

invisible invisible/shutterstock.com

Abstract

Copper-associated hepatopathy (CAH) is an increasingly recognized syndrome in dogs, characterized by pathologic copper accumulation within hepatocytes, resulting in oxidative stress, cell death, and inflammation. Copper overload can lead to chronic hepatitis, end-stage liver disease, and even death. Risk factors are genetic or environmental. Clinical signs are initially nonspecific; however, as the disease progresses, they become more overt and are usually associated with liver failure. Hepatic enzyme (alanine aminotransferase and alkaline phosphatase) activities are nonspecific for detection of CAH; definitive diagnosis is obtained by histologic assessment of the hepatic copper distribution and copper quantification. Treatment is focused mainly on creating a negative copper balance by restricting copper intake through dietary modifications and increasing copper excretion by administering copper-chelating agents. Outcomes are best when treatment is started early in the course of the disease.



INTERNAL MEDICINE

Copper Hepatopathy in Dogs

Adrian Tinoco-Najera, MVZ, EMCPG, MMVZ

Jonathan A. Lidbury, BVMS, MRCVS, PhD, DACVIM, DECVIM-CA

Texas A&M University School of Veterinary Medicine & Biomedical Sciences, College Station, Texas

Copper is a trace element that serves as a cofactor for enzymes involved in many metabolic processes throughout the body. Although essential for life, free copper can be toxic because it can potentially lead to formation of reactive oxygen species via the Fenton reaction; therefore, its absorption, distribution, and excretion are tightly regulated.¹ The major organ for copper metabolism is the liver, which is responsible for copper storage, redistribution of copper in the protein-bound form to other tissues and organs, and elimination of excess copper via biliary excretion.² After copper enters the hepatocyte, it is immediately bound to specialized copper scavenger proteins (called copper chaperones) that assure safe handling and specific delivery of copper to its destination molecules. Copper chaperone antioxidant 1 (ATOX1) is responsible for shuttling copper to the trans-Golgi network,

where the adenosine triphosphatase (ATPase) copper-transporting α and β (ATP7A and ATP7B) reside. Under certain conditions under which copper accumulates, ATP7B will interact with the copper metabolism *Murr1* domain containing 1 (COMMD1) protein, facilitating excess copper excretion into the bile.³

ETIOPATHOGENESIS

Abnormal hepatic copper accumulation can result from primary genetic defects in hepatic copper metabolism, increased dietary copper intake, or both. When hepatic copper transport/binding capacities are overwhelmed, free copper within the hepatocytes will lead to oxidative stress, resulting in hepatocellular cell death and inflammation that commonly begins in the centrilobular regions of the liver (zone 3) but can

Take-Home Points

- Copper-associated hepatopathy (CAH) is an increasingly recognized syndrome in dogs.
- Although certain dog breeds are predisposed to CAH, any breed can be affected.
- Clinical signs usually appear relatively late in the disease and are often initially nonspecific.
- The only way to definitively diagnose CAH is by histologic analysis of a liver biopsy sample and quantitative assessment of hepatic copper concentrations.
- The most effective treatment strategies are dietary copper restriction and chelation therapy with D-penicillamine.



also affect midzonal and portal regions as damage progresses. This pattern is a useful finding when interpreting liver histology for suspected copper-associated hepatopathy (CAH). In cases of severe chronic injury, parenchymal remodeling and fibrosis associated with formation of regenerative nodules can be found.^{4,5} Generally, normal hepatic copper concentrations are 120 to 400 mg/kg dry weight (DW), and potentially harmful concentrations are considered those >600 mg/kg DW.⁵

PREDISPOSING FACTORS

Predisposition to development of CAH can be affected by breed, sex (for some breeds), and diet. Historically, Bedlington terriers, Labrador retrievers, and Doberman pinschers have been considered to be predisposed, but other breeds with a suspected predisposition include West Highland white terriers, Dalmatians, Skye terriers, Anatolian shepherds, Welsh corgis, and Clumber spaniels.⁶ CAH can also develop in dogs of other breeds or of mixed breed.⁵ Usually, dogs of both sexes are equally predisposed, with the exception of Labrador retrievers and Doberman pinschers, for which a predisposition to females has been reported. In Doberman pinschers, immune-mediated chronic hepatitis is also suspected to occur, which may explain the sex predisposition for CAH as autoimmune conditions are generally more common in females.⁷⁻⁹

