Inflammatory Bowel Disease

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Inflammatory bowel disease (IBD) is the result of the accumulation of inflammatory cells within the lining of the stomach, small intestines and/or large intestines (A Summers 2007). IBD is distinguished by persistent, recurrent gastrointestinal (GI) signs and histological evidence of intestinal inflammation (L Merrell 2012). Although the most common clinical signs are chronic vomiting and diarrhea (L Merrell 2012), presenting complaints can include changes in appetite (hyporexia, anorexia or even polyphagia), weight loss, lethargy, abdominal distension, polyuria and polydipsia (PU/PD).

The two most common forms of IBD are lymphocytic-plasmacytic enteritis (LPE) and eosinophilic enteritis (EE). LPE is characterized by infiltration of lymphocytes and/or plasma cells into the intestines. EE is characterized by eosinophilic infiltration of any region of the intestinal mucosa. The exact etiology of IBD remains largely unknown. Environmental and genetic factors as well as abnormal immunologic responses are thought to play a large role however, at this time; IBD is thought to be idiopathic.

Vomiting and diarrhea are among the most common clinical signs of IBD. Other signs can include weight loss, appetite changes, poor hair coat, mucoid feces, tenesmus, abdominal pain, PU/PD, increased frequency of defecation, and hematochezia. Clinical signs may wax and wane, with or without a precipitating factor (L Merrell 2012).

Primarily clinical signs are associated with the region affected. That being said, one would associate large volumes of soft stools, weight loss, and/or melena with small intestinal inflammation while associating the presence of hematochezia, mucus in the stool, dyschezia, tenesmus, and an increased frequency of defecation with large intestinal inflammation.

Table 1.

CLINICAL DIFFERENTIATION BETWEEN CHRONIC SMALL INTESTINAL FROM LARGE INTESTINAL DIARRHEA[21]

Sign	Small Intestinal Disease	Large Intestinal Disease
Weight Loss	To Be Expected	Rare
Polyphagia	Sometimes	Rare to absent
Frequency of Bowel Movements	Often near normal	Sometimes very increased
Soft stool	Expected	Sometimes
Volume of feces	Often increased	Sometimes decreased due to increased frequency
Blood in feces	Melena (rare)	Hematocheziea (sometimes)
Mucus in feces	Uncommon	Sometimes
Tenesmus	Uncommon	Sometimes
Vomiting	May be seen	May be seen
Dyschezia	Uncommon	Sometimes

It is important to note that watery diarrhea can be a component of both small and large bowel inflammation. Large amounts of soft stool without tenesmus, dyschezia and/or mucus is characteristic of small intestinal disease. In addition, failure to lose weight is the most reliable indication that the animal has large bowel disease (Nelson and Couto 2008)

In severe untreated cases it is possible for a patient to have developed protein losing enteropothy (PLE), and/or lymphangiectasia. These cases can present with severe weight loss as well as bicavitary effusion in addition to other edematous states.

Along with the presence of histological findings, which appropriately explain the patient's clinical signs, the diagnosis of IBD is one of exclusion (i.e. ruling out all other possibilities). Diagnostic biopsies are necessary because there are no pathognomonic historical, physical examination, or clinical pathological findings for this disorder (Nelson and Couto 2008).

Diagnosis starts by exclusion of other causes of gastrointestinal inflammation such as parasitic pathologies, diet responsive and antibacterial responsive conditions, pancreatitis, neoplasia, endocrine or metabolic pathologies, foreign bodies and/or extra-intestinal infections.

Food allergies and intolerances must be ruled out. Except for very mild cases of IBD, this disease does not tend to respond to dietary manipulation alone. If a food trial is permissible, a 4 to 6-week trial is recommended, although shorter trials have been adequate (K Dunbar 2011). Food trials should consist of a novel protein/hypoallergenic diet. Client education is essential in order to increase chances of compliance and increase likelihood of a successful outcome.

Table 2.

