

**Practical approach to inflammatory bowel disease**  
Lauren Trepanier, DVM, PhD, Dip. ACVIM. Dip. ACVCP  
Professor, Department of Medical Sciences  
School of Veterinary Medicine  
University of Wisconsin-Madison

**Dietary treatment**

Diet is a critical first step in the management of chronic enteropathies in both dogs and cats.

**Novel protein (elimination) diets** are designed to avoid exposure to proteins to which the gut mucosal immune system may have been previously sensitized.

- Most commercial elimination diets contain a novel protein source, are free of milk, corn, and wheat, and are highly digestible with moderate soluble fiber.
- Diet alone has a fairly high efficacy rate in treating chronic gastrointestinal disease in both dogs and cats, and avoids the side effects of immunosuppressive therapy.
- A commitment to a 4 to 6 week diet trial has previously been recommended, which may dissuade some clinicians and owners. However, this is not appear to be necessary:
  - Up to 50% of referred cats with chronic enteropathies will respond well to an elimination diet (venison and rice was used in the trial cited).
  - Responder cats improve within 2 to 3 days, so shorter diet trials appear to be acceptable
    - Consider a one week total in cats, allowing time for diet transition, as long as compliance is good and the owner is observant.
  - A 56% response rate to an elimination diet was reported in dogs with chronic enteropathies (Purina salmon and rice diet used).
  - Most dogs respond to elimination diets within 5-7 days
    - Consider a 7-10 day trial in dogs, allowing time for diet transition

**Predictors of response to novel protein (elimination) diets**

- **Predictive:**
  - Younger age (except boxers).
  - Less severe clinical signs.
  - Concurrent dermatologic signs with chronic GI signs.
  - Normal hypoechoic jejunal mucosa on abdominal ultrasound.
- **Not predictive:**
  - Severity of mucosal histopathology.
  - Eosinophilia is unreliable.
  - Gastroscopic food sensitivity testing is not helpful.
  - Serum screens for IgE against dietary allergens are **not predictive** of response to elimination diets, and should not be used.
  - Serum screens for IgG and IgM against dietary allergens are **not validated**.

**Hydrolyzed protein diets**, such as Hill's z/d Ultra Allergen Free, Purina HA, or Royal Canin hypoallergenic diets, are designed to minimize the antigenicity of intact dietary proteins.

- Hydrolyzed diets show a more durable response than a standard digestible GI diet dogs with chronic small bowel diarrhea.
- There are no studies comparing the efficacy of hydrolyzed protein diets to novel protein elimination diets.

### **Immunosuppressive drug therapy**

In dogs and cats with a biopsy diagnosis of moderate to severe inflammatory gastrointestinal disease, with clinical signs that are not responsive to dietary change, the standard of care remains immunosuppressive drugs. Hopefully this will be replaced in the future by more specific therapies as we better understand the pathogenesis of IBD.

**Prednisone or prednisolone:** Prednisone is a pro-drug and is converted into active prednisolone after administration.

- This conversion is apparently poor in cats, since oral prednisone dosing leads to much lower plasma concentrations of prednisolone in cats compared to oral prednisolone administered directly.
- Therefore, prednisolone is optimal for glucocorticoid administration in cats, especially those without a prompt response to prednisone.
- In dogs, there is probably no benefit of one over the other.

Anti-inflammatory to low immunosuppressive dosages of prednisolone (1-2 mg/kg/day) are recommended initially.

- Once clinical signs improve, the dosage can be tapered every 3 to 4 weeks to the lowest dose that controls clinical signs.
- Glucocorticoid therapy should be accompanied by a highly digestible diet, ideally a novel or hydrolyzed protein source if accepted.
- In patients with severe malabsorption, treatment with subcutaneous injections of glucocorticoids may improve drug response initially.
  - This can be accomplished with dexamethasone, given at about one-seventh the dosage of prednisolone, to allow for the increased potency of dexamethasone (4 to 10 times that of prednisolone; I use a factor of 7 to convert).
- **Dexamethasone** also has a theoretical advantage in treating patients with IBD that also have significant accompanying heart disease, or dogs with PLE and bicavitary effusions due to hypoalbuminemia, since dexamethasone should not promote sodium retention.