Bedlington Terriers

Bedlington terriers are predisposed to CAH. The main cause has been identified as a mutation responsible for creating a large deletion of the second exon in the *COMMD1* gene. This autosomal recessive disorder will cause altered copper excretion, inducing hepatic copper concentrations of $\geq 10\,000$ $\mu\text{g/g}$ DW, which results in copper toxicosis and chronic hepatitis.¹⁰ Genetic screening for this *COMMD1* deletion, along with selective breeding of Bedlington terriers, has reduced prevalence of CAH. Recently, mutations of a candidate gene (*ABCA12* [adenosine triphosphate-binding cassette subfamily A member 12]), independent of the *COMMD1* deletion, have been implicated in the development of CAH in Bedlington terriers.¹¹

Labrador Retrievers and Doberman Pinschers

A genome-wide association study performed on 235 Labrador retrievers revealed mutations in the

chromosome region coding for the *ATP7B* gene significantly associated with increased hepatic copper levels.¹² The study also reported a mutation in the gene coding for *ATP7A*, which partly protects against copper accumulation; these mutations accounted for only 12% of heritability. A similar study revealed that homozygous mutant offspring in which both parents had at least 1 copy of the *ATP7B* mutation had elevated hepatic copper concentrations with normal alanine aminotransferase (ALT) activity.¹³ Mutations of the *ATP7B* gene have also been reported in a population of Doberman pinschers from the Netherlands and the United States with increased hepatic copper concentrations.¹⁴

Dietary Factors

Over the past 3 decades, prevalence of CAH among dogs has risen considerably; several studies have associated this phenomenon with changes in the quantity and bioavailability of copper in commercial dog foods.^{5,15} First, since the mid- to late-1990s, use of copper chelates (acetate, sulfate, and carbonate), which have relatively high bioavailability, in premix formulations has substantially increased the amount of copper absorbed.¹⁶ Second, many commercial foods contain large variations in copper concentrations and often exceed (by 2 to 4 times) the minimum allowances for dietary copper intake (0.067 mg/kg/d) recommended by the Association of American Food Control Officials and the National Research Council.¹⁷ Third, no upper limit for dietary copper is in place in the United States. Last, a proposed contributing factor is the current trend for owners to feed “alternative diets” (evolutionary or vegetarian diets) that use animal-based ingredients or vegetables with high copper content.¹⁵

CLINICAL PRESENTATION

Dogs with CAH can appear healthy for years before clinical signs develop. The duration of the subclinical period depends mainly on the rate of hepatic copper accumulation, genetic predisposition, and dietary copper intake and can vary between breeds and individuals.¹⁸ The liver has a substantial reserve capacity; therefore, clinical signs usually appear when the disease is more advanced. Because of the long subclinical period, many dogs exhibit no clinical signs, and the first sign of disease may be increased liver enzymes on routine blood work. Initial clinical signs are nonspecific and commonly include anorexia,



lethargy, nausea, vomiting, and weight loss. Signs of more advanced disease are compatible with hepatic failure (e.g., ascites, hepatic encephalopathy, polyuria/polydipsia, icterus).¹⁸ In rare cases, an acute hemolytic crisis can occur when massive amounts of hepatic copper are released into the bloodstream; however, this phenomenon has only been reported in Bedlington terriers.¹⁹

DIAGNOSTIC EVALUATION

Clinicopathologic Findings

Routine serum biochemical analyses can reveal increased activity of liver enzymes (e.g., ALT or alkaline phosphatase [ALP]), but these alterations are not specific for CAH.⁵ Furthermore, measurement of hepatic enzyme activity has not been shown to be sensitive for detecting subclinical stages of CAH.²⁰ In later stages of the disease, when a considerable amount of hepatic parenchyma has been lost, activity of other enzymes (e.g., γ -glutamyl transpeptidase [GGT]) can be slightly elevated, and markers of liver function may be abnormal (e.g., hypoalbuminemia, hypoglycemia, hypocholesterolemia, decreased urea). In patients with end-stage liver disease, liver enzyme activity may decrease and even fall within normal reference intervals.²¹ Hepatic function tests (e.g., total serum bile acids, ammonia, bilirubin, coagulation testing) are useful parameters for detecting liver disease, but, unfortunately, none are specific or sensitive for CAH.⁶ In dogs with CAH, copper can also accumulate within the proximal renal tubular epithelium and lead to tubular injury and dysfunction, triggering a Fanconi-

like syndrome exhibited by low urinary specific gravity, proteinuria, and normoglycemic glucosuria.²²