DIAGNOSITIC FINDINGS MAY INCLUDE:	
CBC	Usually within normal limits although occasional neutrophilia, eosinophilia, lymphopenia, anemia, or thrombocytopenia may be noted
Chemistry Panel	Usually within normal limits but in severe cases of PLE, panhypoproteinemia (hypoalbuminemia and hypoglobulinemia) along with hypocholesterolemia are present
Fecal Floatation Giardia Snap Testing Fecal PCRs	Necessary to rule out parasites such as hookworms, whipworms, and giardia PCRs can also detect chronic bacterial infections like Campylobacteriosis amongst others
Urinalysis	Abnormalities may include a USG <1.010, and an increased protein level may be present

Cobalamin (vitamin B12), the largest of the water-soluble B vitamins, is absorbed in the ileum. Folate (vitamins B10 and B11) is absorbed in the proximal small intestine, specifically the duodenum (A Wortinger 2007) . Animals with IBD may have serum concentrations consistent with active inflammation. Serum concentration levels of these vitamins can thus allow for localization of the inflammation. If both serum levels are decreased, it can indicate malabsorption and thus be a marker for inflammation. While either hypocobalaminemia or hypofolatasemia are consistent with distal or proximal small intestinal disease respectively, hyperfolatasemia should raise the suspicion for the presence of intestinal dysbiosis. Fasting vitamin levels allow for localization of intestinal pathology which may be most likely inflammatory or neoplastic in nature.

Ultrasonography is an important diagnostic tool. Thickening of the large and small intestinal walls as well as enlarged lymph nodes are common ultrasonographic findings. They are characteristic of inflammatory disease processes but are not specific to IBD. Ultrasonography can provide information on the location and severity of lesions, suggesting the location were biopsies may be warranted[8].

Histopathologic findings are required for the proper diagnosis of IBD. Biopsy samples can be obtained either endoscopically or surgically. Endoscopic sampling is less invasive and tends to be less invasive, however endoscopy does have its limitations. Endoscopic sampling allows for only the sampling of the mucosa and submucosa thus many times being unable to sample the muscularis or the serosal layers of the intestinal tract. Endoscopic samples are also limited to the gastric, duodenal, proximal jejunal ileal and colonic areas. Full thickness surgical biopsies are the ideal diagnostic samples especially if deep intestinal layer involvement or multi-organ involvement are suspected. Surgical biopsies are more invasive and require a longer recovery period therefore not being an ideal option older patients, patients with concurrent diseases, or a patient with advanced disease and decreased healing abilities. Full-thickness and extra intestinal biopsies are important diagnostic tools as if they are not obtained, a diagnosis may be missed or a misdiagnosis can be made (e.g., IBD can be easily confused with lymphoma). Although surgical and laparoscopic biopsies are complex, they are estimated to be the gold standard for the diagnosis of IBD (K Dunbar 2011).

The treatment for IBD is aimed at reducing inflammation and in many instances suppressing an overactive immune system. The way to achieve this is multimodal. Case-specific nutrition as well as nutritional supplementation is necessary to help aid and reduce inflammation to the gastrointestinal tract and help the body absorb essential nutrients. Gastroprotectants are commonly used as the primary disease and some of the medications used to treat it can cause gastrointestinal upset. Immunosuppression is often necessary to further aid in controlling inflammation while antimicrobial therapy is used to control intestinal dysbiosis.

As previously discussed, IBD classically presents with main gastrointestinal clinical signs, such as vomiting, diarrhea, flatulence and diarrhea. Part of these clinical signs can due to a concurrent food intolerance and/or allergy. The goal of dietary therapy is to eliminate adverse food reactions (L Merrell 2012). In order to accomplish this, the prescribed diet should meet the patient's nutritional needs, be highly digestible, be low in antigens, and in cases of lymphangiectasia or PLE, be fat restricted. A single novel protein source is ideal. It is important

to remember that there is no perfect food option for IBD, each patient will have different dietary needs and disease process restrictions. There are many options available, in the event that no commercial diet can be found a custom made balanced home-made diet should be considered.

A hydrolyzed protein diet consists of a single protein source that is specially processed to break the structure of the protein down into multiple, tiny particles that the immune system will not recognize as an allergen. It is a chemical process in which a molecule is cleaved into two parts by the addition of a molecule of water. One fragment of the parent molecule gains a hydrogen ion (H +) from the additional water molecule. The other group collects the remaining hydroxyl group (OH −). This method has been used for several years in infant formula to decrease food hypersensitivity. Soy and chicken are common protein sources used in making these diets. Soy may be preferable since fewer dogs seem to have been fed soy based diets previously so it is less likely that they have been sensitized to it. It has been found that hydrolyzed soy is extremely digestible and well absorbed from the gut (M Ryan 2008).

