Rational Treatment for Inflammatory Bowel Disease

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Defining inflammatory bowel disease (IBD)

A. Criteria for diagnosis of IBD (WSAVA GI Standardization group)
   1. www.wsava.org/StandardizationGroup.htm
   2. Gastrointestinal (GI) signs > 3 weeks in duration (vomiting, diarrhea, weight loss)
   3. Incomplete response to diet trials and deworming
   4. Histologic lesions of mucosal inflammation
   5. Response to immunomodulatory therapies

B. Underlying pathogenesis
   1. Considered a disturbance in GI mucosal immunity with loss of mucosal tolerance to intestinal antigens (commensal bacterial, dietary components)
      a. Consistent with this:
         1) Decreased expression of regulatory T cells (which mediate immune tolerance) in dogs with IBD (Junginger 2012)
         2) Upregulation of major histocompatibility complex (MHC) class II molecules found in enterocytes of cats with IBD (Waly 2004)
            a) These allow presentation of foreign antigens to the immune system by enterocytes
   2. Altered mucosal-adherent bacterial flora in dogs with IBD (Suchodolski 2012)
   3. Bacterial adherence to intestinal mucus in affected cats with IBD (Janeczko, 2008) correlates with:
      a. Number of clinical signs
      b. Abnormal duodenal architecture on histopathology
      c. Macrophage and T lymphocyte infiltrates
      d. Up-regulation of inflammatory cytokines
         1) Especially interleukin 8 (IL-8)
   4. Inflammatory markers in dogs with IBD
      a. Lymphocytes in mucosa are primarily cytotoxic T cells (Maeda 2012)
      b. Up-regulated expression of matrix metalloproteinases, IL-8, tumor necrosis factor (TNF), and other pro-inflammatory genes (Wilke 2012)
      c. Increased urinary leukotrienes (LTE4) (Im Hof 2012)
      d. Increased plasma C-reactive protein concentrations (Jergens 2010)

Getting a definitive diagnosis

A. Mucosal biopsies
   1. Endoscopic gastric and duodenal biopsies
      a. May miss a diagnosis of lymphoma in cats
      b. Missed in 4 out of 10 cats, particularly cats with intestinal but not gastric lymphoma involvement (Evans, 2006)
   2. Consider upper and lower endoscopy in cats to reach the ileum
      a. Ileocecocolic junction is common site of GI lymphoma in cats (Scott 2011); will be missed with only upper GI biopsies
   3. Use WSAVA standardization group forms to record biopsy findings at endoscopy (www.wsava.org/StandardizationGroup.htm)
   4. Features of small cell lymphoma vs. feline IBD:
      a. Lymphoid infiltration of the intestinal wall beyond the mucosa, epitheliotropism (especially intraepithelial nests and plaques), cell heterogeneity, and nuclear size of lymphocytes (Kiupel 2011)
      b. In equivocal cases, order:
         1) Immunophenotyping (immunohistochemistry) for CD3e (T cells) and CD79a (B cells)
            a) If single cell type, suggests neoplasia
         2) PCR to determine B or T lymphocyte clonality
            a) Looks for normal rearrangements in T cell receptor and immunoglobulin chains in a heterogenous population of lymphocytes
            b) If clonal (no rearrangement), suggests neoplasia

c) Can be performed on lymph node FNAs or tissue touch preps
   i. www.cvmbs.colostate.edu/ns/departments/mip/cilab/parr.aspx
   ii. 75% sensitive for canine LSA and 65% sensitive for feline LSA

B. Full thickness biopsies
   1. By laparotomy or laparoscopy
   2. Ask your pathologist to follow the WSAVA standardization group guidelines for IBD histopathoogy
      a. Day et al. J Comp Pathol 2008 138 Suppl 1: S1-S43.
   3. Histopathology should describe degree of:
      a. Crypt distortion
      b. Villous blunting and fusion
      c. Fibrosis