Imaging

Abdominal radiographs can be used to assess overall hepatic size, shape, and opacity as well as the presence of ascites, but they lack sensitivity to subtle changes or usefulness for diagnosing a given specific parenchymal disease. The initial imaging tool for hepatic parenchyma evaluation is commonly ultrasonography; however, although it can be sensitive for identifying certain liver and biliary abnormalities, ultrasonography lacks specificity for the diagnosis of CAH. Hepatic ultrasonography images can appear normal in dogs with CAH; common changes associated with chronic inflammation and remodeling that can be observed in dogs with CAH include heterogeneous echotexture, irregular margins, and microhepatica (**FIGURE 1**). Ultrasonography enables identification of alternative diagnoses (e.g., congenital portosystemic shunts) or complicating factors (e.g., portal hypertension, acquired portosystemic collateral blood vessels, ascites, thrombi) and can also be useful for needle biopsy sampling.²³

Cytology

Cytologic detection of copper-laden hepatocytes can be achieved via fine needle aspiration and copper staining (with rhodanine or rubeanic acid). Although this noninvasive approach can be used to detect copper in individual hepatocytes, it has many limitations, such as the inability to evaluate copper distribution, degree of hepatocellular injury, and exact amount of copper. The negative predictive value of this method is, therefore, uncertain.²⁴

Liver Biopsy

The only way to diagnose CAH is by histologic examination of a liver biopsy sample. Hepatic samples can be obtained via laparotomy, laparoscopy (**FIGURE 2**), or percutaneous needle biopsy guided by ultrasonography.⁶ Before biopsy acquisition, bleeding risk assessment is recommended and can be performed by evaluating prothrombin time, activated partial thromboplastin time, plasma fibrinogen concentration, platelet count, viscoelastic coagulation monitor, and, possibly, buccal mucosal bleeding time. Despite the risk for serious postbiopsy hemorrhage, prevalence of this complication seems relatively low.²⁵ Generally, greater

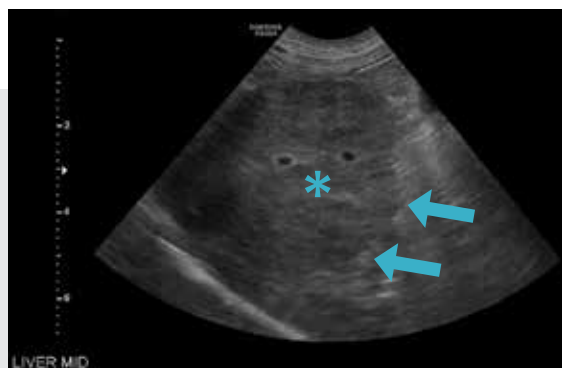


FIGURE 1. Hepatic ultrasonography image of a dog with copper-associated hepatopathy. The liver appears heterogeneous (**asterisk**) and hyperechoic, with irregular margins (**arrows**), suggestive of regenerative changes and concurrent fibrous tissue.



diagnostic quality is achieved with larger biopsy specimens obtained during laparoscopy or laparotomy than with those collected by percutaneous needle biopsy. Biopsy specimens should be obtained from the central and peripheral regions of the hepatic lobes; severely cirrhotic or fibrotic regions should be avoided. Current recommendations for adequate histopathologic examination suggest obtaining a minimum of 5 laparoscopic or surgical biopsy specimens from at least 2 liver lobes.^{5,26}

Histopathologic Analysis

When the primary driving force of liver damage is copper toxicity, the centrilobular regions of the hepatic lobule are initially affected (**FIGURE 3**). Copper overload will trigger a mixed inflammatory infiltrate (lymphohistiocytic infiltrate) that can accumulate at the interface of the perivascular adventitia and regional hepatocytes. As the disease progresses, damage can extend into midzonal and portal regions, eventually affecting hepatocytes in all zones. Affected hepatocytes may display cytosolic copper aggregates. Advanced stages of disease may lead to centrilobular parenchymal collapse and obstruction of sinusoidal flow through hepatic venules with parenchymal remodeling and fibrosis. End-stage disease involves severe cirrhosis, massive necrosis, and lobular collapse, which will distort the architecture of the liver lobule, making it difficult to differentiate between zones.^{5,15,27} Given that copper visualization is not optimal with routine

staining (hematoxylin and eosin), use of high-affinity copper-binding stains (e.g., rhodanine, rubeanic acid) is required for an accurate diagnosis.^{5,6}

Histologic Grading of Copper

Semiquantitative grading schemes to characterize hepatic copper content and distribution correlate well with other quantitative measures. These scoring systems focus mainly on grading the zonal location and the number of hepatocytes and macrophages containing copper granules on a scale from 0 to 5 (**FIGURE 4**). Scores greater than 2 are considered abnormal.^{18,27}