A novel protein diet consists of using a single protein source which the patient has not been exposed to and thus have not been sensitized to in the past. Novel protein diets have more options in terms of potential protein sources as well as canned varieties compared to the hydrolyzed diets. These diets are typically more calorie dense than the hydrolyzed diets so portion control must be followed closely to prevent weight gain. One thing to keep in mind when choosing a diet is that pets with beef allergies may react to venison and pets with chicken allergies may react to duck protein sources (M Ryan 2008)

In the cases of secondary PLE and lymphangiectasia an ultra-low fat diet is indicated. A restricted low fat diet helps to prevent further intestinal lacteal engorgement and subsequent protein loss (Nelson and Couto 2008).

Folate and cobalamin levels are frequently abnormal in patients with IBD. Supplementing these vitamins will aid in proper nutrient absorption and digestion and in some cases increase the patients' appetite. In animals with reduced cobalamin absorption, regardless of the cause, it is reasonable to expect that eventual depletion of body cobalamin stores will occur and cobalamin deficiency will ensue. As all cells in the body require cobalamin for single carbon metabolism, it has been hypothesized that cobalamin deficiency may contribute to the clinical signs and manifestations of gastrointestinal disease in some patients [11]. Supplementation of cobalalmine is thus an important part of treatment. This can be done with a subcutaneous injection given weekly.

Cobalamin is essential in many biochemical processes involving single carbon transfers. Cobalamin deficiencies have been very well described in dogs and cats having gastrointestinal pathologies. Cobalamin deficiency has been associated with worse clinical outcomes in dogs with chronic enteropathies. Cobalamin supplementation has been found to improve clinical signs in cats with chronic enteropathies.

Cobalamin can be measured in fasted serum samples. Supplementation is recommended when the cobalamin level is subnormal or at the low normal range (<300ng/L) (S

Morales 2010).

Supplementation recommendations per the Gastrointestinal Laboratory at Texas A&M have changed as stated below:

Table 5.

SPECIES- WEIGHT	DOSE OF COBALAMIN (µG) GIVEN SUBCUTANEOUSLY/WEEK
Cats	250 µg
Dogs: <10 lbs	250 µg
Dogs: 10-20 lbs	400 µg
Dogs: 20-40 lbs	600 µg
Dogs: 40-60 lbs	800 µg
Dogs: 60-80 lbs	1000 µg
Dogs: 80-100 lbs	1200 µg
Dogs: >100 lbs	1500 µg

It is recommended to give the subcutaneous or IM dose every 7 days for 6 weeks, then a single dose 30 days later, while retesting 30 days after the last dose. If the underlying disease process has been well controlled and the cobalamin stores are replenished, the cobalamin levels should be supranormal. If the cobalamin concentrations are within the normal range, at least monthly supplementation should be continued. If the cobalamin level is still subnormal, then further evaluation of the underlying process needs to be pursued and the cobalamin supplementation should be instituted weekly or bi-weekly (S Morales 2010).

Omega 3 fish oils have been used more recently in IBD therapy because of their anti-inflammatory properties. N-3 fatty acids can be administered orally in an effort to reduce pro inflammatory cytokines synthesized from n-6 fatty acids. Their efficacy has been demonstrated in a number of species and inflammatory conditions, and they are commonly utilized as adjunctive therapy for canine atopy. Preliminary data on n-3 fatty acid use in rodent IBD models and in people is encouraging, although they have yet to be evaluated in dogs and cats for the ancillary treatment of IBD (S Bissett 2007).

Prebiotics and Probiotics can be utilized in inflammatory bowel disease to restore gastrointestinal health. The normal intestinal flora of the immune system is made up of beneficial bacteria that keeps the animal healthy and maintains the health of the gastrointestinal system. Prebiotics are a type of carbohydrates called oligosaccharides that encourage the growth of beneficial bacteria and suppress the growth of pathogenic bacteria (A Wortinger 2010). Probioitics are actual bacteria that enhance intestinal health. They survive the acid and bile in the GI tract, they exclude and reduce pathogenic bacterial adherence, and coaggregate

to help achieve a normal and balanced microflora. They need to be safe, noninvasive and nonpathogenic, and non-carcinogenic to the host (A Wortinger 2010). Care should be taken when using these nutraceuticals as it is not always appropriate to introduce bacteria into the GI tract. If ulcers or hematochezia is present, probiotics can be seen as potentially dangerous. In addition, timing of antibiotics must be noted so that that the patients are receiving the benefits of both medications.

