COMMON CANINE LIVER DISEASES AND HOW I MANAGE THEM
David C. Twedt, DVM, DACVIM
Colorado State University
Fort Collins, CO

The most important and most common primary liver disease in the dog is chronic hepatitis. Chronic hepatitis is not a single disease but rather the inflammatory changes can be due to many of etiologies. The therapy should be directed first at the cause of the inflammation. In most all cases a liver biopsy is required to confirm the diagnosis before effective therapy can be begun.

Chronic hepatitis is an etiologic diverse and morphologically variable condition associated by mixed inflammatory cell infiltrates. It is characterized by hepatocellular apoptosis or necrosis, a variable mononuclear or mixed inflammatory infiltrate, regeneration and fibrosis. The proportion and distribution of these components vary widely. Plasma cells, lymphocytes and macrophages predominate with a lesser number of neutrophils. Because we see non-specific mild portal inflammation as a common non-specific reactive change frequently secondary to intra-abdominal disorders like IBD I need the pathologist to tell me the severity of inflammation and chronicity of the disease. The presence of fibrosis in the hepatic biopsy usually denotes to me more serious consequences. As damage progresses cirrhosis can result with diffuse fibrosis, alteration in hepatic lobular architecture with the formation of regenerative nodules and abnormal vascular anastomoses. Cirrhosis, a sequel of some chronic hepatitis cases, is often associated with portal hypertension, ascites and multiple portosystemic collateral veins. Some may show manifestations of liver failure, e.g., hyperbilirubinemia, coagulopathies, edema due to hypoalbuminemia, ascites and hepatoencephalopathy. This type of chronic inflammation is uncommon in the cat as their inflammatory disease is directed at bile ducts causing cholangitis.

ETIOLOGY

The etiology of this chronic inflammatory condition is generally never determined. To date the best-described etiology of chronic hepatitis is the copper associated hepatitis of the Bedlington terrier (see below copper associated hepatitis). This breed and others are thought to have an inherited copper associated chronic hepatitis. Copper accumulates in hepatocyte from abnormal metabolism to a level that then becomes toxic causing hepatocyte death. There are also likely breeds that have difficulty in handling copper if taken in orally in excess amounts.

Infectious chronic hepatitis in man is most often associated with viral etiologies. The search for a viral etiology of hepatitis in the dog however has been unrewarding. The canine adenovirus type 1 given experimentally to partially immune dogs did caused hepatitis and fibrosis. Others identified a suspected acidophil cell hepatitis virus in dogs that were vaccinated with liver homogenates from dogs dying from chronic hepatitis. The vaccinated dogs developed fibrosis and inflammation in their livers. Subsequent further research or publications into viral etiologies are lacking. Chronic hepatitis has also been associated with leptospirosis with the authors describing "atypical leptospires" in a colony of dogs having hepatitis. However we have examined over 50 dogs livers having hepatitis using PCR for Leptospirosis and did not identify a single positive case. Other infectious agents suggested as a possible etiology include Helicobacter sp, Bartonella, and Leishmaniasis.
Chronic liver injury has also been reported in dogs with aflatoxicosis as well as various drug-induced hepatitis. Some dogs treated with anticonvulsant drugs primidone, phenytoin and phenobarbital will develop chronic hepatitis. We have also observed some dogs treated with NSAIDs to also have hepatitis which asks the question of NSAIDs being related to hepatitis. In man alpha-1-antitrypsin (AAT- also referred to as alpha one protease inhibitor) deficiency is known to cause chronic hepatitis and cirrhosis. Investigation by researchers in Sweden using immunostaining for AAT in hepatocytes found some dogs with chronic hepatitis to be positive for ATT in the hepatocytes but the dogs differ from man in that serum AAT remained in the normal range while humans have low concentrations. It is not known if the AAT accumulation is the cause or the result hepatocyte damage. The breed most often associated with AAT accumulation is thought to be the cocker spaniel.

Finally immune associated hepatitis may also occur in the dog. Autoimmune liver disease in humans is an important cause of chronic hepatitis and is associated with diagnostic circulating autoantibodies. It appears that autoantibodies (ANA, antimitochondrial antibodies [AMA], smooth muscle antibodies [SMA], liver membrane autoantibodies [LMA]) are markers of autoimmune hepatitis in humans. A number of studies have been performed in dogs looking for liver associated antibodies and cell-mediated responses to support autoimmune disease as an etiology. Findings so far suggest autoimmune liver disease exists but studies fail to conclusively prove its existence. The pathogenesis proposed is that an insulting agent damages the hepatocytes thus releasing liver antigens that initiate a secondary immune response perpetuating chronic hepatitis. Nonetheless, immune-mediated mechanisms are thought to occur in some cases of chronic hepatitis and this is further supported by the fact that some dogs respond favorably to immunosuppressive therapy.

