# Common inflammatory liver diseases in the dog (part 2)

**The second article in a two-part series on management of acute and chronic hepatitis in dogs, is presented by Daniel Davies BVMedSci (Hons) BVM BVS (Hons) MRCVS, resident in small animal diagnostic imaging, University College Dublin**


## SYNOPSIS

The most common causes of inflammatory liver disease in dogs include non-specific reactive hepatitis, chronic hepatitis (CH) and acute hepatitis (AH). Other common causes of hepatic disease in dogs include neoplasia, vascular anomalies (ie. portosystemic shunts) and biliary tract disorders.

This is the second of two articles written on the topic of inflammatory liver disease in dogs. This article will briefly summarise the treatment and management options available to vets in first-opinion practice while managing cases of acute and chronic hepatitis in the dog.


## CHRONIC HEPATITIS

CH is the most commonly identified canine inflammatory liver disease (Bexfield, in press). Details of the pathogenesis, clinical signs and diagnosis of this condition were discussed in the first article of this series.

Treatment involves a combination of drug therapy and appropriate dietary management. There is a lack of controlled veterinary studies investigating the pharmacokinetics and effectiveness of many of the commonly used drugs in canine CH.

Many of the current veterinary therapies are, therefore, derived from human hepatology, anecdotal reports, or low-quality veterinary studies (Bexfiled, in press; Willard, 2010). The following summarises common therapies generally accepted in the treatment of CH in dogs.

### GLUCOCORTICOIDS

Glucocorticoids are used in patients with CH for their anti-inflammatory, immune-modulating and antifibrotic properties. Glucocorticoids are indicated if there is histological evidence of ongoing inflammation from liver biopsy, if there is no or only early, mild hepatic fibrosis associated with an inflammatory infiltrate, and if infectious causes of CH have been ruled out.

Inappropriate use of glucocorticoids can have potentially fatal consequences. Adverse effects of glucocorticoids in these patients include increased protein catabolism, fluid retention, gastrointestinal ulceration, increased risk of infection and steroid hepatopathy. Contraindications to using glucocorticoids include the presence of infectious aetiologies (including biliary tract infections), histological evidence of advanced, bridging fibrosis or non-inflammatory fibrosis, in patients with ascites (as portal hypertension pre-disposes patients to gastrointestinal [GI] ulceration) and in patients with hepatic encephalopathy. Dexamethasone tends to cause more severe adverse effects than prednisolone, so should be avoided. Varying dosages and durations of treatment of prednisolone have been prescribed, however there is no clear evidence to date suggesting an immune-mediated cause of disease. Prescribing anti-inflammatory rather than immune-suppressive dosages of prednisolone would therefore seem justified. Bexfield and Watson (2009) suggest a prednisolone dose of 0.5 to 1.0mg/kg once daily, reducing to 0.5mg/kg every other day.

Recommended duration of treatment is unknown, and length of treatment remains empirical. In human patients, corticosteroids are administered for at least six months beyond remission, and occasionally are administered life-long. However, remission is difficult to assess in dogs, especially as glucocorticoids induce hepatic enzymes, making monitoring difficult. Repeat liver biopsies may be useful, but only if representative liver biopsies are taken (as disease may be patchy in distribution).

Some, but not all, animals may need lifelong treatment, ideally at a low-alternate day dose. Other immunosuppressive drugs have been used in dogs with CH; however, their use seems unjustified at present.

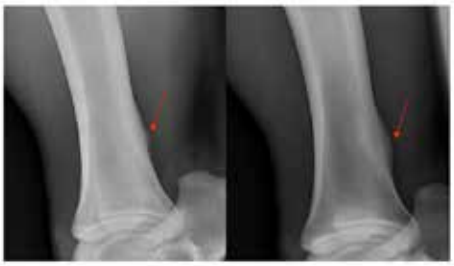

**Figure 1: Corticosteroids are the most widely used anti-inflammatory drugs for treating chronic liver disease. However, they are contraindicated in patients with known or suspected infectious conditions (including ascending biliary tract infection), with advanced bridging fibrosis or non-inflammatory fibrosis, in patients with ascites, and in patients suffering from hepatic encephalopathy. They should not be used in cases of acute hepatitis unless there is a specific and definitive indication.**

## ANTIOXIDANTS

Oxidation is a significant mechanism of hepatocellular damage, therefore providing antioxidant therapy seems reasonable, despite there being no significant evidence to support their use in dogs with CH. Antioxidants include vitamin E, zinc, silymarin (milk thistle) and SAMe. SAMe, which increases hepatic and red blood cell glutathione levels, is widely available as a nutraceutical for dogs. It is helpful for treating toxic hepatopathies in humans, and there is some evidence for the use of both SAMe and silymarin in dogs with acute toxic hepatopathies. Vitamin E has been shown to be an effective antioxidant in dogs with liver disease, and is typically administered at 400 to 600IU, orally, once daily (Rothuizen, 2010). It should be used in cases of copper storage disease, as levels of vitamin E are reduced in such patients.

