Practical Immunomodulatory Treatment of Gastrointestinal and Hepatic Inflammatory Disease. “What to do after biopsy”.

What are the best treatment options for IBD in dogs and cats?

There are many causes of gastrointestinal (GI) inflammation. Inflammatory bowel disease (IBD) is an idiopathic chronic-active inflammation of the GI tract. It is a diagnosis based on the finding of an inflammatory intestinal biopsy and the exclusion of all known causes. Once a diagnosis of idiopathic IBD has been established, the treatment goal is reduction if gastrointestinal inflammation with immunosuppressive or immunomodulatory drug therapy.

CORTICOSTEROIDS
Corticosteroids, most commonly prednisolone, are used as first line therapy. In IBD patients the CCS dosage is initially immunosuppressive and the gradually tapered over time to a reduce dose and frequency that maintains adequate control of the clinical signs. This may be adequate in many cases. However, more severe and refractory IBD patients or patients with intolerable adverse CCS will require alternate non-steroidal immunomodulating therapy.

Budesonide is a potent glucocorticoid (reportedly 15X more potent than prednisolone) with excellent topical activity. This drug formulation has delayed dissolution until it reaches the duodenum with subsequent controlled active drug release, allowing exertion of topical anti-inflammatory activity in the intestines. Following drug is absorption from the gut, the drug enters the portal circulation where it has high first-pass metabolism through the liver and repeat secretion via bile into the intestine again. The unique metabolic activity reduces systemic glucocorticoid effects of the drug and allows for more prolonged exposure of the drug to the intestinal mucosa. While this drug may reduce systemic corticosteroids effects significant suppression of the HPA-axis (and cushinoid side-effects) may still occur in some patients.

The primary indication for this glucocorticoid is its oral use to treat inflammatory intestinal disease in patients refractory to or intolerant of systemic steroids such as prednisone or dexamethasone. Pharmacokinetics have been reported in dogs. The drug has a low bioavailability of 10–20% which is desirable to provide topical intestinal activity

Dogs – 3 mg/m² (0.5–3 mg per dog) PO q 24hr or 1 mg (total dose) PO q 24hr for small dogs and 2 mg (total dose) PO q 24hr for larger dogs. Cats -1 mg (total dose) PO a 12-24hr.

*Budesonide capsules: 3 mg (micronized); Entocort EC®Drug often requires compounding in smaller patients. The enteric-coated sugar spheres found inside the capsule should not be altered or damaged as it may alter activity.

AZATHIOPRINE
Azathioprine is a synthetic purine analog that interferes with DNA and RNA coding and transcription inhibiting antigen induced lymphocyte transformation thus has greater effects on humoral as compared to cell mediated immunity. Azathioprine is metabolized to 6-mercaptopurine which acts as the active component. It has been used successfully as an
adjunct therapy in dogs and cats with severe or refractory IBD. It has a lag time of 2-6 week before clinical effects and improvement is seen. Side effects can include hepatic disease, pancreatitis and bone marrow suppression. It is very toxic in cats causing severe bone marrow suppression. Due to the possibility of this severe side effect other immunosuppressant drugs such as chlorambucil are recommended in cats.

Dogs are started at 2.2 mg/kg q 24 hours for 2 weeks then the frequency of administration is reduced to every other day for an additional 4-8 weeks. If effective dosage reduction may be considered reducing to 0.5-1 mg/kg every other day. Complete blood counts should be done initially to monitor for bone marrow suppression. The drug should be discontinued and replaced if bone marrow suppression occurs.

CHLORAMBUCIL
Chlorambucil is an alkylating agent that interferes with DNA replication & RNA transcription ultimately disrupting nucleic acid formation. It can be used in cats for severe or refractory cases of IBD as an alternative to azathioprine. Chlorambucil is usually used with CCS for refractory or severe IBD in cats. Side effects include vomiting, anorexia, and bone marrow suppression. Cats >4 kg are started at 2mg/cat q 48 hours for 2-4 weeks then tapered to the lowest effective dose (2 mg/cat q 72-96 hours). Cats <4kg are started at 2mg/cat q 72 hours. Complete blood counts should be performed q 2 weeks initially and q 3 months thereafter.

CYCLOSPORINE
Cyclosporine inhibits T cell activation and cytokine and has been used for immunosuppression in dogs & cats. To date, limited studies are available regarding cyclosporine treatment of IBD, but it has been used anecdotally. It is not cytotoxic nor myelotoxic, nor nephrotoxic or hepatotoxic in dogs and cats unless very high levels are maintained. Several preparations are available and possess very different bioavailability. The veterinary formulation of a modified cyclosporine Atopica® is started at a dose of 5-7 mg/kg q 24hr for cats and 5 mg/kg q 12 hours in the dog. The dose can be very individual so it is recommended to evaluate trough blood levels of the drug if a satisfactory response is not seen with initial dosing; aim for 500 ng/ml. It has a very unpleasant taste and should be administered via intact capsules or legend solution.