**Budesonide** is an orally administered glucocorticoid approved for use in humans with Crohn's disease. Budesonide undergoes extensive hepatic clearance in humans, which leads to lower systemic drug concentrations and associated side effects.

- In dogs, budesonide has fewer side effects of polyuria and serum alkaline phosphatase induction.
- However, budesonide can still be absorbed at concentrations sufficient to cause adrenal suppression in dogs.
- Budesonide is effective anecdotally in dogs and cats with IBD.
- 3 mg enteric coated gel caps must be reformulated
- Recommended empirical starting dosages:
  - 0.5 – 0.75 mg per cat per day.
  - 0.75- 2 mg per dog per day.
  - Start with a 10-14 day supply since capsule size may need to be changed.
- Patients on budesonide should still be monitored for systemic side effects of glucocorticoids, such as muscle wasting, urinary tract infections, and glucosuria.

**Cyclosporine** is a potent immunosuppressant that inhibits T cell function, specifically IL-2 production by T cells.

- Cyclosporine is effective in dogs with IBD with clinical signs that are refractory to glucocorticoids.
  - Severe IBD, PLE, or lymphangiectasia
- Cyclosporine is also effective in cats with refractory IBD, anecdotally.
- Dosages: 5 mg/kg once or twice daily.
- Inappetence and vomiting are common side effects, and typically respond to a 50% dose reduction.
  - Metoclopramide (0.2-0.4 mg/kg PO q. 12 h) is also effective anecdotally for cyclosporine-induced GI side effects.

Less common side effects include:

- Gingival hyperplasia, reported in both dogs and cats.
- Secondary fungal infections (often “street” fungi causing subcutaneous nodules)
- Reactivation of subclinical latent infections, such as toxoplasmosis in cats.
- The dosages of prednisone and cyclosporine should always be tapered to the *lowest effective doses* to avoid serious side effects from chronic immunosuppression.

**Azathioprine** is a purine analog that inhibits RNA and DNA synthesis, and thus affects rapidly dividing cells such as lymphocytes. Azathioprine is both anti-inflammatory and immunosuppressive, and may be used as an add-on agent for severe cases of IBD (e.g. PLE/lymphangiectasia).

- Recommended dosage: 50 mg/M<sup>2</sup> daily in dogs only.
- Side effects of azathioprine:
  - Dose-dependent hepatopathy (increased ALT and ALP)
    - Median onset of weeks (Wallisch 2015)
    - German shepherds may be at higher risk
  - Neutropenia, thrombocytopenia
    - Median onset of 7-8 weeks (Wallisch 2015)
  - Possibly pancreatitis

- Contraindicated in cats due to impaired detoxification of azathioprine by thiopurine methyltransferase (TPMT).

**Chlorambucil** is an alkylating agent that cross-links DNA, but is less potent than cyclophosphamide.

- It is effective, with prednisone, for GI small cell lymphoma in cats.
  - Efficacy as an add-on agent in feline IBD (compared to cyclosporine) has not been evaluated.
- Chlorambucil is dosed at 2 mg per cat, every 48 to 72 hours, or alternatively, 20 mg/m<sup>2</sup> as a single dose every 14 days.
- Chlorambucil is well tolerated in most cats. It does not cause hemorrhagic cystitis, and although leukopenia is possible, it is uncommon.
  - CBC should be monitored prior to the first 3 doses if the 20 mg/m<sup>2</sup> protocol is used, then periodically (e.g. every 2-3 months).
- One apparently rare side effect of chlorambucil is a reversible myoclonus, which was observed in one cat given chlorambucil at an incorrect dosing interval.

### **Treating without a biopsy**

IBD cannot be definitively diagnosed without an intestinal biopsy. In some situations, however, a biopsy may not be possible, such as a client with significant financial constraints or a patient with contraindications for anesthesia (e.g. cardiomyopathy, biventricular effusion, or debilitation).