C. Scoring severity of disease
   1. Canine IBD disease activity index (CIBDAI)
      a. Assigns scores for attitude, appetite, vomiting, stool consistency, stool frequency, and weight loss (Jergens, 2003)
      b. Later version of scoring system also includes serum albumin, ascites/peripheral edema, and pruritus (Allenspach, 2007)
   2. Useful for comparing clinical trials, but could also be used to track improvement in individual dogs with IBD
   3. Correlates with histologic severity of disease in dogs with IBD (Rychlik, 2012)

Canine IBD disease activity index (Jergens et al, 2003)

- Attitude/activity:
  - 0=normal 1=slightly decreased 2=moderately decreased 3=severely decreased
- Vomiting:
  - 0=none 1=mild (once per week) 2=moderate (two to three times per week) 3=severe (more than three times per week)
- Stool consistency:
  - 0=normal 1=slightly soft feces or fecal blood and/or mucus 2=very soft feces 3=watery diarrhea
- Appetite:
  - 0=normal 1=slightly decreased 2=moderately decreased 3=severely decreased
- Stool frequency:
  - 0=normal 1=slightly increased (two to three times per day) 2=moderately increased (our to five times per day) 3=severely increased (more than five times per day)
- Weight loss:
  - 0=none 1=mild (<5% loss) 2=moderate (5% to 10% loss) 3=severe (>10% loss)

These scores are summed to yield a total cumulative CIBDAI score of 0-18 (higher score = more severe disease)

Treating without a biopsy

A. Consider age of patient and likelihood of IBD
   1. Dogs and cats < 1 year old – look for parasites, dietary intolerance
   2. Dogs and cats > 8-10 years old – look for neoplasia

B. Abdominal ultrasound
   1. Thickened intestines and mesenteric lymphadenopathy
      a. Cannot distinguish between lymphoma and severe IBD
   2. Loss of normal intestinal wall layering
      a. Suggests lymphoma or severe infiltrative IBD
   3. Gastric lymphoma may have normal ultrasonographic appearance
   4. Intestinal adenocarcinoma has ultrasonographic appearance of mixed echogenicity, segmental, intestinal wall thickening (Rivers 1997)

C. Evidence of protein losing enteropathy
   1. Hyperechoic mucosal striations on abdominal ultrasound
   2. Panhypoproteinemia
      a. Suggests PLE
      b. If also hypocholesterolemia, suggests PLE with lymphangiectasia

D. Long duration of signs (> one year) does not rule out development of GI lymphoma

E. If treating without a biopsy, make sure that owner would not pursue chemotherapy for lymphoma, if present

Treatment options

A. Diet
    1. Novel protein diets
        a. Most commercial elimination diets are also milk-, corn-, and wheat-free
            1) Highly digestible
            2) Moderate soluble fiber
        b. Efficacy of novel protein diets
            1) Up to 50% of referred cats with idiopathic GI signs will respond to an elimination diet trial (e.g. venison and rice; Guilford 2001)
                a) Improvement within 2 to 3 days
                b) Some cats relapse after re-challenge with original diet, within 3 to 4 days
                c) Some stayed in remission despite re-challenge with the original diet
            2) 60% of referred dogs with idiopathic GI signs will respond to an elimination diet trial (e.g. salmon and rice; Luckschander 2006)
                a) Improvement within one week
                b) Improved canine IBD activity index (CIBDAI)
        c. Predictors of response
            1) Concurrent atopic dermatitis and GI signs may increase likelihood of response to diet elimination
            2) Eosinophilia is unreliable
            3) About half of diet responders had "IBD" changes on duodenal biopsy, and about half did not
            4) Serum IgE screens for dietary allergens not predictive of response to elimination diets (Guilford 2001)
                a) False positives and false negatives common
                b) Not thought to be IgE-mediated in most dogs and cats
    2. Hydrolyzed protein diets
        a. Goal is decreased antigenicity of dietary protein
        b. Examples
            1) z/d (Hill's)
            2) Royal Canin hypoallergenic diet
        c. Consider in patients with lack of response to novel protein diets, or for use during initial glucocorticoid induction
        d. Better durable clinical remission and reduction in CIBDAI scores compared to standard highly digestible diets (Mandigers 2010)
    3. Low fat diets
        a. Indicated for PLE with lymphangiectasia