What are the current medical treatments for chronic-active hepatitis?

The treatment of liver disease should be first directed at identifying the inciting etiology and removing the cause of the disease. For example, primary copper associated toxicities should be treated using copper chelators (penicillamine or trientine, 15 mg/kg bid) and infectious causes such as leptospirosis and feline bacterial (neutrophilic) cholangiohepatitis should be treated with appropriate antibiotics.

Idiopathic chronic lymphoplasmacytic inflammatory liver disease is often treated with immunomodulating anti-inflammatory therapy (prednisone, prednisolone 2 mg/kg/day tapered eventually to a dose of 0.5 mg/kg/day or every other day.)
Additional immunomodulating anti-inflammatory activity is necessary in patients with severe disease or that are intolerant to continued corticosteroid therapy. Azathioprine (2.0 mg/kg/day x 2 weeks, then reduced to 2.0 mg/kg qod) is frequently added in dogs with suspected immune mediated chronic hepatitis. Cats can develop rapid bone marrow suppression with azathioprine treatment so chlorambucil is the adjunctive drug of choice (4 mg/m2 po q 48-72 hours); CBC should be monitored for development of significant leucopenia which would require a dose or frequency reduction.

Other accepted pharmacologic agents include colchicine for hepatic fibrosis and ursodeoxycholic acid to protect against the toxic effects of bile acids. The benefit of **colchicine** (0.03 mg/kg/day) in liver disease in small animals is unproven and questionable; gastrointestinal toxicity may also limit its routine use. **Ursodeoxycholic acid** (Ursodiol, 10-15 mg/kg daily) however is shown to have hepatoprotective, antioxidant and anti-inflammatory properties. Additional mechanisms include choleresis by increasing bile flow in cholestatic liver disease. Evidence supports the beneficial effects of ursodeoxycholic acid in many types of cholestatic liver disease being especially important in cats with chronic cholangitis.

If an etiology can’t be identified then the clinician is then left with providing general liver support and treating any complications from liver dysfunction as they occur. Complications associated with liver dysfunction include such conditions as ascites, hepatic encephalopathy, coagulopathies and gastrointestinal ulceration.

**Basic Liver Support**

General liver support is a vague definition that involves promoting an environment conducive for ideal hepatocellular function and regeneration. Liver support should first include appropriate dietary management. Maintaining adequate energy intake with proper protein supplementation is essential for hepatic regeneration. **There is a major misconception about diet and liver disease that states patients should be placed on a protein-restricted diet.** The goal of dietary therapy should be to adjust the quantities and types of nutrients to provide needed nutrient requirements but to avoid the production of excess nitrogen by-products associated with liver disease. Diet is important to provide factors that support liver function and regeneration so protein should only be restricted if the patient has developed hepatoencephalopathic complications.

There has also been recent interest in the management of certain types of liver disease with antioxidants. There is considerable evidence showing that free radicals are generated in liver disease and participate in the pathogenesis of oxidative liver injury in dogs and cats. Normally there is an extensive system of cytosolic and membrane bound enzymatic and nonenzymatic antioxidants which function to prevent oxidative damage by “scavenging” or “quenching” free radicals that are formed. Though the pathogenesis of most types of liver disease is unknown there is considerable evidence showing that free radicals are generated in all types of liver disease and participate in the pathogenesis of liver injury.

**Non-Pharmacologic Hepatic Support** The non-pharmacologic options for liver support are many. Included in this category are vitamins, minerals, nutrient supplements and herbals. Most
of these options are directed at preventing oxidative damage and maintaining hepatic membrane structure and function. Unfortunately many of these compounds have no scientific evidence based support for their use. In many there is limited knowledge of potential toxicity, adequate dosage and therapeutic benefit for small animal liver disease. Recently there is increasing scientific evidence of benefit of several non-pharmacologic compounds for liver support. Included below here are compounds with minimal or no toxicity having evidence of therapeutic benefit in liver support.

**Vitamin E** (alpha tocopherol) is a membrane bound antioxidant that functions in preventing lipid membrane peroxidation in liver disease. Vitamin E has protection against copper, iron, bile acids and certain hepatic toxins. One study we found vitamin E improved the GSH:GSSG ratio (glutathione concentrations as a measure of oxidative damage) in dogs with chronic hepatitis. Doses of 10-15 IU/kg/day are recommended.