- Unfortunately, a long duration of signs (> one year) does not rule out GI lymphoma.
- If treating presumptively for IBD without a biopsy, make sure that owners would not pursue chemotherapy for lymphoma, if present, and understand that a definitive diagnosis is lacking.
- Abdominal ultrasound and PLI, serum folate, and serum cobalamin concentrations are still recommended even if a biopsy is not possible.

### **Other interventions**

**Cobalamin injections:** Cobalamin (vitamin B12) is an essential cofactor involved in many key pathways, including hematopoiesis, DNA synthesis, and fatty acid metabolism.

- Since cobalamin is important for DNA synthesis, its deficiency affects rapidly dividing cells, such as the intestine and bone marrow.

If a deficiency is present, low serum cobalamin should be treated with cyanocobalamin injections.

- Cyanocobalamin is a synthetic but stable precursor of active B12 congeners
- The empirical cobalamin dosage in dogs is 250-1000 mg SC weekly.
- The empirical cobalamin dosage in cats is 250 mg SC weekly.
  - Cobalamin supplementation (with no other treatment changes) in cats with hypcobalaminemia is associated with weight gain, increased appetite, and diminished vomiting and/or diarrhea

- A 6 week trial has been recommended, while the underlying cause of malabsorption is addressed (i.e. treatment of the IBD), but this has not been critically evaluated.

**Metronidazole** is a prodrug with excellent anaerobic and good antiprotozoal spectrum, and has been sometimes advocated either alone or as adjunct to glucocorticoids for IBD in dogs and cats.

- Metronidazole is dosed empirically at 15-20 mg/kg per day in IBD patients.
- Although metronidazole has been reported to have direct immunomodulatory effects, this requires fairly high concentrations
  - For example, inhibition of human lymphocyte proliferation is seen at  $\geq 50$  mg/ml, versus a  $C_{max}$  in cats of about 9 mg/ml.
- In a prospective randomized, controlled study in 54 dogs with IBD, there was no difference in remission rates in dogs treated with prednisone alone versus those treated with prednisone plus metronidazole.
  - One drawback of this study was that all enrolled dogs had previously been treated with an elimination diet, followed by Clavamox or metronidazole, before endoscopy was considered. Therefore, the population may have been biased towards metronidazole non-responders.
- Side effects:
  - Metronidazole is unpalatable, and can cause inappetence in cats.
    - Metronidazole benzoate is reportedly better tolerated by cats
    - This may be due a difference in taste as well as lower plasma concentrations achieved after equivalent dosages of metronidazole benzoate.
    - Because metronidazole benzoate is only about 60% metronidazole by weight, it should be dosed at 25 mg/kg/day to provide the equivalent amount of drug in 15 mg/kg of metronidazole.
  - High doses ( $\geq 58$  mg/kg/day) of metronidazole are associated with neurologic toxicity in both dogs and cats, with signs as severe as obtundation due to brain stem necrosis.
  - Metronidazole is mutagenic at therapeutic dosages in cats.
    - Metronidazole at 12 mg/kg q. 12h for one week to healthy cats was genotoxic to DNA in leukocytes (via comet assay).
    - It took an additional week for changes to resolve after drug was stopped.

**Probiotics** are defined as “live microorganisms that lead to a beneficial microbe balance in the intestinal tract, with positive effects on overall health.”

- Probiotics are non-pathogenic organisms, typically bacteria but sometimes yeast, which can adhere to and populate the intestinal mucosa
  - Probiotics must be resistant to gastric acid and bile when given orally.
  - Examples include Lactobacillus spp., Enterococcus faecium, Bifidobacterium spp., and Saccharomyces.

- Potential beneficial effects of probiotics include modulation of gut flora, inhibition of colonization by pathogenic bacteria, and inhibition of bacterial translocation across the gut wall.
- Probiotic bacterial by-products can have anti-inflammatory effects
  - For example, butyrate is generated by probiotics and inhibits pro-inflammatory cytokine expression in patients with Crohn's disease.

There is some evidence for the efficacy of probiotics in humans, although effects are strain- and dose-specific.

