBTYPES
- Ferret IBD, by the more permissive use of the term, likely consists of a variety of many different diseases that have similar clinical signs and similar histopathologic changes.
- Clinical signs will result depending on which segment of the intestine (and/or abdominal organs) is involved, and the degree (e.g., mild, moderate, severe) of inflammation.
- Specific disease entities in ferrets include the following:
  - Eosinophilic gastroenteritis (see Eosinophilic Gastroenteritis)
  - Epizootic catarrhal enteritis (enteric coronavirus infection) (see Epizootic Catarrhal Enteritis)
  - Helicobacter mustelae-associated gastritis (see Helicobacter mustelae–Associated Gastritis and Ulcers)
  - Proliferative bowel disease (Lawsonia intracellularis) (see Proliferative Bowel Disease)

- Histopathologic features of Crohn’s disease involve the deeper layers of the bowel wall with fissures, sinus tracts, fistulas, and fibrosis, all of which may produce radiographically or endoscopically evident areas of mural thickening and/or luminal stenosis. Most of these features cannot be evaluated in mucosal biopsy specimens and require full-thickness biopsies. Often seen are the following: a mixed inflammatory infiltrate; cryptitis and microabscesses; lymphoid aggregates; branching atrophic crypts; and Paneth cell metaplasia. Crohn’s disease will also exhibit granulomas in the ileum or the colon that are unassociated with crypt rupture; disproportionate

- Hepatobiliary disease (chronic cholangiohepatitis) (see Hepatobiliary Disease)
- Major forms of IBD in humans are Crohn’s disease and ulcerative colitis. The primary difference between them lies in the location and nature of the inflammatory changes.
- Crohn’s disease: affects the terminal ileum and colon, occasionally the small intestine, stomach, and esophagus, and rarely the rectum. On endoscopy, skip lesions (patchy areas of inflammation) are seen grossly.
- Ulcerative colitis: continuous colonic involvement beginning in the rectum. The ileum and the small intestine are rarely involved.

HISTORY, CHIEF COMPLAINT
- Clinical examination
- Complete blood count (CBC) serum biochemistry: often results are unremarkable
- In Crohn’s disease and ulcerative colitis, iron deficiency anemia is seen
- Fecal endoparasite exam (floation) and direct smear

ADVANCED OR CONFIRMATORY TESTING
- Gastroscopic and colonoscopic biopsy and/or surgical biopsy
- Regardless of the portion of the gastrointestinal tract under consideration, histologic abnormalities of IBD are grouped under three broad headings:
  - Changes in mucosal architecture reflecting active or recent epithelial abnormality
  - Increased numbers of leukocytes in the lamina propria
  - Fibrosis within the lamina propria
- Epithelial changes are the most reliable, yet the least prevalent. Subjective impressions of increased numbers of leukocytes within the lamina propria represent the least reliable but the most widely used criterion for a diagnosis, simply because most biopsy samples do not have any other mucosal abnormalities.
- Histopathologic features that are wrongly interpreted as IBD include increased numbers of lamina propria lymphocytes, plasma cells, and eosinophils; increased numbers of goblet cells; villous blunting; and increased intraepithelial lymphocytes. These findings are nonspecific and can be seen in normal ferrets, older animals, and animals with numerous and different gastrointestinal diseases.
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INITIAL DATABASE
- Clinical examination
- Complete blood count (CBC) serum biochemistry: often results are unremarkable

ETIOLOGY AND PATHOPHYSIOLOGY
- Various origins: usually infectious—Helicobacter mustelae, ferret enteric coronavirus, Aleutian disease parvovirus, Giardia spp., Lawsonia intracellularis, Salmonella enterica, (see Salmonellosis, Sec. VI) Campylobacter jejuni, Cryptosporidium spp (see Cryptosporidiosis, Sec. VI). Increased mucosal inflammation
- Dysregulated cytokine production
- Enterocyte destruction

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS
- The spectrum of diseases termed in ferrets includes the following:
  - Food protein intolerance, as to cow’s milk, peanuts, eggs, etc.
  - Gluten hypersensitivity
  - Autoimmune disorders
  - H. mustelae-associated chronic active gastritis
  - Eosinophilic gastroenteritis
  - Giardiasis
  - Microsporidiosis
  - Campylobacteriosis
  - Coccidiosis
  - Enteric coronavirus infection
  - Proliferative bowel disease
  - Salmonellosis
  - Chronic cholangiohepatitis
  - Mycobacteriosis
  - Enteropathy-associated T-cell lymphoma
  - Drug-induced enteropathies
Inflammatory Bowel Disease

submucosal inflammation; transmural lymphoid infiltrates; and serositis.

