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UPDATE ON MEDICAL THERAPY FOR HEPATOBILIARY DISEASE
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INTRODUCTION
There are few controlled studies investigating treatments for liver disease in dogs and cats. The management begins first by removing the primary etiology if it can be identified. The four major goals for therapy should be; 1) dietary manipulation, 2) specific therapy aimed at reducing inflammation, fibrosis or copper, 3) general hepatic support and 4) treating complications secondary to the liver disease.

NUTRITIONAL MANAGEMENT
Metabolic derangements that occur with liver disease can lead to malnutrition, impaired hepatic regeneration, and the clinical consequences of hepatic insufficiency. The liver also has the unique ability to regenerate following injury, and this process occurs through appropriate nutrition. A misconception exists about protein content when feeding animals with liver disease. It was previously thought that patients with liver disease should be placed on a protein-restricted diet to reduce the liver’s workload and the production of detrimental nitrogenous waste products. This is not well substantiated. Many now believe restricting protein could be detrimental, especially if the patients have a negative nitrogen balance. The goals of dietary protein intake are to adjust the quantities and types of nutrients to meet the patient’s nutrient requirements and to avoid the production of excess nitrogen by-products causing hepatic encephalopathy. It is always important to provide the patient with a high-quality, highly digestible protein source. Most quality commercial or prescription liver diets or gastrointestinal diets are suitable for this purpose. As a general recommendation, dietary protein should represent 15% to 20% of the digestible kilocalories (kcal) of the diet.

SPECIFIC THERAPY
Antiinflammatory Therapy. Decreasing inflammation is a specific therapy for chronic hepatitis in the dog to reduce the amount hepatocellular death and fibrosis. One retrospective study found dogs with chronic hepatitis to have a prolonged survival when treated with corticosteroids. It appears that therapy using steroids versus no steroids offered benefit in at least some cases (around 25%) and the responders may in fact represent dogs having immune mediated liver disease. A dose of 1 to 2 mg/kg/day using either prednisone or prednisolone is suggested, and with clinical improvement the dose is then gradually tapered. The only accurate way to evaluate a response to therapy is to re-biopsy the patient because it is impossible determine improvement based on liver enzymes (ALT and ALP) due to the concurrent steroid hepatopathy. Alternatively one can stop steroid administration and recheck the enzymes in 1 to 2 months to determine a response. Azathioprine in combination with corticosteroids are shown to be effective in human chronic hepatitis. This therapy may also be beneficial in dogs. A dose of 2.2 mg/kg/day is the suggested starting dose and after several weeks given every two days. We have recently been using cyclosporine alone in many cases of chronic hepatitis finding a good clinical response. Our experience using 5 mg/kg bid or q 24 hrs has been very encouraging in managing chronic hepatitis in dogs. Using cyclosporine alone one can follow the liver enzymes and direct therapy based on response often without the need for a liver biopsy.

Copper Reduction. When significant abnormal hepatic copper accumulation of greater than 1000 µcg/g dry weight liver (normal < 400 µg/g liver) is present low copper diets and copper chelators and/or zinc therapy should be instituted. Copper chelators, penicillamine or trientine, are the standard therapies used to remove excess hepatic copper in cases of breed-associated copper hepatotoxicity. Chelators bind with copper either in the blood or the tissues and then the copper is removed through the kidneys. Penicillamine is the most frequent copper chelator recommended for use in dogs. The dose for either drug is 15 mg/kg bid given on an empty stomach. Side effects include anorexia and vomiting. Studies evaluating therapy in Bedlington terriers, Doberman pinchers and Labrador retrievers having copper associated hepatitis have shown a reduction of hepatic copper and improvement in the inflammatory damage following therapy.

Zinc therapy has anti-fibrotic and hepatoprotective properties as well as preventing hepatic copper re-accumulation in patients that have been first decoppered with chelators. Oral zinc therapy works by causing an induction of the intestinal copper-binding protein metallothionein. Dietary copper binds to the
metallothionein in the enterocyte with a high affinity that prevents transfer from the intestine into the blood. When the intestinal cell dies and is sloughed into the GI tract the metallothionein bound copper is excreted through the stool. An initial induction dose of approximately 15 mg/kg body weight (or 50 to 100 mg BID) of elemental zinc given twice a day is suggested. Following one to 3 months of an induction period the dose is reduced in approximately half and continued as a maintenance dose.

**Choleretic Drugs.** Decreasing cholestasis has been shown to be of benefit in humans and animals having cholestatic hepatobiliary disease. As serum bile concentrations increase these predominately cytotoxic bile acids cause cell membrane permeability changes and fibrogenesis. Ursodeoxycholic acid (Ursodiol) is a choleretic agent that has hepatoprotective properties. It changes the bile acid pool from the more toxic hydrophobic bile acids to less toxic hydrophilic bile acids. Ursodeoxycholic acid has been shown to increase bile acid dependent flow, reduce hepatocellular inflammatory changes, fibrosis and also has some immunomodulating effects. The hepatoprotective characteristics of ursodeoxycholic make it a good adjunct therapy. The dose for ursodeoxycholic acid is 15 mg/kg daily.