## CHOLERETICS

Ursodeoxycholic acid (UDCA) is a natural hydrophilic bile acid in enterohepatic circulation, which canalso be manufactured into tablet or capsule forms (Rothuizen, 2010). UDCA is used widely in both human and veterinary medicine with no significant adverse effects reported to date. UDCA displaces toxic bile acids, stimulates bile flow (it is a choleretic), is immune modulating and encourages antioxidant activity (Rothuizen, 2010). Its antioxidant activity has reportedly

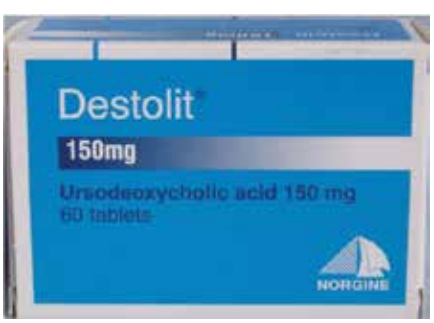


**Figure 2: Ursodeoxycholic acid (UDCA) displaces toxic bile acids, stimulates bile flow (it is a choleretic), is immune modulating and encourages antioxidant activity. Although uncommon, it should be avoided in dogs with complete biliary obstruction.**

synergistic action with SAMe and vitamin E. Although little published evidence supports its use in canine CH, it is probably indicated in all cases, as biliary stasis is invariably present. It should be avoided in dogs with complete biliary obstruction, which is uncommon in dogs due to its potential to cause gall bladder rupture (Bexfield and Watson, 2009).

## DIURETICS AND ASCITES

Ascites in animals with CH is usually due to portal hypertension, however in some animals hypoalbuminaemia may contribute to its pathogenesis (Bexfield and Watson, 2009). It is important to check blood albumin levels, and if low, dietary control by supplementing the animal with a high biological value protein, eg. cottage cheese, is advised. Dietary change may be all that is required to manage the patient's ascites. The administration of blood products, eg. canine plasma or human albumin solutions, is rarely necessary except in acute cases. If protein levels are normal, or close to normal in a dog with CH and ascites, portal hypertension (PH) is likely. PH causes the splanchnic pooling of blood, with a subsequent reduction in systemic arterial pressure, and activation of the renin-angiotensin-aldosterone system (RAAS). RAAS activation leads to the retention of fluid, and contributes to the progression of ascites (Bexfield and Watson, 2009). Spironolactone, a potassium-sparing aldosterone antagonist, is therefore the diuretic of choice for patients with ascites caused by PH. Thiazide diuretics or frusemide can be initially used in combination with spironolactone to 'speed up' diuresis, as spironolactone can take two to three days to take effect when used on its own. Therapeutic paracentesis, which can cause a significant drop in blood albumin levels due to inability of the diseased liver to make up for the loss, should be avoided unless the ascites are life-threatening.

## GASTROPROTECTANTS

PH is common in dogs with CH, and leads to gut-wall oedema, which is at risk of ulceration. Perforation of GI ulcers causing septic peritonitis is a common cause of death in patients with chronic PH. Severe GI bleeding may also lead to the development of an acute encephalopathic crisis due to the high protein content in blood (Bexfield and Watson, 2009). The use of ulcerogenic drugs, eg. corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs), should therefore be avoided wherever possible in patients with PH. Anorexia predisposes a patient to GI ulceration, therefore ensuring adequate enteral nutrition is important. H2 antagonists (traditionally ranitidine as it does not affect cytochrome P450 system) and omeprazole are commonly prescribed to reduce the risk of GI ulceration in these patients; however, their use in these patients has not yet been supported in published studies. Cimetidine may be the preferred choice of H2 antagonist in cases of paracetamol toxicity, as suppression of the P450 enzymes may help suppress paracetamol metabolism.

## COPPER CHELATORS

These drugs should only be used in patients with significant

accumulations of copper in the liver. These drugs are not licensed for use in dogs, and can cause significant adverse reactions. Long-term use may also cause copper deficiencies in some patients. Penicillamine is the most readily available copper chelator in the UK, and the one with the most pharmacokinetic information in the dog. Penacillamine is not useful in an acute crisis as it takes weeks to months for chelation to occur. 2,2,2-tetramine tetrahydrochlodide may be more useful in acute crises (Bexfield and Watson, 2009). Zinc gluconate or acetate (given in capsules one hour before a meal) can be used prophylactically, especially in young dogs known to have copper storage disease, to reduce the absorption of copper from the GI tract and prevent the development of copper-associated hepatitis (Rothuizen, 2010).