- Ulcerative colitis involves the mucosa in a diffuse and continuous fashion and always affects the rectum.
- Colonoscopy reveals erythema, edema, obscured normal vascular pattern, multiple ulcers and/or strictures, and stenosis.
- Other causes of diarrhea should be ruled out by using the appropriate tests (fecal flotation, fecal culture, food trials, serology, and endoscopy).
- Refer to appropriate section/topic for specific diseases.

**TREATMENT**

**THERAPEUTIC GOALS**

- Identifying the cause of the ferret IBD will determine the appropriate treatment.
- In Crohn’s disease and ulcerative colitis, immune suppression is the mainstay of treatment.

**ACUTE GENERAL TREATMENT**

- Immunosuppressive agents that non-specifically reduce inflammation and immunity have been the mainstay of conventional therapies for IBD.
- Novel protein diets for 2 weeks or more to eliminate food intolerance or allergy (also try hydrolyzed peptide based diet); antibiotics (metronidazole 10–15 mg/kg PO q 12-24 h; tylosin 25 mg/kg PO q 12-24 h; tetracycline 20-25 mg (q 8-12 h) to modify intestinal microflora; steroid antiinflammatoryatories (prednisone 2 mg/kg PO q 24 h initially for 1-2 weeks, then taper dose by half every 2 weeks), or immune suppressives (azathioprine 0.9 mg/kg PO q 24-72 h) are often used when a cause of IBD in ferrets cannot be determined.
- Responses to such treatments are unpredictable and all drug doses are strictly empirical. Adverse drug reactions may occur, especially with azathioprine. Regular monitoring of CBC is advised.
  - Mild to moderate disease (mild clinical signs). Try dietary change, antibiotics.
  - Moderate to severe disease (no response to dietary change and antibiotics or pronounced clinical signs). Try above plus corticosteroids (taper dose over 8-12 weeks).
  - Persistent clinical signs (>3 months) despite corticosteroid therapy or cachexia, persistent diarrhea and/or vomiting, abdominal pain. Try azathioprine.
- In Crohn’s disease and ulcerative colitis, the most widely used treatment is mesalamine (5-aminosalicylic acid), an antiinflammatory drug that acts locally in the gastrointestinal tract.

**CHRONIC TREATMENT**

- Chronic treatment of IBD in ferrets is determined by the underlying cause. Treatment is determined by the underlying cause.
- In Crohn’s disease and ulcerative colitis, various antidiarrheals, elemental diets, antibiotics (metronidazole), antiinflammatories (corticosteroids), and immune suppressives (azathioprine, 6-mercaptopurine, methotrexate, cyclosporine) are used. Since 1998, anti-tumor necrosis factor κ monoclonal antibodies—murine-chimeric (infliximab) or human (adalimumab)—have been used to induce and maintain remission of Crohn’s disease. Surgery to remove affected bowel is sometimes required.
- Data using biological agents targeted against cytokines for treatment of IBD is lacking in dogs, cats, and ferrets.

**POSSIBLE COMPLICATIONS**

Care should be taken to differentiate chronic IBD in ferrets from early intestinal lymphoma.

**PROGNOSIS AND OUTCOME**

- The prognosis varies depending on the cause of the ferret IBD.
- Crohn’s disease and ulcerative colitis are lifelong systemic diseases with recurrent flare-ups.

**PEARLS & CONSIDERATIONS**

- IBD is a clinical syndrome for which it is difficult to develop a valid, objective histologic counterpart, and it should be a diagnosis of last resort, made by the clinician after alternatives such as food intolerance, motility disorders, and infectious disease have been ruled out.
- The pathophysiology resulting in IBD, the basis for phenotypic variation and the mechanism for unpredictable response to treatment are not known.
- The thoroughness of the clinical and laboratory investigation before endoscopic biopsy is used is influenced by the amount of time and money available to evaluate what are often elusive functional entities. Endoscopic biopsies are often done early, after symptomatic medical therapy (see Acute General Treatment) has failed to control clinical signs.
- It is not appropriate for a pathologist to issue a diagnosis of “inflammatory bowel disease.” It is more appropriate to list the histologic findings, and to indicate that the changes could be “compatible with” a clinical diagnosis of that syndrome.

**CLIENT EDUCATION**

- Chronic gastrointestinal inflammatory disease in ferrets is not always cured.
- Emphasize that treatment is aimed at controlling clinical signs.

**SUGGESTED READINGS**

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**CROSS-REFERENCES TO OTHER SECTIONS**

Cryptosporidiosis (Section VI)

Eosinophilic Gastroenteritis

Epizootic Catarrhal Enteritis

Helicobacter mustelae—Associated Gastritis and Ulcers

Hepatobiliary Disease

Proliferative Bowel Disease

Salmonellosis (Section VI)

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