B. Immunosuppressive agents
    1. Prednisone/prednisolone
        a. Indications:
            1) Histologic evidence of moderate to severe lymphoplasmacytic or eosinophilic infiltrates with clinical signs
                a) Be conservative in treating minimal to mild infiltrates with immunosuppression
            2) Dosing
                a) Use anti-inflammatory to immunosuppressive dosages initially
                b) 1.0-2.5 mg/kg/day in dogs
                c) 2.0-3.0 mg/kg/day in cats
                d) Prednisolone is more potent than prednisone in cats
                e) If in remission, gradually (q. 3-4 weeks) taper to lowest dose that controls signs
            3) Always accompany with novel or hydrolyzed protein, highly digestible diet
            4) Consider / rule out lymphoma first!
    2. Budesonide
        a. Glucocorticoid with high hepatic clearance (therefore, low systemic blood levels in people)
            1) Fewer systemic side effects than other oral glucocorticoids in humans
        b. Anecdotal efficacy for inflammatory bowel disease in dogs and cats
        c. 3 mg enteric coated gelcaps
            1) 0.5 to 0.75 mg capsule (reformulated) per cat

2) 0.5 to 2.0 mg (reformulated) per dog to start
d. May still cause systemic side effects of glucocorticoids, but may be less so than oral prednisone or prednisolone
e. Will still suppress adrenal function in dogs (both healthy and with IBD; Tumulty 2004; Stroup 2006)

3. Dexamethasone
a. Allows subcutaneous glucocorticoid administration
b. Can be used to induce remission and allow transition to oral prednisolone or budesonide in patients with severe malabsorption
c. Give 1/7 of prednisone/prednisolone dose when using dexamethasone, to account for increased potency of dexamethasone
d. Will not exacerbate ascites in dogs with PLE and severe hypoalbuminemia
1) Dexamethasone lacks mineralocorticoid activity

4. Cyclosporine
a. Second line drug for IBD in both dogs and cats
b. Inhibitor of T cell function
1) Inhibits IL-2 production by T cells
c. Immunosuppressive agent; may deplete T cells in inflammatory diseases
d. Efficacious in dogs with IBD refractory to glucocorticoids (12 out of 14 dogs; Allenspach 2006)
1) Decreased CIBDAI scores
2) Decreased T cells in duodenal biopsies
e. Anecdotal efficacy in cats with IBD
1) May be glucocorticoid sparing
2) May be less likely to cause insulin resistance
f. Dosage: 5 mg/kg once or twice daily
g. Side effects:
1) Vomiting, inappetance
a) Dose dependent
b) May response to metoclopramide
2) Gingival hyperplasia (observed in both dogs and cats)
a) Gingival exam recommended at every visit
3) Secondary fungal infections
a) Observed anecdotally in dogs given the combination of glucocorticoids and cyclosporine
b) Important to use lowest effective dosages of both cyclosporine and prednisolone

5. Azathioprine
a. Second line drug for IBD in dogs only
b. Cats have low TPMT activity – impaired azathioprine detoxification
c. False purine metabolite
1) Inhibits DNA and RNA replication in rapidly dividing cells, including immune cells
2) Effect seen within one week of starting azathioprine (Ogilvie 1988)
d. Efficacy relative to cyclosporine has not been evaluated
e. Dosage in dogs only: 50 mg/M2 per day
f. Side effects:
1) Dose-dependent thrombocytopenia or neutropenia
2) Dose-dependent increases in serum ALT
3) Both CBC and ALT need to be monitored during azathioprine treatment

