CANINE CHRONIC HEPATITIS: DIAGNOSIS & TREATMENT

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Canine Chronic Hepatitis

Yuri Lawrence, DVM, MA, MS, Diplomate ACVIM
Jörg Steiner, MedVet, DrMedVet, PhD, Diplomate ACVIM & ECVIM
Texas A&M University

Chronic hepatitis is the most common liver disease in dogs. The World Small Animal Veterinary Association Liver Standardization Group has published standards for diagnosis of the various forms of chronic hepatitis. This article reviews the current literature on diagnosis and treatment of canine chronic hepatitis.

PROFILE
Chronic hepatitis is characterized by hepatocellular apoptosis or necrosis, a variable mononuclear or mixed inflammatory cell infiltrate, regeneration, and fibrosis on histopathologic examination.

Predisposition
The Doberman, West Highland white terrier, Labrador retriever, Skye terrier, American cocker spaniel, English cocker spaniel, standard poodle, and Bedlington terrier breeds are predisposed to chronic hepatitis.

Causes
In most cases of canine chronic hepatitis, the cause is unknown. Known causes are outlined in Table 1. The cause, if known, should precede the term chronic hepatitis.

INITIAL FINDINGS
Clinical Signs
Patients with chronic hepatitis often present with nonspecific clinical signs, although more specific signs may occur in patients with advanced disease (Table 2). Some affected dogs are asymptomatic at presentation, and clinical signs may be inapparent in patients with compensated advanced disease.

Physical Examination
Physical examination findings for chronic hepatitis are nonspecific, often normal and, in most cases, do not provide any information to identify the

TABLE 1.
Known Causes of Canine Chronic Hepatitis

<table>
<thead>
<tr>
<th>CAUSE</th>
<th>SPECIFIC EXAMPLES</th>
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<tbody>
<tr>
<td>Drug</td>
<td>• Amiodarone</td>
</tr>
<tr>
<td></td>
<td>• Carprofen</td>
</tr>
<tr>
<td></td>
<td>• Diethylcarbamazine–oxibendazole</td>
</tr>
<tr>
<td></td>
<td>• Phenobarbital</td>
</tr>
<tr>
<td></td>
<td>• Trimethoprim/sulfadiazine</td>
</tr>
<tr>
<td>Infectious Disease</td>
<td>• Canine adenovirus type 1</td>
</tr>
<tr>
<td></td>
<td>• Helicobacter species</td>
</tr>
<tr>
<td></td>
<td>• Herpesvirus</td>
</tr>
<tr>
<td></td>
<td>• Leptospirosis</td>
</tr>
<tr>
<td>Genetic Disease/Inherited Defecta</td>
<td>• Alpha-1-proteinase inhibitor deficiency</td>
</tr>
<tr>
<td>Other Disease/Condition</td>
<td>• Autoimmune mechanismsb</td>
</tr>
<tr>
<td></td>
<td>• Copper hepatotoxicosis</td>
</tr>
<tr>
<td></td>
<td>• Episode of acute hepatitis</td>
</tr>
<tr>
<td></td>
<td>• Various toxicities</td>
</tr>
</tbody>
</table>

a. Associated with chronic hepatitis in cocker spaniels, but causation—as described in humans—has not been established in dogs
b. Suggested to cause chronic hepatitis in dogs but have never been confirmed experimentally

c. Identified as negative prognostic indicator in patients with chronic hepatitis