There are also a number of breeds that have an increased incidence of chronic hepatitis and are thought to be inherited. Some of these breeds have copper associated chronic hepatitis and are discussed below. Other breeds not yet associated with copper include the standard poodle, Cocker spaniel, Springer spaniel and Scottish terrier. The pathogenesis of the hepatitis is yet unknown. Cocker spaniels both English and American tend to be more commonly males and ATT accumulation may play a role in their disease. More recently in Europe English Springer Spaniels have been reported to have a breed associated hepatitis. Standard poodles are more commonly females and tend to have prolonged survival with immunosuppressive therapy. We are currently studying the standard poodle at Colorado State University.

**COPPER ASSOCIATED HEPATITIS**

Copper is an essential trace element required as a redox co-factor for many different enzymes. Copper enters the body through the diet and approximately 30% is absorbed by the upper small intestine with unabsorbed copper passing through the feces. Although the exact details of intestinal Cu absorption is not completely delineated it is clear that copper is taken up in the intestine through an active transport mechanism shared with zinc. Intestinal copper is quickly bound to the cytosolic protein metallothionein. Intestinal Cu is subsequently transported to the liver bound to albumin and transcuprein. The liver is responsible for the uptake and storage of copper, as well as the regulation of excretion of this metal into the bile. Hepatic copper is either complexed to ceruloplasmin, an acute phase reactant protein, and transported to peripheral tissues for utilization, or Cu is redistributed among the various metallothioneins in the liver. Metallothioneins are cysteine-rich, cytosolic proteins capable of binding several metal ions, including copper.
Metallothioneins function are to protect the hepatocyte against the toxicity from free Cu catalyzing oxygen free radicals and also to mediate Cu transport into the bile for removal from the body. The normal hepatic copper concentrations in dogs are maintained at approximately 200-400 µg/g dry weight liver.

Recently there has been characterization of the genetic regulation of copper excretion by the liver. A specific gene in humans ATP7b is a copper-transporting ATPase expressed within the secretory pathway of hepatocytes and plays a critical role in copper excretion and ceruloplasmin production. A second gene encoding COMMD1 (MURR1) is expressed in the liver suggesting that this protein also plays a role in hepatic copper transport and biliary copper excretion. Wilson disease in humans is an inherited mutation in the gene encoding human ATP7b and results in hepatic copper overload and decreased Cu-ceruloplasmin production. Bedlington Terriers also have an inherited disorder of copper homeostasis. These animals have impaired copper excretion into bile but no abnormality in copper incorporation into ceruloplasmin suggesting that the defect occurs distal to the function of ATP7b in intracellular copper transport. This disorder in the Bedlington terrier has recently been shown to result from deletion of a gene on chromosome 10 encoding a small cytosolic protein termed COMMD1 (MURR1). Clinically affected dogs have a progressive hepatic Cu accumulation occurring with age ranging from 1,000 to 12,000 µg/g dry weight of liver. The extent of hepatic damage tends to parallel the increasing hepatic Cu concentrations. The morphological changes extend from focal necrosis to chronic hepatitis that may ultimately lead to cirrhosis. In some cases, acute hepatic necrosis and Cu associated hemolytic anemia and acute liver failure may occur.

The pathogenesis of hepatic damage is thought to occur when the metallothionein sequestration ability for Cu becomes exceeded and free copper is released. The mitochondria appear to be the first organelle to become damaged resulting in mitochondrial electron leak initiating lipid membrane peroxidation and eventual cellular death.

The excess hepatic copper is sequestered in lysosomes bound to metallothionein proteins. Routine stained histological sections may show abundant golden-brown refractile hepatocellular lysosomal granules that contain the sequestered Cu. These granules are nonspecific for copper, but may indicate abnormal copper accumulation. A more reliable semi-quantitative estimation involves histochemical staining for hepatic Cu. Reliable tissue bound copper stains include rhodanine and rubeanic acid. The copper tends to accumulate in a centrilobular location. A grading system of 1-5 estimating the quantity of Cu granules correlates roughly with quantitative determination of hepatic Cu when the values approach >750 µg/g dry liver weight.

Definitive determination of the amount of hepatic Cu requires a quantitative analysis of tissue Cu. Hepatic copper content is measured using atomic absorption spectroscopy and can be determined on needle biopsy samples, although larger samples provide better accuracy. Samples for analysis should be placed in a Cu free container (such as a serum blood tube) for analysis. Normal canine hepatic Cu concentrations are less than 400 µg/g dry weight liver. The concentration at which abnormal hepatic Cu contributes to hepatic damage is unknown. It is possible to take adequate size biopsy sample embedded in paraffin for histology and de-paraffinize the sample to obtain a quantitation of copper.