**Antifibrotic Drugs.** The key in reducing or preventing fibrosis is to stop inflammation that is the signal for fibrosis production. Corticosteroids, zinc and penicillamine all have some anti-fibrotic effects but are used predominately for their other properties. Colchicine has been used to treat people with chronic hepatitis and other types of liver fibrosis. This drug is reported to interfere with the deposition of hepatic collagen and to stimulate collagenase activity breaking down deposited fibrous tissue in the liver. It also is shown to have some anti-inflammatory properties. There is still the lack of convincing data in humans and dogs with liver disease that colchicine is beneficial. There are but 2 case reports of colchicine in dogs both having questionable results. A dose of 0.03 mg/kg/day has been suggested. Recently losartan, an angiotensin II receptor antagonist drug used for treating high blood pressure has shown to have some effects in preventing hepatic fibrosis by preventing up-regulation of the collagen producing stellate cells in the liver. Clinical response to losartan has been noted in human studies of hepatitis but there are no reports of use in dogs.11

**Antibiotics.** Antibiotics are indicated for primary hepatic infections such as bacterial hepatitis, cholangitis or leptospirosis. Selection of appropriate antibiotics is based on culture and sensitivity. There is however also evidence that bacterial colonization may take place secondarily in a diseased liver. Kupffer cells, a fixed hepatic macrophage, functions in filtering the portal blood of bacteria and other toxic products. Kupffer cell dysfunction occurs in liver disease and could account for secondary bacterial infections. It therefore may be prudent to consider antibiotic therapy for at least a trial of several weeks in patients having significant hepatic disease (i.e. chronic hepatitis). Amoxicillin, amoxicillin-clavulanic acid, cephalosporin, or metronidazole (7.5-10 mg/kg bid) is suggested. Metronidazole may have some immunosuppressive properties as well as its anaerobic antibacterial mechanisms.

**Liver Support**

There is considerable interest in the management of certain types of liver disease using antioxidants and various nutraceuticals to provide an environment for optimal liver function. There are however few published reports showing the benefit of their clinical use. The following section will discuss some of the current information on liver support therapy.

**Vitamin E** (dl-alpha-tocopherol) functions as a cellular membrane-bound antioxidant. Evidence now shows that oxidative damage occurs during liver disease from free radical generation. Cellular damage in liver disease is probably multifactorial but free radicals formation may play an important role in initiating or perpetuating hepatic damage. Vitamin E is a major membrane-bound intracellular antioxidant that protects membrane phospholipids from peroxidative damage when free radicals are formed. Evidence shows that dietary supplementation with vitamin E reduces oxidant injury to hepatic tissue. Bedlington terriers with copper-associated hepatopathy have oxidant damage in their mitochondria and reduced mitochondrial vitamin E concentrations. Vitamin E has also shown a protective effect in the liver from copper-related oxidant damage and bile acids. Vitamin E is inexpensive and safe when supplemented at a dose of 10 IU/kg/day. dl-alpha-tocopherol, the natural form of vitamin E, is recommended because of greater uptake, dispersion, and bioactivity compared with the more common synthetic dl-alpha-tocopherol formulation.

**S-adenosylmethionine** (SAMe) is a naturally occurring molecule synthesized in all living cells and is essential in intermediary metabolism. It has both hepatoprotective and antioxidant properties. SAMe is produced from the amino acid methionine and subsequently initiates one of three metabolic pathways involving membrane function, glutathione production or in cell regeneration and renewal. There are a number of studies supporting the
benefit of SAMe as an adjunct therapy in liver disease.14

**Milk thistle** extract silymarin or the active sterioisomer silibin has been used for more than 2,000 years as a medical remedy for liver disease. Mounting evidence suggests that milk thistle has medicinal benefits for various types of liver disease as well as a protective effect against hepatotoxins. A recent poll of liver patients at one U.S. hepatology clinic found that 31% were also using alternative agents for their disease and that milk thistle was the most commonly used nontraditional therapy.15 Specifically, silibin inhibits lipid peroxidation of hepatocyte and microsomal membranes and protects against gene damage by suppressing hydrogen peroxide, superoxide anions, and lipoxygenase. Silymarin also increases hepatic glutathione content and appears to retard hepatic collagen formation. Evidence also suggests that silymarin has hepatoprotective effects through the inhibition of Kupffer cell function by inhibiting leukotriene B4 production and hepatotoxin binding to receptor sites on hepatocyte membranes, which provide additional stability against xenobiotic injury.15 The purity and potency of commercial milk thistle products vary by manufacturer, and the therapeutic dosage for dogs and cats is unknown. Suggested doses for silymarin range from 50 to 250 mg/day. Milk thistle is reported to have an extremely low toxicity and has been used extensively in clinical patients with little concern for side effects. When the active isomer silybin is complexed with phosphatidylcholine, oral uptake and bioavailability is greater.16

**SUMMARY**

It is critical to recognize the complexity of the medical and nutritional needs of patients with liver disease. The dietary and treatment plan should be individualized for each patient. Careful monitoring and adjustment of the treatment as indicated based on the clinical response, laboratory changes or histology findings.

**REFERENCES**