Quantitative Assessment of Hepatic Copper

Atomic absorption spectroscopy remains the gold standard for hepatic copper quantification and requires approximately 50 mg of wet tissue (or 10 mg DW) for an accurate determination. Normal hepatic copper concentrations for dogs are <400 mg/kg DW; pathologic concentrations are >600 mg/kg DW.²⁸ Digital copper quantification of rhodanine-stained biopsy sections is accurate, and it reduces the effects of varied copper content among biopsy specimens due to several sections being evaluated simultaneously.²⁹

TREATMENT

Because copper has the potential to create oxidative damage, abnormal hepatic copper concentrations (>600 mg/kg DW) in susceptible patients should be managed. The main goal for treatment focuses on creating a negative copper balance by restricting copper intake and/or increasing copper excretion by using

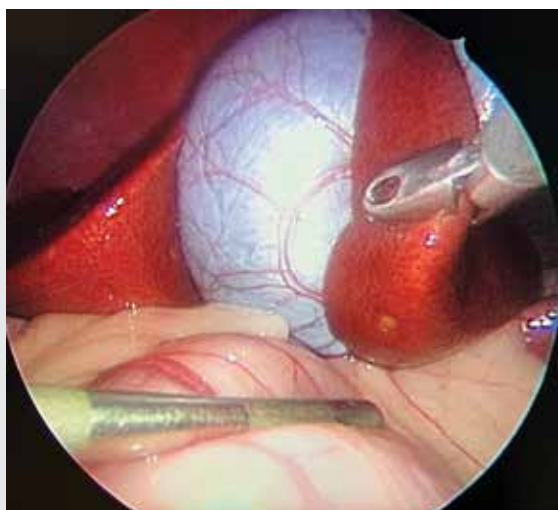


FIGURE 2. Acquisition of hepatic biopsy sample via laparoscopy from a dog with copper-associated hepatopathy. The liver is of normal size and has smooth margins. A probe is being used to displace the omentum.

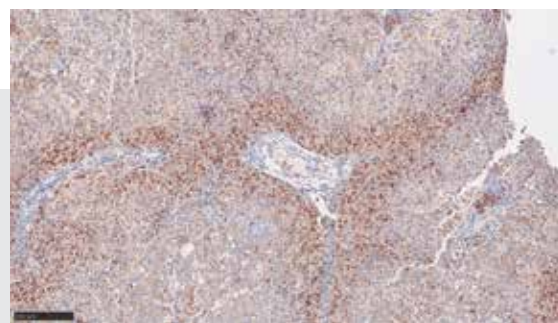


FIGURE 3. Microscopic image of a dog liver. Centrilobular copper distribution (brown granules) of a liver biopsy sample stained with rhodanine from a dog with copper-associated hepatopathy.

Figure 2: courtesy Dr. Jesús Méndez-Flores, Hospital Veterinario de Alta Especialidad Delta, México. Figures 3 and 4 (A through F): courtesy Dr. João Pedro Cavasin, Gastrointestinal Laboratory at Texas A&M University.



copper-chelating agents.⁵ To achieve the best outcome, treatment should ideally be started early in the course of the disease (subclinical phase if possible). Dogs with no clinical signs and only moderately increased hepatic copper levels (i.e., 400 to 600 mg/kg DW) may benefit from dietary copper restriction alone. Dogs with clinical signs and a higher copper concentration (i.e., >600 mg/kg DW) typically receive a copper-chelating agent in addition to a copper-restricted diet.^{6,30}

Dietary Copper Restriction

Patients with CAH may require lifelong dietary

management.^{5,30} Copper-restricted diets usually provide less than 0.12 mg/100 kcal of copper, which can reduce hepatic copper accumulation.³⁰ Given that most commercially available copper-restricted diets are also protein restricted, additional supplementation with low-copper protein is sometimes recommended (e.g., egg white, cottage cheese, white meat chicken/turkey). Homemade low-copper diets can also be formulated; however, a board-certified veterinary nutritionist should make these formulations. Copper intake from water should also be considered. The copper concentration in water should be checked in houses that are supplied with well water or that have copper