**Other Breeds.** Since the discovery of the Bedlington terrier copper hepatopathy other breeds have been found to have abnormal concentrations of hepatic copper and hepatitis. The mechanism of copper sequestration in other breeds is unknown but thought
to be different than the Bedlington terrier. Doberman hepatitis is a form of chronic hepatitis. The incidence is unknown but may occur in as high as 4 to 6% of dogs. The high percent suggests a genetic predisposition. Females seem to be over-represented. The disease begins in young dogs (1-3 years) with increased ALT concentrations and having sub-clinical hepatitis. Clinical evidence of liver disease usually begins around 4-7 years of age with chronic hepatitis and cirrhosis. Copper appears to be associated with the disease and recent studies suggest that copper is often increased prior to development of clinical hepatitis. Cu$^{64}$ isotope studies demonstrate affected dogs have an impaired biliary excretion of copper. Copper chelator therapy in sub-clinical dogs normalized copper concentrations with improvement in the grade of histological damage. In affected dogs the copper concentrations generally range from 1000-2000 µg/g DW liver. At this point no specific gene has been identified for this disease to determine the mode of genetic transmission. The above evidence suggests a primary defect in copper metabolism in the breed but awaits further confirmation. An autoimmune mechanism is also suggested but this too requires further investigation.

A retrospective study summarizes 10 Dalmatians suspected of having hepatic copper toxicosis. Two of the dogs were related and all presented for gastrointestinal clinical signs, had elevated liver enzymes and necroinflammatory hepatic changes associated with copper-laden hepatocytes most prominent in a centrilobular location. The mean hepatic copper concentration was 3,197µg/d dry weight liver. In 5 of these 9 dogs, hepatic copper concentrations exceeded 2,000 µg/d DW liver with several dogs having copper levels as high as those observed in Bedlington Terriers. These findings support the hypothesis that a primary metabolic defect in hepatic copper metabolism occurs in the Dalmatian breed. The mechanism and genetic basis of this condition is under further study.

The West Highland White terrier has been associated with liver disease and hepatic copper accumulation. The clinical findings appear to be different than other breeds associated with copper accumulation. Dogs reported showed evidence of hepatitis or cirrhosis and had increased hepatic copper ranging from 1000-3000 µg/g dry weight liver. Twenty-four dogs described ranged from 3-7 years of age. Some dogs in this report had high copper concentrations but no evidence of liver disease while others did. While the Bedlington Terrier tends to accumulate Cu with age it was not apparent in this group of dogs. Affected dogs that were bred produced offspring with elevated copper concentrations supporting a genetic defect. Several dogs were treated with zinc therapy and showed reduction in hepatic copper concentrations.

Chronic hepatitis is reported to be common in this breed and there is evidence that copper accumulation is associated with some, but not all the cases. We find females are more commonly affected and the diagnosis is generally made between 2 to 7 years of age. Hepatic copper concentrations generally range between 750 to 2000 µg/g dry weight liver. The histological location of the Cu being centrilobular suggests that Cu elevation is probably not secondary to cholestasis. It appears that copper chelation is beneficial in some dogs with hepatitis and copper accumulation.

The Skye Terrier, Anatolian Shepherd, and possibly the Keeshond as well as other breeds have also been reported with liver disease and increased copper accumulation. The exact mechanism or extensive description in specific breeds is lacking.

**Secondary Copper Accumulation**

Copper may also concentrate in the liver secondary to cholestatic liver disease or from increased oral copper intake. Recently the Labrador retriever is reported to have
copper associated hepatitis and when chelated and then placed on a low copper diet the 
liver copper concentrations remain low. The author believes most all commercial dog 
foods meeting AFFCO feeding standards contain too much copper and some dogs or 
possibly breeds can not handle those copper concentrations and subsequently develop 
hepatitis. This newer and emerging problem appears to have become accentuated when 
the dog food companies changed the type of copper they supplement in the diet to a form 
that is much more biologically available. The prescription liver diets contain low copper 
concentrations.