TABLE 2.
Chronic Hepatitis: Clinical Signs & Physical Examination Findings

<table>
<thead>
<tr>
<th>CLINICAL SIGNS</th>
<th>PHYSICAL EXAMINATION FINDINGS</th>
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<tbody>
<tr>
<td>• Abdominal distensionb</td>
<td>• Ascitesc</td>
</tr>
<tr>
<td>• Emesis/diarrhea</td>
<td>• Abnormal mucous membrane color (due to jaundice)</td>
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<tr>
<td>• Hepatoencephalopathy</td>
<td>• Abnormal capillary refill time (due to hypovolemia)</td>
</tr>
<tr>
<td>• Hyporexia</td>
<td>• Icterus</td>
</tr>
<tr>
<td>• Jaundice</td>
<td></td>
</tr>
<tr>
<td>• Lethargy</td>
<td></td>
</tr>
<tr>
<td>• Polydipsia/polyuria</td>
<td></td>
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<tr>
<td>• Weight loss</td>
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</table>

a. Accompanies advanced disease
b. Due to ascites from portal hypertension and/or hypoproteinemia
c. Identified as negative prognostic indicator in patients with chronic hepatitis
affected system unless the patient has jaundice (Table 2). Laboratory investigation is required to further evaluate patients for chronic hepatitis.

LABORATORY FINDINGS
A complete biochemical profile, complete blood cell count, and urinalysis are generally adequate to screen for abnormalities.

Hepatic Abnormalities

Enzyme Activities & Bilirubin. Particular attention should be given to any elevation of hepatobiliary enzyme activities and bilirubin:

- Elevated total serum bilirubin concentration has been identified as a negative prognostic indicator.\(^\text{12}\)
- Increased hepatobiliary enzyme activities, such as alanine aminotransferase and aspartate aminotransferase, are consistent with hepatocellular damage.
- Variable degrees of elevated hepatobiliary enzyme activities, such as alkaline phosphatase and gamma-glutamyl transpeptidase, are consistent with cholestasis.
- Disturbances in markers of hepatocellular damage often predominate in dogs with chronic hepatitis, with 90% of patients demonstrating elevated serum alanine aminotransferase activity.\(^\text{13}\)

Serum hepatobiliary enzyme activities may be normal, or only mildly increased, in patients with end-stage chronic hepatitis; therefore, even mild elevations may be significant, if persistent and when other potential causes have been excluded. Since dogs with significant liver disease can be clinically silent, in those with elevated liver enzyme activities that persist longer than 4 to 6 weeks, we recommend screening for an underlying etiology.

Liver Function. Specific tests of liver function are often warranted, but there is no consensus on which liver function test is most appropriate. In our opinion, the most useful test (in the absence of hyperbilirubinemia), is the provocative serum total bile acids test, which includes a fasted preprandial and 2-hour postprandial (provoked) serum total bile acid concentration.

Other liver function tests include fasted preprandial serum total bile acid concentration, postprandial serum total bile acid concentration, and basal plasma $NH_3$ concentration.

HematoLogic Abnormalities

Blood Cells. Nonregenerative anemia due to decreased mobilization of systemic iron stores may be present in dogs with chronic hepatitis; regenerative anemia may be present if associated with gastrointestinal blood loss. Morphologic erythrocyte abnormalities due to altered lipoprotein content may also be seen.

Coagulation. Coagulation status should be assessed because altered hemostasis can contribute to clinical disease and may affect diagnostic testing options. Available tests are listed in Table 3, but no individual test predicts clinically significant bleeding and, thus, evaluation of primary and secondary hemostasis is recommended. Abnormalities can result from hepatic synthetic failure, vitamin K deficiency, disseminated intravascular coagulation, and qualitative or quantitative platelet defects.

Serology. Serology for leptospirosis can be submitted to determine the potential role of this pathogen.

ULTRASONOGRAPHY
Complete abdominal ultrasonography is an essential component of further diagnostic evaluation that allows screening for concurrent disease and acquisition of bile.

