# DIAGNOSIS AND MANAGEMENT OF CHRONIC HEPATITIS IN DOGS

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Chronic hepatitis represents one of the most common hepatopathies in dogs and can be caused by a variety of underlying causes, including infectious, drugs and toxins (most commonly copper), metabolic, and immune-mediated causes. Many cases of chronic hepatitis in dogs are idiopathic; however, copper-associated hepatitis (CAH) and immune chronic hepatitis (IHC) represent two of the most common causes. The key histologic features of chronic hepatitis include the presence of lymphocytic, plasmacytic, or histiocytic inflammation (portal, multifocal, zonal, or panlobular) or some combination of these along with hepatocyte cell death and variable severity of fibrosis and regeneration.

**COPPER-ASSOCIATED HEPATITIS (CAH):**

The abnormal accumulation of copper within hepatic lysosomes has been associated with hepatocellular damage in several breeds, most notably the Bedlington Terrier, West Highland White Terrier, Skye Terrier, and Doberman Pinscher. The excess copper promotes reactive oxygen species that causes oxidative damage to the DNA, cell membrane, and organelles (especially mitochondria) that can result in cell death. The copper accumulation typically occurs in the **centrilobular** hepatocytes. Studies of copper associated hepatotoxicity in the Bedlington Terrier have proven the disease to be an inherited autosomal recessive trait resulting in the aberrant expression of the copper binding protein metallothionein. Copper accumulates in an age-related process within hepatocyte lysosomes, often reaching levels of 10,000 parts per million (ppm). Normal hepatic copper levels are < 400 ppm. Most commercial dog foods contain an excess of copper, so deficiencies are uncommon. Absorption of copper is enhanced by amino acids and high dietary protein, and reduced by zinc, ascorbate, and fiber.

There is compelling evidence that the prevalence of chronic hepatitis has increased over the past 25 years, and this increase has occurred in both predisposed (e.g., Labrador retriever, Doberman pinscher) and non-predisposed breeds. In addition, the increase in prevalence of chronic hepatitis appears to coincide with a change in AAFCO (Association of American Feed Control Officials) regulations of copper in dog food. In 1997, AAFCO recommended replacing copper oxide with a more bioavailable form, copper sulfate. An ACVIM Consensus Panel believes that the National Research Council (NRC) and AAFCO dietary guidelines, along with a change to more bio-available Cu chelate premixes in commercial dog food, are linked with an increased prevalence of hepatic Cu accumulation in dogs. The Cu concentrations in dog foods often exceed NRC recommendations by >2-4 times. The table below provides compelling evidence of the excessive amounts of copper in commercial dog foods:

| | NRC[a] minimum | AAFCO[b] minimum | Average dog food | Hepatic diets[c] |
|---|---|---|---|---|
| Copper concentration (mg/kg DM/d) | 6[d] | 7.3[e] | ~15-25 | ~4.9 |

**Diagnosis:**
The diagnosis of CAH requires liver biopsies of multiple liver lobes because the copper accumulation can be variable from lobe to lobe. The most important histologic feature is evidence of chronic hepatitis associated with hepatic copper accumulation in the centrilobular areas (Zone 3) of the liver. Histochemical copper staining (e.g., rhodanine) will accentuate the copper granules that accumulate in the centrilobular hepatocytes. Other features include apoptosis, copper granulomas, and centrilobular hepatic injury (lymphohistiocytic infiltrates), which can progress to parenchymal collapse, remodeling, fibrosis, and ultimately, cirrhosis. Hepatic copper quantitation via atomic absorption spectroscopy or digital image analysis of rhodanine stained sections can reveal tissue concentrations > 1000 ppm (µg/g) dry weight liver.

Management of Copper-associated Hepatopathy:

**Dietary Copper Restriction**
The management of copper hepatopathy is directed at reducing copper stores in the body. Dietary restriction has most potential for managing young dogs affected with an inherited hepatic metabolism defect (Bedlington Terriers and West Highland White Terriers) or dogs with chronic hepatitis and concurrent copper hepatotoxicity (Doberman Pinscher, Labrador Retriever). A minimum dietary copper requirement has been established as 2.9 ppm available copper (DM basis) for growth. A minimum dietary copper allowance of 7.3 ppm for growth and adult maintenance has been established for typical dog foods. Commercially available copper restricted diets are manufactured by Hills (Hills l/d), Royal Canin (Royal Canin Hepatic), and Purina (Purina ProPlan HP Hepatic (Europe only). One can also prepare a homemade balanced diet that is restricted in copper. Homemade diets should exclude liver, shellfish, and organ meats that are all high in copper content. Vitamin E may help protect against copper-induced lipid peroxidation and should be supplemented at levels of 500 mg/day.

**Zinc**
Zinc salts are effective in preventing copper accumulation in the livers of humans with Wilson's disease. Zinc ions induce the synthesis of metallothionein, which binds copper tightly, rendering it unabsorbable from the intestine and possibly detoxifying it in the liver. The copper is lost in the feces when the intestinal cell is sloughed. Zinc acetate or zinc gluconate is recommended, since the sulfate form is associated with gastric irritation and vomiting in humans. The zinc should be given separate from meals unless nausea and vomiting occur. In those cases, zinc can be given with a small amount of food. Reduced hepatic copper concentrations, decreased hepatic enzyme activity and improved hepatic histologic features were noted after 2 years of zinc therapy in a small number of affected dogs. Zinc is administered

1 hour before meals at 5 to 10 mg/kg twice daily. Excess zinc will interfere with the absorption and utilization of iron and copper and can cause a chronic copper deficiency manifested by a microcytic-hypochromic anemia and neutropenia.