CLINICAL FINDINGS
The incidence of chronic hepatitis makes up approximately one fourth of the cases 
having liver biopsies at Colorado State University (based on a review of 150 consecutive 
liver biopsies). Chronic hepatitis is more common in female dogs. The average of 
presentation ranges from 4 to 10 years. It is interesting to note that in both our series and 
in studies by others it is uncommon to observe chronic hepatitis/cirrhosis in dogs older 
than 10 years of age. As a general rule old dogs (> 11 years of age) don't generally 
present with chronic hepatitis/cirrhosis or if they do they are at or near end stage disease. 
The clinical signs parallel the extent of hepatic damage. Early in the disease there 
are usually no or minimal clinical signs. Only after the disease progresses do the clinical 
signs specific for liver disease becomes evident. Frequent early signs are gastrointestinal 
associated with vomiting, diarrhea and poor appetite or anorexia. Ascites, jaundice and 
hepatic encephalopathy may then occur as the disease progresses. With development of 
these late signs the long-term prognosis is generally poor.

The laboratory findings include consistently elevated ALT and ALP. The magnitude 
of rise need not be marked however. One report found 75% of the cases with abnormal 
bilirubin elevation (mean elevation of 2.6 mg/dl). Serum proteins are variable. As the 
lesions become more severe albumin levels decline. Serum bile acids are abnormal in 
most cases having significant chronic hepatitis and measurement of bile acids appear to 
be a good screening test for the patient with unexplained elevations in ALT and ALP. In 
our study all dogs evaluated with chronic hepatitis had abnormal bile acid concentrations. 
In a second study only 8/26 dogs with chronic hepatitis had normal fasting bile acids. 
However, postprandial samples were not determined in these cases. Determining 
postprandial bile acids has been shown to increase the sensitivity of this test.

A presumptive diagnosis is made based on the clinical features and persistent 
increases of ALP and ALT values. A definitive diagnosis requires a hepatic biopsy 
showing characteristic morphological patterns. Needle aspirates are not helpful in making 
the diagnosis of chronic hepatitis because it is important to see the architecture of the liver 
and location and extent of the inflammation. One must work with the pathologist when 
making the diagnosis of chronic hepatitis and to be certain that characteristic abnormalities 
found in chronic hepatitis are present.

PROGNOSIS
There is little information of the prognosis with and without therapy. The prognosis 
in dogs with advanced chronic hepatitis and cirrhosis is guarded. In a study by Strombeck 
found mean survivals ranging from 6 to 16 months with therapy. This study also identified 
that dogs with hypoalbuminemia, hypoglycemia and coagulopathies have very guarded 
prognostic factors and many died within 1 week of diagnosis. A second study of 79 dogs 
found that dogs with cirrhosis had a survival of less than one month and dogs with chronic 
hepatitis had a mean survival in the range of about 20 to 30 months. Most of these dogs 
were not advanced in their disease and had concurrent corticosteroid treatment.
TREATMENT

The management for chronic hepatitis involves removing the primary etiology. Short of treating the primary etiology all other therapies suggested are unproven in the management of chronic hepatitis in dogs. We are still waiting for good clinical studies proving efficacy in treatments. Such studies are hindered even from the start owing to the multiple etiologies of hepatitis and the inconsistent histological descriptions. To date we have only limited case studies and clinical impressions of efficacy in the management of chronic hepatitis.

It is first important to rule out both infectious disease (Leptospirosis) and copper associated liver disease. The copper associated conditions are treated with chelators, low copper diets and possibly zinc to block copper absorption from the GI tract. Without an etiology and significant inflammation and necrosis I use anti-inflammatory therapy. The traditional therapy is to use corticosteroids. The problems with steroids are the side effects, the steroid hepatopathy and the inability to know if the dog is responding short of a liver biopsy. We have more recently been using cyclosporine with good success and can easily document improvement of liver enzymes. Initial dose has been 5 mg/kg bid. Other therapy may include ursodeoxycholic acid and liver support medications. Please refer to lectures on liver therapy for further information and detail.

The discussion below is directed at therapy for chronic hepatitis but much of what is presented can also be extrapolated to other types of liver disease in both the dog and cat. I have four general goals in therapy: 1) remove the etiology, 2) provide an adequate diet, 3) give specific therapy and 4) providing general liver support. First step in the therapy for chronic hepatitis and other liver diseases involves removing the primary etiology if it can be identified. Short of treating the primary etiology all other therapies suggested are unproven in the management of liver disease in dogs. Much of the therapy is directed at providing adequate liver support. This often involves the use of multiple therapies.

Diet. Adjusting diet therapy should be considered in all cases however only general guidelines should be given. First, palatability is important to assure adequate energy requirements are met. Next, there is a misconception about diet and liver disease that liver patients should be placed on a protein restricted diet. Protein restriction should only be instituted in the patient that has clinical evidence of protein intolerance (i.e. hepatic encephalopathy). The goal of dietary therapy is to adjust the quantities and types of nutrients to provide nutrient requirements but to avoid the production of excess nitrogen by-products associated with liver disease. As a general recommendation the dietary protein should represent 17 to 22% of digestible Kcal.