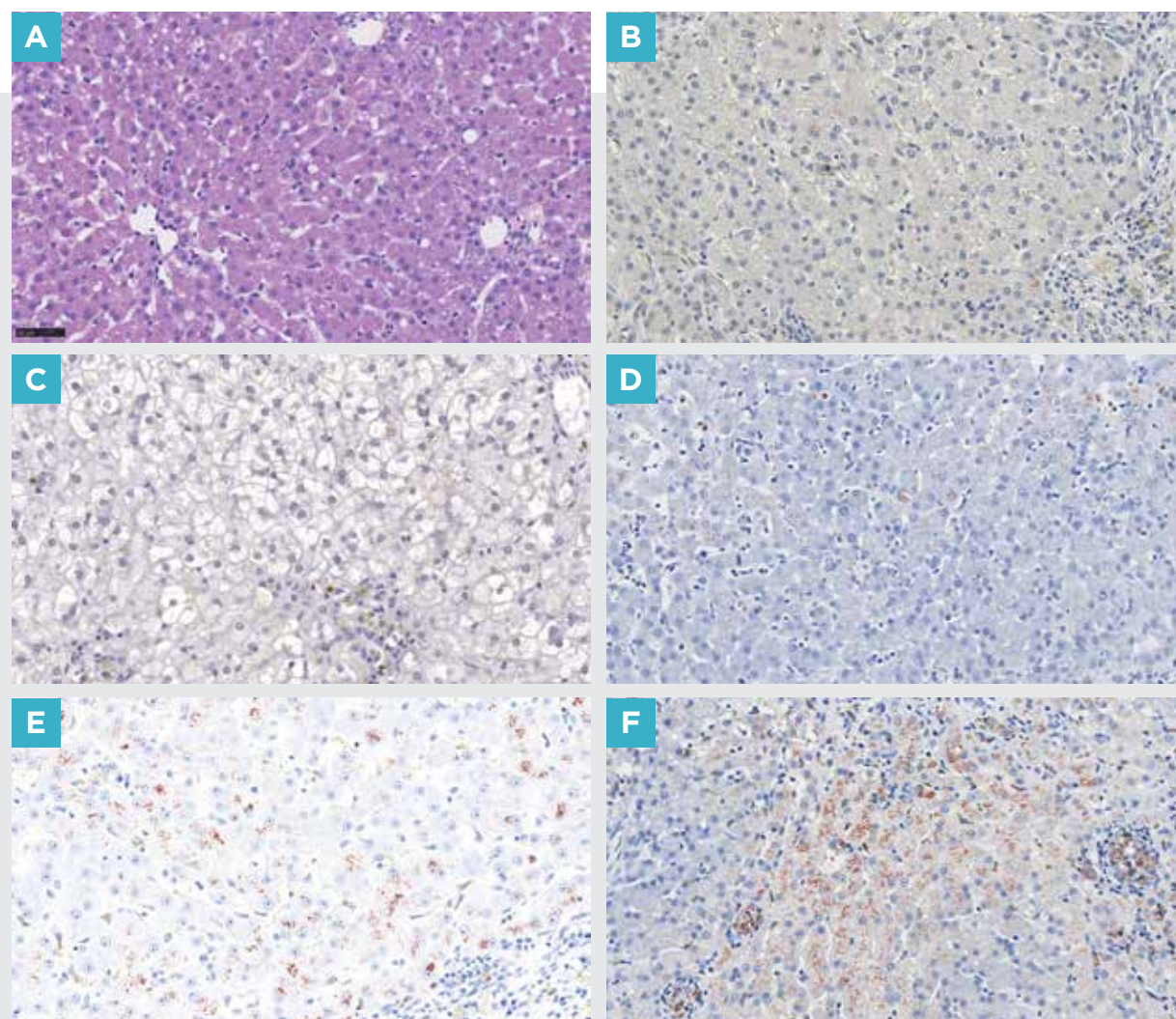


FIGURE 4. Histochemical hepatic copper scoring system. **(A)** Score 0: normal liver tissue with no copper; stained with hematoxylin and eosin. **(B)** Score 1: isolated hepatocytes containing copper granules; stained with rhodanine. **(C)** Score 2: small groups of hepatocytes containing moderate amounts of copper granules; stained with rhodanine. **(D)** Score 3: larger groups of hepatocytes containing moderate amounts of copper granules; stained with rhodanine. **(E)** Score 4: large areas of hepatocytes, reticulohistiocytic cells, and macrophages containing copper granules; stained with rhodanine. **(F)** Score 5: diffuse panlobular presence of hepatocytes, reticulohistiocytic cells, and macrophages containing copper granules; stained with rhodanine.



pipings. If the copper concentration is more than 100 µg/L, it should not be used.