6. Chlorambucil
a. Alkylating agent
1) Cross-links DNA
2) Less potent than cyclophosphamide
b. Efficacy, with prednisone, for small cell GI lymphoma in cats (Kiselow 2008)
1) Option for IBD refractory to diet and glucocorticoids, or for severe lymphoplasmacytic IBD that is difficult to differentiate from low grade lymphoma in cats
c. Dosing
1) 2 mg per cat, every 48 to 72 hours
2) Taper to lowest effective dose and interval
d. Side effects

1) Leukopenia at higher dosages
2) Unlike cyclophosphamide, no risk of hemorrhagic cystitis
3) Myoclonus (reversible) reported in one cat with dosing interval error (Benitah 2003)

C. Probiotics and prebiotics
1. Probiotics
a. Defined as live microorganisms that lead to a beneficial microbe balance in the intestinal tract, with positive effects on overall health
b. Non-pathogenic organisms
1) Resistant to gastric acid and bile
2) Adhere to the intestinal mucosa
3) Ideally derived from species to be treated
c. Examples
1) Lactobacillus spp.
2) Enterococcus faecium
3) Bifidobacterium spp.
4) Saccharomyces
5) Effects are strain- and dose-specific
d. Potential benefits
1) Modulation of gut flora
2) Inhibition of colonization by pathogenic bacteria
3) Inhibition of bacterial translocation
e. Mechanisms of action
1) Decreased intestinal lumen pH (lactic and butyric acid formation)
a) May inhibit pathogenic anaerobes
2) Butyrate may also have anti-inflammatory effects
a) Inhibits NF-kB translocation and pro-inflammatory inflammatory cytokine expression (Segain 2000)
3) Production of bacteriocins
a) Peptides that kill other bacterial populations
4) Enhanced mucosal barrier function
f. Clinical evidence for probiotic efficacy
1) In humans
a) Decreased incidence of antibiotic-induced diarrhea
b) Some efficacy for maintenance of remission in ulcerative colitis (Hedin 2007)
2) Evidence in dogs
a) Decreased fecal Clostridial counts in healthy dogs given Enterococcus faecium probiotic (Vhjan 2003) or Lactobacillus (Baillon 2004; Biagi 2007)
b) Increased expression of duodenal IL-10 in canine biopsy samples exposed to Lactobacillus *ex vivo* (Sauter 2005)
c) However, no advantage of probiotic cocktail over limited antigen diet alone in 21 dogs with IBD (Sauter 2006)
3) Evidence in cats
a) Decreased Clostridial counts and plasma endotoxin concentrations in healthy cats given Lactobacillus acidophilus (DSM12341, Waltham) (Marshall-Jones, 2006)
g. Veterinary probiotic products
1) Proviable™ (Nutramax)
a) Cocktail of Enterococcus, Streptococcus, Lactobacillus, and Bifidobacterium, plus prebiotics
b) Encapsulated
2) Fortiflora™ (Purina)
a) Encapsulated Enterococcus faecium (strain SF68)
b) Decreased fecal concentrations of Clostridium perfringens in treated kittens
3) ProStora™ (Iams)
a) Bifidobacterium animalis
b) Only clinical study reported also allowed antibiotic use at the clinicians' discretion (!)

4) Many other marketed veterinary probiotics have been shown not to contain viable organisms as labeled (e.g. Nutrigest) or to have no label claims and low viable counts as tested (Probiotic paste from Pet Perfection, Pediatric Health tabs from Pet Perfection, Fel-Addase, Can-Addase) (Weese 2002)

2. Prebiotics
   a. Non-digestible food ingredient that promotes growth of certain populations of bacteria in the gut
   b. Usually selectively fermentable short chain carbohydrates
   c. Examples
      1) Soluble fiber (beet pulp, psyllium)
         a) Fermented to butyrate (short chain fatty acid)
            i. Nutrient for colonocytes
            ii. Decreases pro-inflammatory cytokines
      2) Fructo-oligosaccharides
      3) Lactulose
   d. Efficacy
      1) No overall changes in duodenal bacterial flora in healthy cats supplemented with fructo-oligosaccharides for 32 weeks (Sparkes 1998)