High carbohydrate and moderate fat content is important to supply caloric needs. Mineral supplementation containing high concentrations of both copper and iron should be avoided.

There is also evidence that fiber may have several beneficial actions in patients having liver disease. First, dietary fiber effectively binds bile acids in the intestinal tract and promotes their removal. Secondly soluble fiber appears to have some benefit in managing hepatic encephalopathy by generation of fermentation products (short chain fatty acids). These act by impairing the intestinal uptake of the surrogate marker of HE, ammonia. Soluble dietary fiber has a similar effect as lactulose and would provide a logical long-term nutritional approach in the management of some animals with hepatic encephalopathy. Psyllium, as a source of soluble fiber given at a dose of 1-3 tsp/day can be used as a dietary supplement.
Diets low in copper are recommended for the dogs that have copper associated liver disease based on biopsy. The restriction of dietary copper may do little to lower hepatic copper concentrations in diseased dogs having large amounts of hepatic copper. Diet will lessen further absorption of the metal. It is difficult to limit dietary copper because most commercial dog foods contain supplemental copper that meet, or more frequently exceed the minimal dietary requirements. Most formulated “liver diets” have lower copper concentrations and are often supplemented with additional zinc. Homemade diets can also be prepared that do not to contain excess copper. These diets should exclude liver, shellfish, organ meats and cereals that are all high in copper content. Vitamins or mineral supplements should not contain copper or iron.

**Antiinflammatory Therapy.** Decreasing inflammation as a specific therapy for chronic hepatitis in the dog or cholangitis in the cat is unproven although the author’s clinical impression suggests anti-inflammatory therapy is beneficial in some cases. The treatment of chronic hepatitis is quite controversial and there are as yet no good controlled studies in animals to support corticosteroids use in every case. Anti-inflammatory therapy is indicated in suspected immune mediated chronic hepatitis.

In a study by Strombeck found that some dogs with chronic hepatitis tend to have a prolonged survival when treated with corticosteroids. This retrospective study is one with a wide diversity of diseases and concurrent therapies. But none-the-less, it appears that corticosteroids offer benefit in at least some cases (possibly around 25%). A suggested dose of 1 to 2 mg/kg/day using either prednisone or prednisolone should be instituted. When clinical improvement is suspected or after several weeks the dose is then gradually tapered eventually to a dose of 0.5 mg/kg/day or every other day. The only accurate way to evaluate a response to any therapy is to re-biopsy the patient in 6 months to 1 year because the patient will develop a concurrent steroid hepatopathy with increased liver enzymes making laboratory determination of any improvement impossible. Alternatively one could stop steroids and recheck enzymes in 1 to 2 months. There is also evidence of improvement of immune hepatitis in humans when treated with budesonide. These patients had also less clinical signs because of the more "topical" effect on the liver subsequent hepatic clearance.

Because of the side effects of corticosteroids and the failure to successfully monitor liver enzymes while receiving steroids other immune suppressive therapy may be more rational approach. Azathioprine is an effective immunosuppressant drug that has shown to increase survival in man when treated for chronic hepatitis in conjunction with corticosteroids. This therapy may also be beneficial in dogs (don’t use in cats) by increasing the immunosuppressive response and enabling a reduction of both steroid dose and their side effects. A dose of 2.2 mg/kg/day is the suggested starting dose and after several weeks given every two days. The level of glucocorticoids can frequently be reduced when using azathioprine. It is important to note that azathioprine has been infrequently been associated with a drug induced hepatic necrosis or acute pancreatitis. We have more recently been using cyclosporine A in some cases with a good clinical response. Our experience using 5 mg/kg bid or q 24 hrs (without steroids) has been very encouraging in dogs that are thought to have immune mediated chronic hepatitis. The veterinary formulation Atopica™ is a microemulsified preparation with the identical properties to Neoral™ (also sold as modified generic cyclosporine) that ensures more consistent bioavailability and better than the other human product Sandimmune™.

Generally after 48 hours or longer I will get a blood level at the trough (right before the next pill). The ideal range of blood levels are within 400-600 ng/ml. Many dogs will develop
gingival hyperplasia at the higher concentrations of cyclosporine. Azithromycin 10 mg/kg/day for 4-6 weeks will decrease the gingival hyperplasia. The most common side effect I observe is nausea and vomiting. Often signs resolve after several days but if not try giving the cyclosporine with food or freeze the capsules and give frozen. With evidence of clinical response at 5 mg/kg bid I will often decrease to once a day therapy. Using cyclosporine alone one can follow the liver enzymes making the need for a liver biopsy less frequently required.