**Zinc** is an essential trace element and often deficient in chronic liver disease. We have found it is not unusual to have patients with chronic hepatitis to have subnormal hepatic zinc concentrations. Zinc functions in intermediary metabolism but also has antioxidant function. In a canine study of copper associated liver toxicity zinc given orally at high concentrations for a prolonged course prevented intestinal copper intake and depleted excessive hepatic copper concentrations. There are no studies evaluating zinc as an antioxidant in liver disease in small animals. Doses of 2-3 mg/kg of zinc per day have been suggested with much higher doses to block copper absorption (approximately 50 mg bid).

**Silymarin** is an extract from the plant milk thistle and has been shown to act as a free radical scavenger in liver disease. *In Vitro* studies suggest it will protect against lipid peroxidation and increase GSH concentrations in the liver. In one canine mushroom hepatotoxicity study dogs given silybin had a beneficial protective effect against the toxin. Unfortunately, the purity of commercial products and therapeutic dosage is unknown. Dosage of milk thistle ranges from 50 to 250 mg bid. Milk thistle is also reported to have an extremely low toxicity in humans and animals and has been used extensively in clinical patients with little concern for side effects. Silybin is the active steroisomer of silymarin and is shown to exert the main biological hepatoprotective effects. Because of silymarin and silybin’s poor GI absorption characteristics a silybin-phosphatidylcholine complex (Marin™) is now available for use. The phosphatidylcholine increases GI absorption. In preliminary pharmacokinetic studies using normal cats no clinical outward signs of toxicity were observed when giving a dose of 5 mg/kg. For dogs Marin™ also contains vitamin E and zinc and for cats it contains vitamin E.

**S-adenosylmethionine** The naturally occurring molecule, S-adenosylmethionine (SAMe), is synthesized in all living cells and is essential in intermediary metabolism having both hepatoprotective and antioxidant properties. Some of the highest concentrations of SAMe occur in the liver. SAMe is derived from the amino acid methionine and ATP driven by the enzyme SAMe synthetase. The liver normally produces abundant SAMe but there is also evidence to suggest conversion from methionine to SAMe by SAMe synthetase mediated is hindered in liver disease. Once SAMe is formed it then is used in three major biochemical pathways of metabolism: transmethylation, transsulfuration and aminopropylation. The products of SAMe
have an influence on modulating inflammation, promotion of cell replication, and protein synthesis. SAMe also plays a major role in membrane function and is an essential precursor for the essential intracellular antioxidant GSH.

SAMe pharmacology has been studied in both dogs and cats. Oral SAMe is bound to a stable salt and should be enteric coated. Without enteric coating the product can be oxidized readily and broken down. Tablets should be foil wrapped and should not be divided to prevent breakdown. When given on an empty stomach there is also better bioavailability. SAMe is rapidly absorbed and peak plasma levels can be detected for up to 6-8 hours. Studies in normal dogs and cats given SAMe for 12 and 16 weeks respectively found it was well tolerated without adverse side effects. Doses used were 20 mg/kg/day. Studies have also found that all SAMe products are not similar in bioavailability and the concentration of SAMe in the product. SAMe is available as Denosyl™. Recently a combination product, Denamarin™, containing both SAMe and Silybin has become available. Clinical experience with SAMe is considerable both with experimental studies and through management of clinical cases in dogs and cats. We performed a placebo-controlled feline model of oxidant injury from acetaminophen and found SAMe treated cats had reduced Heinz body formation and erythrocyte destruction and evidence of protection in hepatic GSH in the treated cats as well.

Management of specific hepatic complications

Complications associated with liver dysfunction also include such conditions as ascites, hepatic encephalopathy, coagulopathies and gastrointestinal ulceration.

Gastrointestinal ulceration and bleeding can be a common consequence of chronic liver disease and predisposes to hepatoencephalopathy development. Antacid therapy may be helpful in reducing gastric erosions and ulcerations by reducing gastric hydrochloric acid production and mitigating its effects on the gastric mucosa.

The only antacids that are reliably able to suppress gastric acid production are famotidine (0.5mg/kg po qd-bid) and omeprazole (0.5mg/kg po qd-bid). Cimetidine and ranitidine are weak antacids and should not be used in dogs or cats with liver disease.

Diuretic therapy is indicated for patient with significant ascites formation. Furosemide or hydrochlorothiazide is usually adequate to control fluid accumulation. Careful monitoring to avoid electrolyte disturbances or hypotension associated with diuretic use.