Copper Chelation Therapy

The most commonly used copper chelator in dogs with CAH is D-penicillamine,⁷ which is a byproduct of penicillin that possesses a high affinity for copper and facilitates its urinary excretion. The recommended dosage for dogs is 10 to 15 mg/kg PO q12h (without food for best absorption). Common side effects are usually gastrointestinal (anorexia and vomiting) but are usually manageable by temporarily decreasing the dose, giving antiemetics, or administering a short course of low-dose corticosteroids to stimulate appetite.³¹ Treatment effectiveness is best determined by repeated quantification of hepatic copper concentrations, but repeated biopsies are often not performed. For most cases, a successful surrogate marker is serum ALT activity. Treatment typically lasts 6 to 9 months and is usually extended for 1 additional month after ALT activities normalize. Some dogs may need repeated or even lifelong treatment.⁵

Other chelating agents include bis-choline tetrathiomolybdate, trientine, and 2,3,2-tetramine; however, studies in dogs are limited and some of these agents are not commercially available. Trientine can be administered at 5 to 7.5 mg/kg, but brand name forms are prohibitively expensive and this drug may cause acute kidney injury.³²

Zinc

Zinc interferes with copper uptake by enterocytes via

metallothionein induction. However, effectiveness is questionable, and at least 3 months of administration is needed to obtain a clinical response; thus, zinc is not a viable option for dogs with acute or severe cases. Zinc supplementation should not be combined with D-penicillamine therapy as it may decrease effectiveness of both agents. The recommended dosage of elemental zinc is 5 to 10 mg/kg PO q12h without food, and plasma concentrations should be monitored to avoid toxic levels (>1000 µg/dL) that may result in hemolysis. Acetate and gluconate salts of zinc are recommended as they produce fewer gastrointestinal side effects.^{5,6,33}

Supportive Therapy

In dogs with CAH, antioxidant defense mechanisms are commonly depleted; therefore, using cytoprotective/antioxidant agents (**TABLE 1**) is advised.⁵ However, these supplements have not been proven to improve outcomes for dogs with CAH.

PROGNOSIS

Prognosis is variable; best outcomes follow early and aggressive treatment. The mean survival time after initial diagnosis is estimated to be 18 months, but it can be drastically shorter for dogs with biopsy-proven cirrhosis. Other reported negative prognostic factors include ascites, cirrhosis/bridging fibrosis, increased serum bilirubin, icterus, enlarged portal lymph nodes, and neutrophilia.⁵

SUMMARY

CAH is caused by the pathologic accumulation of

TABLE 1 Common Hepatoprotective Drugs Used for Copper-Associated Hepatopathy⁵

AGENT	MECHANISM OF ACTION	DOSAGE	SIDE EFFECTS
S-adenosylmethionine	Increased intracellular cysteine, leading to increased hepatic glutathione synthesis	<ul style="list-style-type: none"> 20 mg/kg PO q24h without food 	Nausea (rare)
Silymarin (milk thistle)	Antioxidant, anti-inflammatory, antifibrotic, choleretic	<ul style="list-style-type: none"> Native form: 4–8 mg/kg PO, 2–3 times/day Phosphatidylcholine complex: 0.7–6 mg/kg PO q24h 	Inhibited cytochrome P450 enzymes and p-glycoprotein
Ursodeoxycholic acid	Antioxidant, choleretic, immunomodulatory, anti-inflammatory	<ul style="list-style-type: none"> 15 mg/kg PO q24h with food 	Nausea, diarrhea, mildly increased total bile acids
Vitamin E (α-tocopherol)	Antifibrotic, anti-inflammatory, protection against lipid peroxidation	<ul style="list-style-type: none"> 10 IU/kg PO q24h with food Do not exceed 400 IU 	Possibly impaired vitamin K activity and increased risk for oxidative injury



copper in the liver, which can lead to hepatic inflammation, liver failure, and death if not treated effectively. Although certain breeds are predisposed, any breed of dog can be affected. The only way to accurately diagnose CAH is by histologic analysis of a liver biopsy sample paired with quantitative assessment of hepatic copper concentrations. Treatment is focused mainly on decreasing hepatic copper levels by enhancing copper excretion and is usually achieved by dietary copper restriction and use of copper chelators. Treatment response is best when started early in the course of the disease. Survival times depend greatly on the extent of preexisting hepatic damage. **TVP**