- Probiotics can decrease the incidence of antibiotic-induced diarrhea in humans, and may have some efficacy for maintenance of remission in ulcerative colitis.
- In healthy cats, administration of *Lactobacillus acidophilus* (DSM12341, Waltham), decreased both fecal *Clostridia* counts and plasma endotoxin concentrations.
- In healthy kittens, administration of Purina Fortiflora (encapsulated *Enterococcus faecium*) is reported by the manufacturer to decrease fecal *Clostridium perfringens* counts and decrease the incidence of diarrhea.
- In healthy dogs, the probiotics *Enterococcus faecium* or *Lactobacillus* can decrease fecal *Clostridial* counts.
- However, there was no demonstrated advantage of a probiotic cocktail over limited antigen diet alone in 21 dogs with IBD.

If IBD is indeed caused in part by a loss of mucosal immune tolerance to certain bacterial flora, then probiotics may have some benefit in this disease.

- Note: Many marketed probiotics do not contain viable organisms as labeled, or have no label claims and low viable counts as tested.
- Use only products for which viable bacteria have been documented and that have been shown to colonize the intestinal tract of dogs or cats.

**Prebiotics** are non-digestible food ingredients that promote the growth of certain populations of bacteria in the gut. These compounds are usually selectively fermentable short chain carbohydrates, such as soluble fiber in beet pulp and psyllium.

- Prebiotics are fermented to short chain fatty acid such as butyrate, a nutrient for colonocytes that can also decrease the generation of pro-inflammatory cytokines.
  - Butyrate has some efficacy in the treatment of Crohn's disease, with significant improvement in endoscopic changes, histologic scores, and mucosal cytokine levels in some patients.
- There is only one published study of prebiotic therapy in cats, in which there were no overall changes in duodenal bacterial flora in healthy cats supplemented with fructo-oligosaccharides for 32 weeks.

**Omega-3 polyunsaturated fatty acids (PUFAs):** Another option for adjunct therapy of IBD is omega-3 polyunsaturated fatty acids (PUFAs). These compounds decrease generation of leukotrienes such as LTB<sub>4</sub>, which is a potent neutrophil chemotactant and pro-inflammatory molecule.

- Enteric-coated PUFAs have been effective in maintaining remission in people with Crohn's disease in some studies.

Dosing is empirical, since studies are lacking in dogs and cats.

- A starting point would be the dosages used in humans: eicosapentanoic acid at 17-25 mg/kg/day and docosahexaenoic acid at 8-18 mg/kg/day.
- Enteric coated PUFAs are available over the counter in fish oil supplements such as Fisol (Nature's Way; 150 mg eicosapentanoic acid and 100 mg docosahexaenoic acid per soft gel).
- PUFAs should be added as a single agent with a dose titration, since they can be unpalatable, and diarrhea is a common side effect.

### **Treatment of specific syndromes**

#### **Histiocytic ulcerative colitis (a.k.a. granulomatous colitis)**

- Seen in young boxers, Frenchies, and English bulldogs
- Combined large and small bowel diarrhea – soft to liquid blood diarrhea
- Responds to 6 to 8 weeks of an oral fluoroquinolone
- Do not stop early!

#### **Protein-losing enteropathy**

- Treatment is similar to that for IBD, but more aggressive
- Novel or hydrolyzed protein diet
- Prednisone **and** either cyclosporine or azathioprine
  - If severe malabsorption, start with SC dexamethasone until in remission
- Diuretics for ascites
  - Spironolactone/hydrochlorthiazide at 1 mg/kg q. 12h
- Low dose aspirin or clopidogrel to prevent thrombosis
- Fair to guarded prognosis

#### **Lymphangiectasia**

- Treatment is similar to that for PLE, but even more aggressive
- **Low fat diet**
- Glucocorticoids plus cyclosporine (or azathioprine)
  - May need to start with SC dexamethasone until in remission
- Diuretics for ascites
  - Spironolactone/hydrochlorthiazide at 1 mg/kg q. 12h
- Low dose aspirin or clopidogrel to prevent thrombosis
- Oral calcium carbonate and calcitriol for ionized hypocalcemia
- Guarded prognosis but can do well if managed carefully