Metronidazole is a broad-spectrum antibacterial and antiprotozoal agent. It is usually the first antimicrobial of choice for IBD patients due to its ability to balance intestinal microflora, reduce obligate anaerobe load and reduce inflammation (K Dubar 2011). Metronidazole (10mg/kg PO BID) is recommended. Special care should be taken in animals that are on long-term metronidazole therapy because of potential risks of neurotoxicosis and hepatotoxicosis (Purcell and Cook 2010). Other antimicrobials that may be used include tylosin (10-20mg/kg PO BID). There is currently little evidence to support the use of antibiotics in combination with glucocorticoid therapy. The mechanism by which the antibiotics exert their effect is poorly understood but may involve decreased bacterial adhesion, altered intestinal flora populations, and anti-inflammatory effects. Lower doses can be used chronically for both medications if the clinical signs, especially diarrhea, flatulence and borborygmi, return as the antibiotic therapy is discontinued (Boyle and Bissett 2007).

Corticosteroids are the most commonly used immunosuppressive agents for the treatment of IBD. Commonly used oral corticosteroids include prednisone, prednisolone and budesonide. An initial dose for immunosuppression is 1-2mg/kg PO BID ideally given for 2-4 weeks and then slowly tapered over the next several months. Ideally patients should be weaned off corticoid therapy completely once clinical signs have resolved. It is important for the veterinary team to reassess these patients every 2-3 weeks as they slowly wean this therapy. It is likely that many patients need to be on long-term low-dose corticosteroid therapy. It is up to the medical team to find the lowest most effective dose of glucocorticoids. A CBC and chemistry should be performed 2 weeks after starting therapy to monitor for any acute reactions. After that testing a CBC every 2-4 weeks is important in order to monitor for bone marrow suppression. Iatrogenic hyperadrenocorticism is a possibility; therefore, a chemistry panel should be performed every 2-3 months in order to screen patient's elevated cholesterol and triglyceride levels which would let us know about developing hyperadrenocorticism. In addition, proteinuria is a possibility on chronic prednisone therapy so a urinalysis should be performed with the chemistry. Feline patients have 50% the glucocorticoid receptors as dogs and therefore do not suffer side effects to the same level as dogs however, still need to be carefully monitored. Cats can have an increase in insulin resistance as a result of glucocorticoid therapy thus making them more vulnerable to developing diabetes. Patient on chronic glucocorticoid therapies are also prone to urinary tract infections and thus a urinalysis and a urine culture should be performed at least once to twice yearly. Due to their side effects and long term iatrogenic risks it is important to monitor these patients closely and reduce/discontinue therapy when it is deemed to be safe. If discontinuation of high doses of steroid therapy is not possible then concurrent therapy with other non-steroid immunosuppressive agents may be indicated in order to maintain control of the disease while minimizing the potential life-threatening side effects of glucocorticoids.

Budesonide is also a glucocorticoid that can be a good option for patients that have severe side effects while on prednisone or prednisolone. Budesonide is relatively new on the market and was originally developed to help humans with certain types of IBD that were suffering the side effects of other corticosteroids. Budesonide differs from other glucocorticoids because it reportedly has reportedly had potent topical anti-inflammatory activity on the GI

mucosa and minimal systemic side effects (Fogel and Bissett 2007). While budesonide is a good option for patients suffering from side effects, the medication can still pose the same threat of iatrogenic hyperdrenocorticism and adrenal atrophy. Because of this, clients will still need to be educated well on potential risks, side effects and a titration schedule will need to be implemented once clinical signs are under control. Budesonide (dogs: 2 mg/dog/day, PO; cats: 1 mg/cat/day, PO) (D Plumb 2005).

Azathioprine is an option for dogs that are already on glucocorticoids and need additional suppression. It can also replace a glucocorticoid if the patient did not respond well to the original therapy. Azathioprine takes 2-3 weeks to become fully effective, therefore, if the goal is to wean off of glucocorticoids with the addition of azathioprine the patient should not begin tapering until three weeks into therapy. Azathioprine can cause bone marrow suppression therefore complete blood counts (CBC's) should be performed every 4-6 weeks. A biochemical profile should also be done due to azathioprine's association with hepatotoxicity and pancreatitis. Cats should not receive azathioprine because of rapid, lethal bone marrow suppression. Azathioprine (dogs: 2.2mg/kg PO once daily) (D Plumb 2005).

Cyclosporine is heavily used in human medicine for transplant and immune-mediated patients. It has proven to be beneficial in dogs and cats with immune-mediated disease. Cyclosporine works by inhibiting cellular immunity; it is metabolized by the liver and excreted into the bile. When dosing cyclosporine it is important to make sure the client is getting the recommended product. Neoral/Atopica® (L Merrell 2012) is much more effective in small animals because of a higher bioavailabilty then Sandimmune® (L Merrell 2012). Cyclosporine should be administered on an empty stomach and can cause GI side effects such as vomiting, anorexia, and diarrhea, these signs can usually be treated with gastrointestinal protectants such as famotidine, metoclopramide, and maropitant. Cyclosporine is one of the most commonly used second-line immunosuppressant. Cyclosporine (dogs: 5-10mg/kg/day PO; cats: 1-5mg/kg/day divided BID) (D Plumb 2005).

