SEVC SOUTHERN EUROPEAN VETERINARY CONFERENCE
SEVILLE, 23-25 October 2025

UPDATE ON CHRONIC HEPATITIS MANAGEMENT

Thomas Butler
Cave Veterinary Specialists
Department: Internal Medicine
George's Farm, West Buckland, Nr. Wellington, Somerset, TA21 9LE
United Kingdom

TREATMENT AIMS

When treating canine chronic hepatitis (CH), it is important to consider the goals of treatment, which are to identify and treat the specific underlying disease (where possible), slow progression, manage and prevent secondary complications, and avoid drug-related toxicity.

COPPER ASSOCIATED CHRONIC HEPATITIS

Copper-associated chronic hepatitis (CuCH) can occur in any breed, but the Bedlington Terrier, Labrador Retriever, Doberman Pinscher and Dalmatian are predisposed. Differentiation of primary and secondary CuCH can be difficult, but an increased hepatic copper concentration (>600μg/g dry weight) should always prompt treatment. Treatment of CuCH involves two stages: 1) removal of hepatic copper, 2) lifelong copper restriction.

Removal of hepatic copper requires dietary copper restriction combined with copper chelation. Copper-restricted diets should have copper concentration of <0.12mg/100kcal and it is important to recognize that most hepatic diets, whilst appropriately copper restricted, are protein restricted. Dogs with chronic hepatitis do not require protein restriction and this may be detrimental to outcomes, so if a commercial hepatic diet is used it is recommended to supplement protein (ideally with a vegetarian or dairy based protein source to minimize ammoniagenesis and risk of hepatic encephalopathy[1]). If a patient will not consume a commercial hepatic diet, a homemade copper-restricted diet can be more palatable; formulation by a clinical veterinary nutritionist is recommended. D-penicillamine is the first-choice copper chelator in dogs. It binds to hepatic copper leading to urinary excretion and has anti-fibrotic and anti-inflammatory properties. Food decreases bioavailability so it is best given on an empty stomach. Gastrointestinal side effects are most prevalent with D-penicillamine (inappetence and vomiting), although more rare adverse effects include glomerulonephritis and immunological reactions. Gastrointestinal adverse effects are best managed by administration with a small amount of food, concurrent use of anti-emetics or by gradual dose escalation. D-penicillamine should not be given alongside zinc therapy. Most dogs require copper chelation for at least 6-9 months, depending on starting hepatic copper concentrations. Best practice to assess the normalization of hepatic copper concentrations is via repeat biopsy for copper quantification, however serum alanine aminotransferase (ALT) is often used as a surrogate marker; copper chelation should continue for at least 1 month after normalization of serum ALT activity[2].

Following successful chelation therapy, lifelong dietary copper restriction is recommended. Additional treatments for CuCH include antioxidant medications such as s-adenosyl-methionine and vitamin E (see general treatment principles).

IMMUNE HEPATITIS

There is increasing evidence for a subset of dogs with CH that respond to immunosuppressive therapies, although there are no established diagnostic criteria or treatment protocols. Ultimately, diagnosis of immune hepatitis relies on response to treatment, but initial case selection is also important. Clinicians should have ruled out CH of infectious, neoplastic and toxic etiology and be aware that most reported cases in the literature have a lymphocytic infiltrate on hepatic biopsy. A neutrophilic or granulomatous histopathology should raise concern of an undiagnosed infectious or neoplastic process.

Where immunosuppressive therapy is selected, there is evidence to suggest that corticosteroids (usually prednisolone 1mg/kg/day) can be effective as a first-line treatment[3, 4], however, clinicians should be aware of the increased risk of complications in dogs with CH, including gastrointestinal ulceration (associated with portal hypertension), sodium and water retention leading to ascites and protein catabolism leading to increased risk of hepatic encephalopathy. In addition, corticosteroid-related adverse effects such as liver enzyme activity induction, polyuria/polydipsia and vacuolar hepatopathy can make it difficult to monitor treatment response. I favor the use of cyclosporine (5mg/kg every 12 hours) as a first-line treatment for immune hepatitis, with 76% of dogs experiencing normalization of serum ALT in one study[5] and an improved side effect profile compared to prednisolone. Once patients have achieved ALT normalization, cyclosporine can be reduced to once daily. Mycophenolate mofetil has also recently become more widely available and affordable, with some limited data to suggest efficacy in immune hepatitis[6]. There is currently no consensus on duration of treatment, but once clinical remission (i.e., normalization of ALT) is achieved, it is reasonable to taper immunosuppressive therapy, with close monitoring of serum liver enzyme activities in case of relapse.