**Copper Reduction.** If the liver biopsy of a dog with chronic hepatitis indicates significant abnormal hepatic copper accumulation, copper chelators or zinc therapy should be considered. Hepatic copper levels of greater than 750 µcg/g dry weight liver requires therapy to reduce copper concentrations (zinc or chelator). Animals having greater than 2,000 µcg/g dry weight copper content should all have chelator therapy for at least some period of time.

Zinc therapy has a number of potential benefits in dogs with chronic hepatitis. Zinc has anti-fibrotic and hepatoprotective properties. Zinc given as the acetate, sulfate, gluconate or other salt has also been proven effective in preventing hepatic copper re-accumulation in Wilson’s disease humans that have been decoppered with chelators. When patients were given oral zinc hepatic copper concentrations did not increase. Oral zinc therapy works by causing an induction of the intestinal copper-binding protein metallothionein. Dietary copper binds to the metallothionein with a high affinity that prevents transfer from the intestine into the blood. When the intestinal cell dies and is sloughed, the metallothionein bound copper becomes excreted through the stool. An initial induction dose of 5-10 mg/kg body weight divided BID of elemental zinc. Following one to 3 months of induction the dose can be reduced in approximately half. The goal is to get serum zinc concentrations greater than 200µg/dl but less than 500. The zinc must be administered on an empty stomach and has the frequent side effect of vomiting. Replacement zinc therapy is administered at a dose of 2-3 mg/kg/day and is given for its antioxidant effects and replacement value in animals having zinc depletion in their liver.

Chelator treatment has a proven beneficial effect in dogs with abnormal hepatic copper concentrations. Chelators bind with copper either in the blood or the tissues and then promote copper removal through the kidneys. Penicillamine (Cuprimine™ -250 mg capsules) is the most frequent copper chelator recommended for use in dogs. The dose is 10-15 mg/kg bid given on an empty stomach. Side effects include anorexia and vomiting. Therapy using penicillamine is a slow and prolonged process taking months to years to cause a substantial reduction in hepatic copper concentrations however recent studies suggest penicillamine also has a protective effect in the liver beyond chelation therapy. It is believed penicillamine induces a hepatic copper binding protein, metallothionein, thus binding and sequestering copper in a nontoxic form in the liver. A second copper chelator is trientine (Syprine™) that has been produced to use in patients intolerant to penicillamine. This drug is also given at the same dose, has less gastrointestinal adverse side effects but is expensive and sometimes difficult to obtain. The length of chelation therapy is variable but based on past experience. As a recommendation if copper is less than 1000ppm I generally treat for 3-4 months, if 1000-2000ppm I treat for 6 months and if greater than 2000ppm 6-9 months. I monitor ALT levels and if they become normal I often discontinue therapy, maintain on a low copper diet and will consider zinc supplementation as well. Of course the ideal recommendation is

**Antifibrotic Drugs.** Corticosteroids, zinc and penicillamine all have anti-fibrotic effects. Colchicine is a drug that has been used in treating persons with chronic hepatitis
and other types of liver fibrosis. This drug interferes with the deposition of hepatic collagen and also stimulates collagenase activity to breakdown deposited fibrous tissue in the liver. It also is shown to have anti-inflammatory properties. There is still the lack of convincing data in humans and dogs with liver disease that colchicine is beneficial. A critical appraisal of colchicine in human liver disease having chronic hepatitis now questions its effectiveness and failed to show benefit in a placebo controlled metaanalysis. There are only 3 case reports of colchicine in dogs having questionable results. A dose of 0.03 mg/kg/day has been suggested. The drug given as a generic is inexpensive with only minimal gastrointestinal side effects sometimes noted at high doses. Recently it was found that angiotensin II inhibitor Losartan (Zestril™, 0.25-0.5 mg/kg/Day) has effects in reducing or preventing fibrosis in humans by effecting function of stellate (fibrosis producing) cells.

**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 are predominately cytotoxic bile acids) they can cause cell membrane permeability changes and fibrogenesis. Ursodeoxycholic acid (Ursodiol - Actigall™, 300 mg caps) is a choleretic agent developed to dissolve gallstones but later found to have positive effects in patients with chronic hepatitis. This drug is a synthetic hydrophilic bile acid that essentially changes the bile acid pool from the more toxic hydrophobic bile acids to less toxic hydrophylic bile acids. Ursodeoxycholic acid has been shown to increase bile acid dependent flow, reduce hepatocellular inflammatory changes, fibrosis and possibly some immunomodulating effects. The hepatoprotective characteristics makes one believe ursodeoxycholic acts as an antioxidant. The dose for ursodeoxycholic acid is 15 mg/kg daily. No toxicity has been observed in dogs and cats at this dose. There has been a concern raised by some that it should not be used if there is any possibility of a bile duct obstruction for fear of biliary rupture. Although with obstruction surgery is indicated ursodeoxycholic acid is not a prokinetic and will not cause a rupture. In fact in experimental bile duct obstructions there was less secondary "toxic" changes in the liver in rats given ursodiol than placebo.