- In chronic hepatitis, the liver is variable and can be normal upon examination.
- Sonographic changes consistent with chronic hepatitis include uniform increases in liver

<table>
<thead>
<tr>
<th>TABLE 3. Coagulation Tests for Chronic Hepatitis*</th>
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<tbody>
<tr>
<td>Activated partial thromboplastin time (aPTT)</td>
</tr>
<tr>
<td>Buccal mucosal bleeding time (BMBT)</td>
</tr>
<tr>
<td>D-dimers</td>
</tr>
<tr>
<td>Fibrinogen</td>
</tr>
<tr>
<td>Platelet count</td>
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<tr>
<td>Prothrombin time (PT)</td>
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<td>Thromboelastography</td>
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</table>

* The authors frequently evaluate platelet count, PT, aPTT, and BMBT to evaluate primary and secondary hemostasis.
echogenicity, decreased distinction of portal vein margins, and normal to small liver size.

- The liver parenchyma, biliary tree, portal vein, and peritoneum should be assessed for abnormalities, acquired shunting, and presence of free peritoneal fluid.

CHOLECYSTOCENTESIS

Cholecystocentesis to acquire bile for cytologic evaluation and aerobic/anaerobic bacterial culture and sensitivity should be routinely performed in patients suspected of having chronic hepatitis. This technique can be safely performed via ultrasound guidance, laparoscopic guidance, or direct visualization during laparotomy (Figure 1).

Bacterial cholecystitis can result in clinical signs and clinicopathologic anomalies indistinguishable from chronic hepatitis and, thus, exclusion of this disease is an important component of the diagnostic evaluation.

DIAGNOSTIC LIVER BIOPSY

Liver biopsy is essential for establishing a definitive diagnosis in dogs suspected of having chronic hepatitis. Several biopsy techniques are available for acquiring histology-grade liver tissue; however, fine-needle aspiration is NOT adequate for diagnosis of any type of inflammatory liver disease.

Histopathologic diagnosis of chronic hepatitis requires demonstration of the characteristic components: hepatocellular necrosis or apoptosis, mononuclear or mixed inflammatory cell infiltrate composed primarily of lymphocytes and plasma cells, regeneration, and fibrosis.1

- Pattern and distribution of characteristic components of chronic hepatitis are variable.
- Disease severity is determined by amount of inflammation present and extent of hepatocellular necrosis and apoptosis.
- Stage of disease is determined by the extent and pattern of fibrosis.
- Qualitative increases in copper may be detected with special stains if levels exceed 400 ppm. The pattern of copper accumulation can also provide additional information about the disease process, with qualitative staining techniques revealing that:
  - Cholestatic diseases result in periportal (zone 1) copper accumulation
  - Copper-associated chronic hepatitis results in centrilobular (zone 3) accumulation.

Percutaneous Ultrasound-Guided Needle Biopsy

Percutaneous ultrasound-guided needle biopsy uses an automated, semi-automated, or manual biopsy needle to acquire hepatic tissue. Percutaneous TruCut (carefusion.com) liver biopsies require ultrasound guidance and may be limited by a small liver or small patient size. Particular care should be taken to ensure adequate sampling (3–6 tissue specimens/samples; 14-gauge for large/medium dogs or 16-gauge for small dogs).

Advantages include that the technique can be performed under sedation, is minimally invasive, and isolated lesions within the hepatic parenchyma can be
specifically sampled. Disadvantages include relatively smaller biopsy samples and inability to control hemorrhage directly. Sampling may be limited if the liver or the patient is of small size.

**Laparoscopic Biopsy**

Laparoscopic liver biopsy is performed under general anesthesia, and the liver is sampled with biopsy forceps. Gross examination of the liver and associated structures and targeted sampling of multiple identified lesions can be performed (Figure 2). After sample acquisition, the biopsy sites can be visually inspected for hemorrhage (Figure 3).

Advantages of this technique include direct visualization of the liver; relatively large tissue samples; ability to control hemorrhage directly with a palpation probe or a hemostatic agent, such as gel foam; and access to multiple liver lobes for sampling. Disadvantages include need for specialized equipment and specific skills, general anesthesia, and cost.

**Wedge Biopsy**

Wedge biopsy by laparotomy can be performed by transfixion or biopsy punch. Advantages and disadvantages of this technique are similar to those for laparoscopy. Additional consideration for this technique is degree of invasiveness; however, it can be combined with other surgical procedures in the abdomen.