References

- Kim B-E, Nevitt T, Thiele DJ. Mechanisms for copper acquisition, distribution and regulation. *Nat Chem Biol*. 2008;4(3):176-185. doi:10.1038/nchembio.72
- Harris ED. Cellular copper transport and metabolism. *Annu Rev Nutr*. 2000;20:291-310. doi:10.1146/annurev.nutr.20.1.291
- Palumaa P. Copper chaperones. The concept of conformational control in the metabolism of copper. *FEBS Lett*. 2013;587(13):1902-1910. doi:10.1016/j.febslet.2013.05.019
- Sokol RJ, Twedt D, McKim JM Jr, et al. Oxidant injury to hepatic mitochondria in patients with Wilson's disease and Bedlington terriers with copper toxicosis. *Gastroenterology*. 1994;107(6):1788-1798. doi:10.1016/0016-5085(94)90822-2
- Webster CRL, Center SA, Cullen JM, et al. ACVIM consensus statement on the diagnosis and treatment of chronic hepatitis in dogs. *J Vet Intern Med*. 2019;33(3):1173-1200. doi:10.1111/jvim.15467
- Dirksen K, Fieten H. Canine copper-associated hepatitis. *Vet Clin North Am Small Anim Pract*. 2017;47(3):631-644. doi:10.1016/j.cvsm.2016.11.011
- Hoffmann G, van den Ingh TSGAM, Bode P, Rothuizen J. Copper-associated chronic hepatitis in Labrador retrievers. *J Vet Intern Med*. 2006;20(4):856-861. doi:10.1892/0891-6640(2006)20[856:cchilr]2.0.co;2
- Mandigers PJ, van den Ingh TSGAM, Bode P, Teske E, Rothuizen J. Association between liver copper concentration and subclinical hepatitis in Doberman pinschers. *J Vet Intern Med*. 2004;18(5):647-650. doi:10.1892/0891-6640(2004)18<647:ablcca>2.0.co;2
- Thornburg LP, Rottinghaus G, McGowan M, Kupka K, Crawford S, Forbes S. Hepatic copper concentrations in purebred and mixed-breed dogs. *Vet Pathol*. 1990;27(2):81-88. doi:10.1177/030098589002700202
- van De Sluis B, Rothuizen J, Pearson PL, van Oost BA, Wijmenga C. Identification of a new copper metabolism gene by positional cloning in a purebred dog population. *Hum Mol Genet*. 2002;11(2):165-173. doi:10.1093/hmg/11.2.165
- Haywood S, Boursnell M, Loughran MJ, et al. Copper toxicosis in non-COMMD1 Bedlington terriers is associated with metal transport gene *ABCA12*. *J Trace Elem Med Biol*. 2016;35:83-89. doi:10.1016/j.jtemb.2016.01.015
- Fieten H, Gill Y, Martin AJ, et al. The Menkes and Wilson disease genes counteract in copper toxicosis in Labrador retrievers: a new canine model for copper-metabolism disorders. *Dis Model Mech*. 2016;9(1):25-38. doi:10.1242/dmm.020263
- Pindar S, Ramirez C. Predicting copper toxicosis: relationship between the *ATP7A* and *ATP7B* gene mutations and hepatic copper quantification in dogs. *Hum Genet*. 2019;138(5):541-546. doi:10.1007/s00439-019-02010-y
- Wu X, Mandigers PJJ, Watson AL, van den Ingh TSGAM, Leegwater PAJ, Fieten H. Association of the canine *ATP7A* and *ATP7B* with hepatic copper accumulation in Doberman dogs. *J Vet Intern Med*. 2019;33(4):1646-1652. doi:10.1111/jvim.15536
- Center SA, Richter KP, Twedt DC, Wakshlag JJ, Watson PJ, Webster CRL. Is it time to reconsider current guidelines for copper content in commercial dog foods? *JAVMA*. 2021;258(4):357-364. doi:10.2460/javma.258.4.357
- Baker DH. Cupric oxide should not be used as a copper supplement for either animals or humans. *J Nutr*. 1999;129(12):2278-2279. doi:10.1093/jn/129.12.2278
- Gagné JW, Wakshlag JJ, Center SA, Rutzke MA, Glahn RP. Evaluation of calcium, phosphorus, and selected trace mineral status in commercially available dry foods formulated for dogs. *JAVMA*. 2013;243(5):658-666. doi:10.2460/javma.243.5.658
- Hoffmann G. Copper-associated liver diseases. *Vet Clin North Am Small Anim Pract*. 2009;39(3):489-511. doi:10.1016/j.cvsm.2009.02.001
- Watson AD, Middleton DJ, Ilkiw JE. Copper storage disease with intravascular haemolysis in a Bedlington terrier. *Aust Vet J*. 1983;60(10):305-307. doi:10.1111/j.1751-0813.1983.tb02815.x
- Favier RP, Spee B, Schotanus BA, et al. *COMMD1*-deficient dogs accumulate copper in hepatocytes and provide a good model for chronic hepatitis and fibrosis. *PLoS One*. 2012;7(8):e42158. doi:10.1371/journal.pone.0042158
- Elhiblu MA, Dua K, Mohindroo J, Mahajan SK, Sood NK, Dhaliwal PS. Clinico-hemato-biochemical profile of dogs with liver cirrhosis. *Vet World*. 2015;8(4):487-491. doi:10.14202/vetworld.2015.487-491
- Hill TL, Breitschwerdt EB, Cecere T, Vaden S. Concurrent hepatic copper toxicosis and Fanconi's syndrome in a dog. *J Vet Intern Med*. 2008;22(1):219-222. doi:10.1111/j.1939-1676.2007.0040.x
- Marolf AJ. Diagnostic imaging of the hepatobiliary system: an update. *Vet Clin North Am Small Anim Pract*. 2017;47(3):555-568. doi:10.1016/j.cvsm.2016.11.006
- Teske E, Brinkhuis BG, Bode P, van den Ingh TS, Rothuizen J. Cytological detection of copper for the diagnosis of inherited copper toxicosis in Bedlington terriers. *Vet Rec*. 1992;131(2):30-32. doi:10.1136/vr.131.2.30