GENERAL TREATMENT PRINCIPLES AND MANAGEMENT OF IDIOPATHIC CHRONIC HEPATITIS

Most cases of canine CH are considered idiopathic due to the absence of an identifiable etiology. Without a specific pathophysiology to treat, the focus of treatment is in slowing the progression of CH, avoiding drug-related toxicities and in preventing and managing common secondary complications. These principles should also be applied to treatment of any canine CH patient.

Hepatoprotective medications, especially antioxidants, are indicated in all CH cases as oxidative stress is common, through a combination of inflammation, reduced hepatic blood flow and mitochondrial damage. The most commonly used hepatic antioxidant is s-adenosyl-methionine (SAMe), which is converted to the antioxidant glutathione in the liver and erythrocytes, actively replenishing hepatic glutathione stores, which are frequently depleted during oxidant injury. There is data documenting efficacy in lomustine- and paracetamol-associated oxidant hepatic injury and SAMe has a proven safety profile, so is recommended and commonly employed despite limited data on efficacy in canine CH. SAMe products should always be sourced from reputable manufacturers with proven and reported bioavailability and pharmacokinetics, as one study has shown significant variation in SAMe content between products[7]. Other antioxidants used in dogs include vitamin E, silymarin, and N-acetylcysteine.

Ursodeoxycholic acid (UDCA) is a hydrophilic bile acid that displaces toxic hydrophobic bile acids but has also been documented to have other effects in humans including synergistic antioxidant effects with SAMe, anti-inflammatory, anti-apoptotic, immunomodulatory and cytoprotective effects. Due to these probable beneficial properties, and wide safety profile, UDCA is indicated in almost all cases of liver disease, especially when associated with biliary stasis. The main contraindication for use is complete biliary obstruction, due to the risk of biliary rupture and bile peritonitis.

Dogs with CH are considered at increased risk of drug-induced hepatic injury due to reduced hepatic metabolic processes and reduced hepatic blood flow. Clinicians should carefully consider every drug used in patients with CH, as pharmacokinetics may be unpredictable. Drugs with known hepatotoxicities or strong hepatic metabolism should be avoided, including phenobarbital, amiodarone, lomustine, carprofen and primidone. Non-steroidal anti-inflammatory drugs are metabolized by the liver and have a risk of gastrointestinal ulceration; given the risk of ulceration already associated with CH, these drugs should be avoided.

COMPLICATIONS OF CHRONIC HEPATITIS

The four main complications associated with CH are hepatic encephalopathy, ascites, gastrointestinal ulceration and coagulopathy.

Hepatic encephalopathy (HE) has a complex and poorly understood pathophysiology involving a combination of altered neurotransmission, blood-brain barrier disruption, astrocyte swelling and mitochondrial dysfunction, leading to cerebral oedema. Diagnosis is made based on clinical signs (which are highly variable but include lethargy, ataxia, behavior/mentation changes, head-pressing, circling and

seizures) and response to treatment. Elevated serum ammonia is common, but normal serum concentrations do not rule out HE. Clinicians should recognize the many precipitating factors for HE, to proactively prevent them or effectively identify and manage this condition. Precipitating factors include an increased ammonia load (high protein meal, gastrointestinal bleeding, uremia, diarrhea, constipation or blood transfusion with a unit >7 days old), electrolyte disturbances (metabolic alkalosis, hyponatremia, hypokalemia), dehydration, infection/inflammation, hypoglycemia and sedation or general anesthesia. Treatment in the chronic context involves nutritional management, lactulose and antibiotics. Dietary modifications include using a high quality, highly digestible protein, fed little and often. Soy or dairy-based protein sources have been shown to be lower in aromatic amino acids, leading to less ammonia generation[1]. Protein should not be severely restricted, as endogenous protein catabolism will worsen HE. Increasing fiber content of meals also leads to increased colonic motility and nitrogen clearance and acidifies the gut lumen (via increased short-chain fatty acid production), leading to ammonia trapping. Lactulose is a fermentable fiber that acts to decrease colonic pH, trapping ammonia, and to decrease gut transit time. Use of antibiotics in HE is controversial, and they are likely over-utilized, however they may be used in the acute setting with the goal of reducing urease-producing gut flora concentration to decrease ammonia production. Their long-term use cannot be justified due to risks of anti-microbial resistance.