**Other Biopsy Techniques**

A transjugular liver biopsy technique has been recently described in dog cadavers but due to the high potential complication rate, which included perforations of the liver capsule in 13 of 16 dogs (81%), further studies are needed before this technique can be recommended.\(^4\)

**BIOPSY TECHNIQUE & EVALUATION**

**Biopsy Technique**

All techniques suffer from sampling artifact and, thus, multiple samples should be acquired and multiple

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**FIGURE 3.** Laparoscopic image of liver after biopsy; demonstrates normal degree of postprocedural hemorrhage with normal coagulation.

**FIGURE 4.** Corresponding sections of liver tissue show evidence of severe chronic hepatitis secondary to excess copper accumulation. Note the different features highlighted by the respective stains: (A) hematoxylin–eosin staining highlighting inflammatory infiltrate in portal triad (arrow), (B) Rhodanine staining highlighting copper granules (arrow), (C) Perls’ iron stain highlighting blue iron granules (arrow), and (D) Sirius red staining highlighting red collagen fibrils (arrow) (all images: original magnification, 20×). Courtesy Dr. John Cullen, North Carolina State University
lobes biopsied. A recent study reported that if the liver biopsy specimen contains at least 3 to 12 portal triads, all biopsy techniques carry a similar diagnostic utility.\textsuperscript{15}

**Histopathologic Evaluation**
Liver tissue samples should be submitted for histopathologic evaluation (Figure 4, page 29):
- Routine stains include hematoxylin–eosin.
- Special stains to characterize fibrosis or cirrhotic changes include Sirius red, Masson trichrome stain, van Gieson stain, and the reticulin stain according to Gordon and Sweet.\textsuperscript{1}
- Additional stains may also be used to detect certain substances, such as:
  - Copper (rubeanic acid or rhodanine stain)
  - Iron (Perls’ iron stain)
  - Glycogen (periodic acid–Schiff stain).

**Tissue Preparation**
Additional special stains, immunohistochemical techniques, and polymerase chain reaction techniques can be performed on formalin-fixed tissue but provide better results in unfixed frozen tissue; therefore, an additional biopsy specimen should be freshly frozen. Approximately 1 gram of fresh liver tissue in a serum blood tube is required for atomic absorption analysis; however, formalin-fixed tissue may also be submitted for copper quantification. Copper quantification and aerobic/anaerobic bacterial culture and sensitivity should be considered a routine part of the diagnostic evaluation.

**THERAPEUTIC APPROACH**
The initiating factor in most cases of chronic hepatitis remains unknown. General principles guiding the treatment of idiopathic canine chronic hepatitis include (Table 4):
- Immunosuppressive therapy to resolve or control the inflammatory process
- Antioxidant therapy to prevent oxidative stress
- Antifibrotic therapy to inhibit fibrosis.

Available evidence suggests that humans and dogs have similar mechanisms for hepatic fibrosis in chronic hepatitis; thus, most treatment recommendations are extrapolated from the human literature.\textsuperscript{16,17} Compliance is essential for treatment success. Therefore, facilitating drug administration by limiting the number of medications to those most appropriate is prudent.

**Symptomatic Therapy**
Treatment of canine chronic hepatitis in most cases is symptomatic, supportive, and aimed at slowing progression of fibrosis (Table 4):
- Nausea: Antiemetic therapy
- Gastrointestinal ulceration: Appropriate antacid therapy
- Portal hypertension: Inhibition of renin-angiotensin system
- Hepatic encephalopathy: Appropriate dietary, probiotic, antimicrobial, and lactulose therapy.