**Antibiotics.** Antibiotics are indicated for primary hepatic infections. There however may be evidence that bacterial colonization may take place in a diseased liver. Kupffer cell dysfunction could be a reason for secondary bacterial infections. It may be prudent for antibiotic therapy or trial for several weeks in patients having significant hepatic disease (i.e. chronic hepatitis). Amoxicillin, cephalosporin, or metronidazole are suggested. Metronidazole may have some immunosuppressive properties as well as antibacterial mechanisms. For liver disease I would use 7.5-10 mg/kg bid a much lower dose used for other bacterial infections because of hepatic metabolism of the drug.

**Antioxidants.** There has been recent interest in the management of certain types of liver disease using antioxidants. Antioxidants in general provide liver support to promote optimal hepatic function. Considerable evidence shows that free radicals are generated in chronic hepatitis 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 non-enzymatic antioxidants which function to prevent oxidative damage by "scavenging" or "quenching" free radicals that are formed. It is reported that close to half the dogs and cats with liver disease have reduced glutathione concentrations in the blood and liver supporting that oxidative damage is present. 

*Vitamin E,* d-alpha tocopherol, functions a major membrane bound intracellular antioxidant, protecting membrane phosepholipids from peroxidative damage when free
radicals are formed. Vitamin E is shown to protect against the effects of copper, bile acids and other hepatotoxins. In a small study of dogs having chronic hepatitis we found all dogs had evidence of oxidative damage. In a three-month placebo controlled study treating only with vitamin E there was evidence improvement in the oxidant status of the treated dogs however we did not identify changes in clinical, laboratory or histology during this short treatment period. A suggested vitamin E dose is 50 to 400 IU a day. The d-alpha tocopheryl formulation is much more potent than the most common commercial form (dL-alpha tocopheryl). Since bile acids are required for fat-soluble vitamin E absorption and may be reduced in cholestatic liver disease, a water-soluble formulation is suggested. For a water soluble form I use Twin labs Liqui-E. The vitamin E is derived from TPGS (d-alpha tocopheryl polyethylene glycol 1000 succinate) and has a rapid absorption. Because of the potential benefits of vitamin E, the lack of side effects and since the drug is inexpensive I place most all my liver patients on E therapy.

*S-Adenosylmethionine (SAMe) [Denosyl™, Nutramax Laboratories]* is a naturally occurring molecule found in all living organisms and is involved in a number of metabolic pathways that appear to be beneficial to the liver as well as other tissues. SAMe is involved in three major biochemical pathways. It is involved in cell replication and protein synthesis, has a modulating influence on inflammation and plays a role as a precursor of the antioxidant glutathione in the hepatocyte. Research has demonstrated that the exogenous administration of SAMe to have potential beneficial effects for a number of types of liver damage. In one study giving acetaminophen to cats at a sub-lethal dose we observed protective effects of SAMe when measuring markers of hepatic oxidative damage and RBC fragility. Studies investigating naturally occurring liver disease in animals are required to determine the benefit of SAMe administration in liver disease. I will routinely prescribe SAMe (Denosyl™) in patients having acute liver toxicity and in many cases having chronic liver disease or other liver disorders. A recommended dose range is 20 mg/kg/day. It should be given on an empty stomach and the tablets not broken. There are numerous commercial sources of SAMe each having variable concentration or purity of the compound. Foil wrapped tablets produced by a company that provides reliable purity and potency is recommended.

*Milk thistle* has been used for centuries as a natural remedy for diseases of the liver and biliary tract. Silymarin the active extract consists of bioflavonolignans that have been reported to work as antioxidants, scavenging free radicals and inhibiting lipid peroxidation. Several recent human clinical trials have assessed the efficacy of silymarin in the treatment of liver disease. The data is somewhat difficult to interpret because of the limited number of patients, poor study design, variable etiologies, lack of standardization of silymarin preparations with different dosing protocols. There is however compelling evidence to suggest silymarin has a therapeutic effect in acute viral hepatitis, alcoholic liver disease, patients with cirrhosis, and in toxin or drug-induced hepatitis. Unfortunately, the purity of commercial products, and therapeutic dosage is unknown. Clinical trials are limited in small animals and reported success is only anecdotal. Dosage of milk thistle ranges from 50 to 250 mg bid. Milk thistle is 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. To date there is only one published clinical study evaluating the efficacy of silymarin in the treatment of liver disease in dogs. In this placebo controlled experimental study dogs were poisoned with the *Amanita phalloides* mushroom. Researchers showed silymarin to have a significant effect on liver enzymes, the extent of histological liver damage and survival outcome. Based on this canine study and several clinical reports in
humans poisoned with *Amanita* and treated with silymarin having a favorable outcome many physicians in Europe now accept silymarin as part of the standard protocol for mushroom poisoning.