practicehub

**PRESCRIBING
PROCESS
SLOWING
YOU DOWN?
WE'LL HELP
SPEED IT UP.**

Our free companion software lets you digitally create and approve Rx. Learn more at **ChewyHealth.com**

chewy
health



Your business is caring for animals. Our business is helping you succeed.

Veterinary care is a calling.

It's also a business. The passion for helping
pets and animals comes naturally.

The business acumen to manage and
grow a veterinary practice or animal
hospital might be a bit more challenging.

That's why we developed a professional
certification that can help put your
business and your future in focus.



**Certified
Veterinary
Business
Leader**



Offered exclusively through
VetFolio. Grow your business and
get certified today at
vetfolio.com/pages/certifications.

25. Petre SL, McClaran JK, Bergman PJ, Monette S. Safety and efficacy of laparoscopic hepatic biopsy in dogs: 80 cases (2004-2009). *JAVMA*. 2012;240(2):181-185. doi:10.2460/javma.240.2.181
26. Lidbury JA. Getting the most out of liver biopsy. *Vet Clin North Am Small Anim Pract*. 2017;47(3):569-583. doi:10.1016/j.cvsm.2016.11.007
27. Routhuizen J, Bunch SE, Charles JA, et al. *WSAVA Standards for Clinical and Histological Diagnosis of Canine and Feline Liver Disease*. Saunders Elsevier; 2006.
28. Puls R. *Mineral Levels in Animal Health: Diagnostic Data*. Sherpa International; 1988.
29. Center SA, McDonough SP, Bogdanovic L. Digital image analysis of rhodanine-stained liver biopsy specimens for calculation of hepatic copper concentrations in dogs. *Am J Vet Res*. 2013;74(12):1474-1480. doi:10.2460/ajvr.74.12.1474
30. Fieten H, Biourge VC, Watson AL, Leegwater PAJ, van den Ingh TSGAM, Routhuizen J. Dietary management of Labrador retrievers with subclinical hepatic copper accumulation. *J Vet Intern Med*. 2015;29(3):822-827. doi:10.1111/jvim.12574
31. Fieten H, Dirksen K, van den Ingh TSGAM, et al. D-penicillamine treatment of copper-associated hepatitis in Labrador retrievers. *Vet J*. 2013;196(3):522-527. doi:10.1016/j.tvjl.2012.12.013
32. Allen KG, Twedt DC, Hunsaker HA. Tetramine cupruric agents: a comparison in dogs. *Am J Vet Res*. 1987;48(1):28-30.
33. Brewer GJ, Dick RD, Schall W, et al. Use of zinc acetate to treat copper toxicosis in dogs. *JAVMA* 1992;201:564-568.



Adrian Tinoco-Najera

Dr. Tinoco-Najera received his veterinary degree from the National Autonomous University of Mexico in 2009. In 2013, he received his specialty degree in small animal internal medicine and surgery from the same university. In 2018, he obtained his master's degree in small animal gastroenterology. In 2019, he joined the Gastrointestinal Laboratory at Texas A&M University and is currently pursuing a PhD degree. His research focuses on the discovery of noninvasive inflammatory biomarkers for canine chronic liver disease.



Jonathan A. Lidbury

Dr. Lidbury received his veterinary degree from the University of Glasgow, Scotland, in 2002. In 2007, he joined the Gastrointestinal Laboratory at Texas A&M University as a PhD student and small animal internal medicine resident. He currently serves as an associate professor in the department of veterinary small animal clinical sciences at Texas A&M University.