Exceptions to limiting treatment to symptomatic therapy include:
- Copper-associated chronic hepatitis: Specific treatment includes low-copper diet, copper chelator, and potentially increased alimentary zinc
- Infection-associated chronic hepatitis: Appropriate use of antimicrobial agents

**Immunosuppressive Therapy**
Corticosteroid therapy with prednisone/prednisolone is the most common immunosuppressive medication used in dogs with chronic hepatitis. It has been shown to prolong survival, improve hepatic histologic changes, and induce remission.\textsuperscript{18,19} Adjunctive immunosuppressive therapy, such as leflunomide, can be added for steroid-sparing effects and/or additional immunosuppression to achieve disease remission.

In our opinion, remission is best determined by
repeat liver biopsy. Serial monitoring every 2 weeks for normalization or marked reduction of alanine transaminase activity can be used as a surrogate marker of disease remission and to indicate repeat liver biopsy. Glucocorticoids frequently result in variable increases in alanine transaminase, alkaline phosphatase, and gamma-glutamyl transpeptidase activity; therefore, a relative significant decrease or normalization in alanine transaminase activity is often used in lieu of a second liver biopsy.

**Antioxidant Therapy**
The use of antioxidants as an adjunct to standard therapy is advocated to reduce hepatic injury and fibrosis in dogs with chronic hepatitis.20

- Studies of human patients with chronic hepatitis

| TABLE 4. Common Drugs & Nutraceuticals for Management of Canine Chronic Hepatitis |
|-----------------|-----------------|-----------------|
| **DRUG NAME**   | **DOSE**        | **INDICATION/COMMENTS** |
| Azathioprine    | 2 mg/kg PO Q 24 H for 10–14 D; then Q 48 H | Anti-inflammatory ▪ Immunosuppressive (not preferred) |
| Cyclosporine    | 5–10 mg/kg PO Q 12 H | Anti-inflammatory ▪ Immunosuppressive |
| Lactulose       | 0.1–0.5 mL/kg PO Q 8–12 H | Decreases ammonia absorption |
| Leflunomide     | 4–6 mg/kg PO Q 24 H | Antifibrotic ▪ Anti-inflammatory ▪ Immunosuppressive |
| Losartan        | 0.25–0.5 mg/kg PO Q 24 H | Antifibrotic |
| Metronidazole   | 8–10 mg/kg PO Q 12 H | Anti-inflammatory ▪ Decreases ammonia-producing bacteria |
| Mycophenolate   | 10–12 mg/kg PO Q 24 H | Anti-inflammatory ▪ Immunosuppressive |
| Neomycin        | 22 mg/kg PO Q 8 H | Decreases ammonia-producing bacteria |
| Omeprazole      | 1–2 mg/kg PO Q 12 H | Antacid |
| Penicillamine   | 10–15 mg/kg PO Q 12 H; administer 30–60 min before meals | Antioxidant ▪ Copper chelator |
| Prednisone/prednisolone | 1–2 mg/kg PO Q 24 H until 2–3 weeks after clinical remission; then slowly taper to lowest effective dose | Antifibrotic ▪ Anti-inflammatory ▪ Immunosuppressive |
| Probiotic therapy | Per labeled instructions | Displaces ammonia-producing bacteria |
| S-adenosylmethionine | 20 mg/kg PO Q 24 H in fasted patient to increase absorption | Antifibrotic ▪ Anti-inflammatory |
| Silymarin/silybinin | 20–50 mg/kg PO Q 24 H | Antioxidant |
| Spironolactone  | 1–2 mg/kg PO Q 12 H | Diuretic for portal hypertension and ascites |
| Sucralfate      | 0.5–1 g PO Q 8 H (slurry); administer at least 2 H before or after all other medications | Anti-ulcer therapy |
| Trientine       | 10–15 mg/kg PO Q 12 H | Copper chelator (expensive, with few clinical data in dogs) |
| Ursodeoxycholic acid | 10–15 mg/kg PO Q 24 H; dose can be divided Q 12 H | Anti-inflammatory ▪ Antioxidant ▪ Choleretic |
| Vitamin E       | 250–400 IU/day PO | Antioxidant |
| Vitamin K       | 0.5–1.5 mg/kg SC or PO Q 24 H | Deficiency |
| Zinc (elemental zinc) | 10 mg/kg PO Q 12 H | Antifibrotic ▪ Antioxidant |
have documented that those with persistent oxidative stress benefit from antioxidant supplementation.21–24