D. Adjunct therapies
   1. Cobalamin
      a. Low serum cobalamin concentrations are common in patients with chronic small intestinal diarrhea, particularly cats
         1) Especially cats with low body condition score (Reed 2007)
         2) Low cobalamin impairs normal enterocyte function (needed for DNA replication and cell division)
      b. Causes
         1) Ileal malabsorption
         2) Pancreatitis
            a) Impaired release of pancreatic intrinsic factor, necessary for cobalamin absorption
            b) Impaired secretion of bicarbonate into the duodenum
               i. Neutralization of gastric acid in duodenum necessary for cobalamin binding to intrinsic factor
            c) Low cobalamin more common in cats with IBD and high fPLI concentrations (Bailey 2010)
      c. Associated abnormalities
         1) Hypocobalaminemia associated with low serum folate and low serum phosphorous levels in cats (Reed 2007)
         2) Macrocytosis is not a reliable marker of low cobalamin in cats, but has been reported (Simpson 2001)
      d. Treatment
         1) Cobalamin (B12) 250-1000 ug SC weekly
         2) Treatment associated with weight gain, increased appetite, and diminished vomiting in affected cats (Ruaux 2005)
         3) Circulating cobalamin half-life of approximately 5 days in treated sick cats (Simpson 2001)
   2. Metronidazole
      a. Anecdotal recommendations for mild IBD, or as adjunct to glucococorticoids
         1) Response may be related to finding of Clostridium spp. in duodenal epithelia of cats with IBD (Janeczko 2008)
         2) No real effect on immune function *in vitro* at therapeutic concentrations (Anderson 1979)
         3) No benefit when added to prednisone in dogs with IBD (Jergens 2010)
      b. Dosing
         1) 10 mg/kg per day
      c. Side effects
         1) Unpalatable, anorexia
         2) Neurologic toxicity at high dosages in both dogs and cats
            a) 55 mg/kg/day

3. Omega-3 polyunsaturated fatty acid (PUFA) supplementation
   a. Decreased generation of leukotrienes such as LTB4, a potent neutrophil chemotactant and pro-inflammatory molecule
   b. Effective in maintaining remission in people with Crohn's disease in some studies (Belluzzi 1996), although not supported by meta-analyses (Feagan 2008)
   c. Dosing
      1) Very empirical
         a) Eicosapentanoic acid 22 mg/kg/day (recommended for dogs with atopy)
         b) Dietary omega-6:omega-3 PUFA ratio of 5:1 (recommended for dogs with chronic renal disease)
      2) Add as single agent and titrate dose
   d. Side effects
      1) Unpalatable
      2) Diarrhea common

4. Treatment for vitamin D malabsorption
   a. Dogs with PLE and severe hypoalbuminemia may have ionized hypocalcemia (and hypomagnesemia) due to vitamin D malabsorption
   b. High index of suspicion for clinically significant hypocalcemia in Yorkies with PLE/lymphangiectasia
      1) Low serum 25-OH-D3 concentrations
      2) Secondary increase in PTH
   c. Treat with oral calcitriol
      1) 20–30 nanograms/kg PO daily x 3–4 days; then 5–15 nanograms/kg PO daily
      2) Monitor both calcium and magnesium

E. IBD treatment failures
   1. Dietary compliance?
      a. Need to individualize diet
      b. May need to try several diets in series
      c. One to two week trials adequate based on response data in cats with IBD (Guilford, 2001)
   2. Is the dosage of prednisone / prednisolone adequate?
   3. Is the prednisone / prednisolone being absorbed?
      a. Consider SC dexamethasone to induce remission in severe malabsorption cases
   4. Is there accompanying disease?
      a. Cobalamin deficiency
      b. Occult parasites or bacterial overgrowth
      c. Undiagnosed GI lymphosarcoma
      d. Pancreatitis
      e. Chronic cholangiohepatitis
      f. Diabetes
         1) May emerge during glucocorticoid therapy in cats
         2) Have owners check for glucosuria periodically
            a) Purina Gluco-test strips in litter for cats every 2 weeks