Mycophenolate mofetil is an immunosuppressant that is increasingly used in dogs. While it is used commonly in human medicine it is fairly new to veterinary medicine. Mycophenolate suppresses the immune system by suppressing lymphocyte proliferation and decreasing antibody production Mycophenolate is not the first medication of choice because we have limited information on long-term effects. In addition, mycophenolate should be used with caution in patients with IBD because it can be the cause of inflammatory diarrhea (Fogel and Bissett 2007). Serial monitoring of CBC's and chemistries and electrolytes should be performed to detect cell suppression, bone marrow suppression, acute liver and kidney reactions. Mycophenolate mofetil (dogs: 12-39 mg/kg/day) (L Merrell 2012).

Chlorambucil is an anti-cancer agent with effective immunosuppressive properties. It has a 2-4 week delay of action therefore any decreasing of glucocorticoids should begin 3-4 weeks after starting chlorambucil. Chlorambucil is one of the most commonly used second line immunosuppressants. Serial monitoring of CBC's in necessary in order to monitor for myelosuppression that can manifest in anemia, leukopenia, thrombocytopenia, and gastrointestinal toxicity (D Plumb 2005). Chlorambucil (dogs: 0.1-0.2mg/kg once daily PO; cats: 0.25-0.5mg/kg q48-72 hours) (D Plumb 2005).

Many of the medications used in the treatment of IBD can have gastrointestinal side effects such as, lack of appetite, borborygmus, vomiting, diarrhea, and GI ulcerations. Because of this supportive agents like H_2 blockers, H pump inhibitors, and motility modifiers should be considered as adjunct therapy.

Table 6.

Medicat	Function:	Canine Dose	Feline Dose	Warnings:
Famotdi (pepcid®	H_2 receptor antagonist use to reduce GI acid productio	0.5 -1 mg/kg SID-BID	0.5mg/kg P once daily	H_2 have been demonstrated to be relatively safe and exhibit minimal adverse effects.
Metoclop mide (reglan®	Stimulates upper GI motilit and has antiemetic propert	0.2-0.4mg/kg BID-TID	0.2-0.4mg/k PO BID-TID	Behavior changes; Changes in mentition, behav disorientation and constipation.
Maropita (cerenia	neurokinin (NK1) receptor antagonist that blocks the pharmacological action of substance P in th central nervous system (CNS)[35]	2mg/kg PO o daily for four days	Off label for cats	has not been evaluated in dogs used for breedir pregnant or lactating bitches, dogs with gastrointestinal obstruction, or dogs that have ingested toxins. Use with caution in dogs with hepatic dysfunctio
Ondanse n (zofrar	5-HT_3 receptor antagonist f severe vomiting	0.1-1mg/kg F SID-BID	0.22mg/kg E TID	Potential of constipation, extrapyramidal sympto arrhythmias and hypotension
Sulcralfa (carafate	Locally acting treatment fo ulcers	0.5-1 gram P BID-QID	0.25-0.5 gra PO BID-TID	Constipation possible Should be administered on an empty stomach
Omempr le (prilos	Proton pump inhibitor used GI Ulcers and erosion	0.5-1 mg/kg I SID	0.7 mg/kg P SID	Hypersensitivity is possible Caution should be taken in patient with hepatic or renal disease

The prognosis for IBD is usually good. Contributing factors in prognosis include how far along in the disease process the patient is, how compliant the client is, and the patient's response to treatment. In addition, concurrent disease processes or secondary diseases must be taken into consideration. Patients with secondary pancreatitis, lymphangiectasia or protein losing enteropathy tend to have a poorer prognosis and a different response to treatment.

The role that a technician plays in educating the pet owner about IBD is an extremely important part of the overall therapeutic plan. The veterinary technician should be able to answer questions for the client spanning from the initial diagnostics to specific medical treatments and side effects. Nutritional counseling and the importance of owner compliance in regards to diet should be able to be communicated by the technician. The technician can play a very important role in helping the owner understand and preparing them for what lays ahead as the treatment develops. With excellent communication with the veterinary staff, positive patient response and owner compliance this is a disease that can have a favorable prognosis.

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