• Glutathione, a potent antioxidant, has been reported to be decreased in dogs with necroinflammatory liver disease.25
• Vitamin E, S-adenosylmethionine, silibinin, N-acetylcysteine, and ursodeoxycholic acid are antioxidants commonly used as ancillary treatments in dogs with chronic hepatitis. In various studies, these nutraceuticals show inhibition of hepatic stellate cell activation, protection of hepatocytes from apoptosis, and attenuation of experimental liver fibrosis.26-28
• Veterinarians should be aware, however, that limited to no evidence supports the general use of antioxidants in preventing or treating chronic hepatitis, and few studies document beneficial effects of these antioxidants in vivo.

Antifibrotic Therapy
There is no standard treatment for hepatic fibrosis. Experimental studies have identified targets to inhibit fibrosis in rodents, but the efficacy of most treatments has not been investigated in dogs. Also, the need to perform serial liver biopsies to accurately assess changes in liver fibrosis makes studies documenting treatment efficacy difficult.

The development of reliable noninvasive markers for liver fibrosis may enhance the management of these patients. Drugs with theoretical and limited experimental evidence for the treatment of fibrosis include colchicine, corticosteroids, penicillamine, zinc, angiotensin inhibitors, and angiotensin-receptor blockers.13,19,29,30

However, the clinical utility of colchicine for the reversal or prevention of hepatic fibrosis is limited, and because of the associated adverse effects, which include vomiting, diarrhea, and inappetance, we do not recommend routine use of this drug.

Protein Restriction
Protein restriction should be limited to the maximum tolerated level that prevents signs of hepatic encephalopathy; therefore, it may not be appropriate to start with the severe protein restriction provided by a prescription liver diet.

If protein restriction is required, diets that contain moderate amounts of protein, such as prescription renal diets and geriatric diets, may be suitable alternatives to a prescription liver diet. Diets may also be supplemented with high-quality protein, such as egg whites.

A consultation with a board-certified veterinary nutritionist may be necessary for patients with comorbid conditions or those in which homemade diets are indicated.

Anticopper Therapy
Anticopper drug therapy is generally reserved for cases with documented primary or secondary excess copper accumulation.

• The chelator, penicillamine, is typically used, and has additional anti-inflammatory and antifibrotic effects.
• Trientine can serve as an alternative if penicillamine is not tolerated.
• Copper chelators should be used for 3 to 6 months before a second liver biopsy is performed to ensure adequate disease remission and normalization of copper levels; then followed by zinc therapy, if appropriate to prevent copper reaccumulation.
• Zinc toxicity can result from oral zinc administration; periodic monitoring of blood zinc concentration is recommended with use of elemental zinc therapy.

PROGNOSIS
The prognosis for dogs with chronic hepatitis varies. Median survival durations of 18.3 to 36.4 months have been reported. However, patients with hypoalbuminemia, hypoglycemia, prolonged clotting times, bridging fibrosis, and ascites have shorter survival times.2,11,18,31

Early diagnosis and intervention are important for successful treatment of dogs with chronic hepatitis because patients with
end-stage disease and signs of decompensated liver function have a poorer prognosis.

IN SUMMARY
There is still much unknown about the etiology and treatment of chronic hepatitis in dogs. The World Small Animal Veterinary Association guidelines provide an important scaffolding of the etiology and treatment of this disease that should build on our current knowledge and facilitate multicenter studies, with the hope of improving patient survival and outcome.

aPTT = activated partial thromboplastin time; BMBT = buccal mucosal bleeding time; BUN = blood urea nitrogen; PT = prothrombin time

References