**Copper Chelating Agents**

*Copper chelating agents should not be administered concurrently with zinc to avoid zinc chelation*. Copper chelators bind copper either in the blood or tissues and promote its urinary excretion and are typically recommended when hepatic copper concentrations exceed 1000 ppm, or when concentrations exceed 600 ppm if histologic lesions are seen in association with hepatocyte copper accumulation or if fluctuating serum alanine transaminase activities are seen with no plausible alternative cause. *D-penicillamine*, the most frequent copper chelator recommended for use in dogs, should be given at a dose of 10 to 15 mg/kg twice a day on an empty stomach. Vomiting is the most common side-effect in dogs and can be alleviated by reducing the dose and giving it more frequently. D- penicillamine therapy has also been associated with a pyridoxine deficiency in human patients. Although this problem has not been recognized to occur in dogs, the diet should be high in this B-vitamin, or supplemental amounts should be given daily.

*Trientine* (2,2,2-tetramine) is another chelating agent with comparable effects to D-penicillamine, but with fewer adverse effects. Trientine is usually dosed orally at 10-15 mg/kg body weight twice daily. Modification of 2,2,2-tetramine to 2,3,2-tetramine increases potency as a copper chelating agent. Use of 2,3,2-tetramine in affected Bedlington terriers reduced liver copper concentrations significantly after 200 days of treatment at a dose of 15 mg/kg body weight. This drug is not commercially available but can be obtained from chemical supply companies in the form of N, N'-bis(2-aminoethyl)-1,3-propanediamine and prepared as a salt for oral administration. Periodic liver biopsies are suggested with the use of copper chelators to monitor hepatic copper levels and response to therapy. Anti-inflammatory agents such as prednisone may be of benefit in the management of chronic hepatitis in Bedlington Terriers, West Highland White Terriers, and Labradors.

**Antioxidants:**

**Vitamin E, Milk thistle, and S-Adenosyl-methionine (sAMe)**

In vitro studies have documented the benefits of various antioxidants in maintaining hepatocellular membrane integrity and hepatocellular function. S-adenosylmethionine increases hepatic glutathione levels in dogs and cats. Glutathione is a potent antioxidant that protects hepatocytes from toxins and death. *Denamarin* is a commercially available antioxidant manufactured by Nutramax that contains sAMe and silybin. Silybin is the active part of an extract from milk thistle, known as silymarin.

**Ursodeoxycholic acid:**

This is a choleretic drug (enhances bile flow) that has additional benefits, including anti-inflammatory and antifibrotic effects. Additional information about this drug is provided below under the “Chronic Hepatitis” section.

**IMMUNE CHRONIC HEPATITIS (ICH)**

A presumptive clinical diagnosis of immune-mediated CH in the dog requires elimination of other etiologies and a favorable response to immunosuppressive treatment. Currently, the lack of commercially available tests to detect liver-specific antibody-antigen interactions or cell immunosensitization in dogs with ICH limits the definitive determination of an immune-mediated etiology.

The mechanisms involved in the development and progression of chronic hepatobiliary disease in the dog are poorly understood. As a result, selection of appropriate clinical management is often symptomatic or based on histologic changes observed on liver biopsy. Definitive treatment of chronic hepatitis should ideally be based on results of liver biopsy. Histologic features indicative of chronic hepatitis includes the presence of mononuclear inflammatory cells and/or the presence of fibrosis. Despite the apparent benefit of corticosteroids or cyclosporine for the management of chronic hepatitis, immunologic criteria to support an immune mediated basis for this disease in dogs are lacking.

**Corticosteroid therapy**
Corticosteroids probably reduce inflammation and perhaps increase appetite and a feeling of well-being. They may also minimize fibrosis during the healing phase following an acute insult. However, they may increase severity and mortality in viral hepatitis and bacterial cholangitis and may worsen signs of hepatic encephalopathy by promoting protein catabolism.

**Cyclosporine** is currently the preferred immunosuppressive agent and has the added benefit of not altering ALT and ALP activity. The current recommended starting dose is 5mg/kg q12h; however, there is preliminary evidence that lower doses may be equally effective with fewer adverse effects.

Anti-fibrotic agents used to treat human chronic liver disease include **colchicine** and zinc gluconate. Some specialists have reported apparent beneficial effects following administration of colchicine to dogs with chronic hepatitis/cirrhosis.

**Acid Suppressants** (PPIs or H2-receptor antagonists): There is currently little evidence to support the routine use of acid suppressants in animals with liver disease, unless there is increased risk of GI ulceration (for example, patients with PSS) or patients with evidence of portal hypertension.

**Diuretics (lasix and spirinolactone)** - Ascites, if present, can be treated by diuretic therapy if the fluid accumulation is impairing the patient's respiration.

**Ursodeoxycholic acid (Actigall)** is a choleretic drug (enhances bile flow) at a dose of 10 - 15 mg/kg q24hr and is effective in reducing the rate of progression of chronic hepatitis in people. It works by replacing endogenous hepatotoxic bile acids in the enterohepatic circulation. The drug is also touted to have anti-inflammatory and antifibrotic effects. It is expensive, but

the only likely side-effect is diarrhea if large doses are given. It is a relatively safe drug and may be very effective. Reports of its use in dogs and cats are very favorable.

**Antioxidant:**

**Vitamin E, Milk thistle, and S-Adenosyl-methionine (sAMe) –** Antioxidants are recommended for the management of dogs with chronic hepatitis, even if copper hepatotoxicity is not documented (see section on copper hepatotoxicity for more detail).