Silibin appears to be a principle active isomer of the silymarin extract. Although silibin is a potent compound GI absorption is poor. Bioavailability is increased by complexing with phosphatidylcholine (siliphos™). We have evaluated a commercially available complex (Siliphos™, Indea labs) in a preliminary pharmacokinetic study normal cats and found no clinical outward signs of toxicity giving a dose up to 5 mg/kg and have found improvement in oxidant status in the blood of normal cats and cats having liver disease. Marin™ (Nutramax Labs) contains silybin-phosphatidylcholine complex and for cats it contains vitamin E and for dogs it has zinc and vitamin E. A new compound Denamarin™ is available containing SAMe and silybin and is available in a chewable formulation. It appears that the combination of both compounds have good a absorption. The Denamarin product appears to be very stable and not oxidized like the other SAMe products. I personally have no experience with other SAMe or milk thistle products.

**General Support Therapy.** The remainder of the therapy for chronic hepatitis involves treatment of secondary complications. These occur as the disease becomes advanced. Hepatic encephalopathy, GI ulceration and ascites are common clinical occurrences in advanced hepatitis or cirrhosis.

The first step in the management of hepatic encephalopathy includes the use of enemas to clean the colon of both bacteria and protein substrates for ammonia production. Slightly acidic enemas will lower the pH of the colon thus ionizing ammonia and reducing its absorption. Povidone iodine (betadine) can safely be given by enema as a 10% solution (weak tea color) that will both acidify the colon and have an antiseptic action reducing bacterial numbers. Nonabsorbable intestinal antibiotics are used to alter bowel flora and suppress urease-producing organisms important in formation of factors causing hepatic encephalopathy. Antibiotic suggestions include oral ampicillin, aminoglycosides (neomycin, kanamycin or gentamicin) or metronidazole. Metronidazole given at 7-10 mg/kg BID has been useful in controlling anaerobic urease producing bacteria. One should be careful as metronidazole is partially metabolized in the liver and a lower dose range is suggested.

A nondigestible disaccharide lactulose (Cephulac™ or Chronulac™) given orally acidifies the colon converting ammonia to ammonium that is poorly absorbable thus trapping ammonia in the colon. The fermentation products of lactulose will also act as an osmotic laxative reducing colonic bacteria and protein substrates. A dose of 1-10 ml orally TID is generally effective. Lactulose is not absorbed systemically and thus considered safe. The dose should be adjusted to cause 3 or 4 soft stools a day. If diarrhea develops the dose should be reduced. Lactulose can also be given by enema in treating the severe case of hepatic encephalopathy.

*Gastrointestinal ulceration* not only causes gastrointestinal signs such as vomiting and anorexia but blood loss into the intestinal tract promotes hepatic encephalopathy as blood is an excellent protein source for ammonia production. Gastric ulcers should be treated with the H2 blocker such as ranitidine (2-5 mg/kg BID/TID) and oral sucralfate (Carafate™ 1 mg tab/25 kg TID given 1 hour before ranitidine). Cimetidine is to be avoided in liver disease because it is metabolized by the liver and is an enzyme suppressor altering hepatic metabolism of other drugs.

*Ascites* occurs in chronic hepatitis when portal hypertension, hypoalbuminemia and renal sodium and water retention work in concert to cause fluid exudation. Diuretics are
the major means of managing ascites in small animals. Too rapid removal of ascitic fluid can cause metabolic complications and can precipitate hepatic encephalopathy. The goal of diuretic therapy should be a gentle water diuresis. The two diuretics most commonly used are furosemide and spironolactone. The consensus of most is that spironolactone is more effective with liver disease. The loop diuretic furosemide (Lasix) can however cause marked dehydration and loss of potassium. With liver disease, sodium reabsorption at the distal tubule may be great and counter the effects of furosemide due to elevated aldosterone concentrations (at reported to occur in some dogs with liver disease). Spironolactone (Aldactone 1-2 mg/kg/day) is consequently the first line diuretic. Furosemide can be added latter if necessary. If an animal has tense ascites, paracentesis should be performed to decrease the intra-abdominal pressure, relieve compression of the venous circulation, and to increase patient comfort.