Ascites in CH is often caused by a combination of portal hypertension, hypoalbuminemia and renal sodium and water retention (due to splanchnic pooling). Diuretics are preferred to abdominocentesis for treatment, and spironolactone is the drug of choice. Spironolactone is an aldosterone antagonist and is potassium sparing (reducing the risk of precipitating HE) but takes 2-3 days to reach peak diuretic effect. Recent studies have identified antifibrotic effects in humans and dogs, but further studies are needed into the use of spironolactone for this reason. Due to the lag-time in peak diuretic effect of spironolactone, short-term use of furosemide can be considered. Furosemide can rapidly induce hypokalemia and dehydration (risk factors for HE), and so it is recommended for short-term use (3-5 days) only and should be titrated to effect with regular monitoring of electrolytes and renal values. Abdominocentesis should be considered if ascites is causing respiratory compromise or abdominal discomfort. It has the benefit of relieving venous compression and improving voluntary feed intake, but risks depleting serum albumin and decreasing renal perfusion. If multiple or large volumes of fluid are removed, clinicians should consider concurrent plasma or albumin transfusions to provide circulatory support.

Dogs with CH are at increased risk of gastrointestinal ulceration, which is suspected to be due to splanchnic congestion and decreased gastrointestinal blood flow. Ulceration is a frequent cause of death in dogs with chronic portal hypertension. Treatment should be based on clinical signs (melena, hematochezia, hematemesis) and follow the recent ACVIM Consensus statement guidelines[8], with twice daily omeprazole being the gastroprotectant of choice. Clinicians should also avoid ulcerogenic medications such as corticosteroids or non-steroidal anti-inflammatory drugs.

The most common manifestation of coagulopathy in canine CH patients is gastrointestinal haemorrhage in end-stage disease, often associated with ulceration. Spontaneous bleeding in general is relatively uncommon. Treatment of active haemorrhage is best managed with fresh frozen plasma transfusion in the emergent setting. Dogs with CH are also at increased risk of portal vein thrombosis and hypercoagulable state. Anticoagulant medications all carry the risk of gastrointestinal haemorrhage, particularly in patients with portal hypertension, and so clinicians should carefully assess the risk/benefit of their use. Clopidogrel requires hepatic activation to be effective, and rivaroxaban is albumin-bound and inactivated by hepatic metabolism, making neither drug ideal for use in CH cases.

References

1. Proot, S., Biourge, V., Teske, E. & Rothuizen, J. Soy Protein Isolate versus Meat-Based Low-Protein Diet for Dogs with Congenital Portosystemic Shunts. *J. Vet. Intern. Med.* **23**, 794–800 (2009).
2. Webster, C. R. L. *et al.* ACVIM consensus statement on the diagnosis and treatment of chronic hepatitis in dogs. *J Vet Intern Med* **33**, 1173–1200 (2019).
3. Bayton, W., Watson, P. J. & Bexfield, N. H. Prednisolone therapy for chronic hepatitis in English springer spaniels: a prospective study of 12 cases. *Vet. Rec.* **186**, e21–e21 (2020).

4. Favier R. P., Poldervaart J. H., van den Ingh T. S. G. A. M., Penning L. C. & Rothuizen J. A retrospective study of oral prednisolone treatment in canine chronic hepatitis. *Vet. Q.* **33**, 113–120 (2013).
5. Ullal, T., Ambrosini, Y., Rao, S., Webster, C. R. L. & Twedt, D. Retrospective evaluation of cyclosporine in the treatment of presumed idiopathic chronic hepatitis in dogs. *J. Vet. Intern. Med.* **33**, 2046–2056 (2019).
6. Beehler, M. K., Kearns, S. A. & Crouse, Z. J. Mycophenolate mofetil as a treatment for presumed idiopathic chronic hepatitis in dogs: Six cases (2010–2022). *Vet. Med. Sci.* **9**, 2527–2533 (2023).
7. Sturgess, C. P. Measurement of the S-adenosyl methionine (SAMe) content in a range of commercial veterinary SAMe supplements. *J. Small Anim. Pr.* **55**, 447–450 (2014).
8. Marks, S. L., Kook, P. H., Papich, M. G., Tolbert, M. K. & Willard, M. D. ACVIM consensus statement: Support for rational administration of gastrointestinal protectants to dogs and cats. *J Vet Intern Med* **32**, 1823–1840 (2018).