**ANTIBIOTICS**

Most dogs with CH do not have an underlying bacterial aetiology, and do not require antibiotics. However, antibiotics may be justified in cases where a patient develops secondary infections due to a compromised reticuloendothelial system due to CH. Dogs suffering from clinical signs of hepatic encephalopathy should, however, be treated with antibiotics. Appropriate antibiotics include ampicillin, amoxicillin, cephalexin, fluroquinolones, and metronidazole due to their efficacy against enteric organisms and ability to concentrate in bile. Metronidazole relies upon hepatic clearance, and should therefore be prescribed at half the routine dose in order to reduce the risk of toxicity in animals with compromised liver function (Bexfield and Watson, 2009).

**ANTIFIBROTICS**

Colchicine is a specific antifibrotic and may be useful in dogs with moderate to marked fibrosis on liver biopsy, however it is not licensed for use in dogs. There are limited reports of its use in dogs, and severe adverse effects include marrow suppression, diarrhoea and anorexia, which occur in a significant proportion of cases. Duration of treatment is unknown, and biopsy is necessary to assess response to treatment. Many specialist medicine clinicians do not prescribe this drug routinely.

**DIETARY MANAGEMENT**

Diet should be tailored individually to fit each patient's needs. Key points to dietary management include: Feeding a highly palatable diet little and often (four to six times a day), as dogs may be inappetent. Frequent feeding also reduces the development of hepatic encephalopathy. Feed a highly digestible, good-quality protein, in normal amounts, if possible. Good-quality commercial diets should be acceptable, however if a patient's body weight or blood albumin is decreasing, additional supplementation with high quality proteins such as cottage cheese, chicken, fish and soya is beneficial. Feeding protein should only be restricted

in patients that develop HE. Fat should only be restricted in cases where dogs develop steatorrhoea. Fermentable fibre helps prevent constipation, a predisposing factor for HE. It also helps trap ammonia in the gut by acidifying the colon and also reduces bacterial ammonia production.
Dietary copper intake should be restricted in dogs that have excess hepatic copper accumulation (Rothuizen, 2010). Zinc supplementation may help reduce copper absorption form the gut. Zinc may also have anti-inflammatory, antifibrotic and antioxidant effects (Bexfield, in press).
Vitamin E may be supplemented as mentioned above.
Vitamin K supplementation is sometimes needed in patients with prolonged clotting times (especially prior to liver biopsy).
Vitamin B, a water-soluble vitamin, can also be supplemented as there can be an increase loss due to polyuria. Prognosis for patients with CH is again variable, likely due to the varieties of possible aetiologies, and stage of disease at diagnosis. Studies of dogs with CH from a variety of breeds have suggested mean survival times of approximately 14-18 months, with wide ranges within these groups. Negative prognostic indicators include the presence of ascites, and elevated total serum bilirubin, hypoalbuminaemia, prolonged clotting times and thrombocytopenia (Bexfield, in press).

## ACUTE HEPATITIS

Therapy for AH should be aimed at the underlying cause if known. However, as already mentioned in the first article of this series, most cases are idiopathic. Cases of AH may recover spontaneously with only anti-emetics (in patients which are vomiting) and fluid therapy (in those which are dehydrated or anorexic) given as supportive care (Rothuizen, 2010). It would not seem unreasonable to prescribe antioxidant treatment, eg. SAMe, to patients with AH, as oxidative intracellular damage may be part of the pathogenesis of the condition, however evidence for the positive effect of antioxidant treatment is lacking. Unless otherwise indicated (eg. for treatment of leptospirosis), antibiotic treatment should not be given in treating cases of AH as the disease is rarely caused by bacterial infection (Rothuizen, 2010). Corticosteroid treatment should be avoided due to the potential of an infectious viral aetiology (Rothuizen, 2010; and Bexfield book). Short-term nutritional support is sometimes required (Bexfield, in press).
Prognosis is variable for dogs with AH and is likely dependant on many variables, eg. underlying aetiology and how early treatment is instigated. AH may occasionally develop into CH in some dogs, with some authors also recommending routine liver biopsies four to five weeks after the diagnosis of acute idiopathic hepatitis. This recommendation is given so that the clinician can monitor for (histological) signs of disease progression from AH to CH, which would then enable appropriate and timely treatment for CH to be instigated, if necessary (Rothuizen, 2010)

## NON-SPECIFIC REACTIVE HEPATITIS

Non-specific reactive hepatitis represents a non-specific response to extrahepatic disease, especially febrile illness or inflammation somewhere in the splanchnic bed. It results as a consequence of disease occurring outside of the liver, and often does not require specific treatment of the liver. Treatment should be targeted on the underlying primary extrahepatic disease.

## AUTHOR'S NOTE

The two short articles in this series are intended to summarise the pathogenesis, clinical signs, diagnostic investigation and treatment of acute and chronic hepatitis in the dog only. Many of the drugs discussed above are not licensed for use in veterinary species, and informed owner consent should be sought before their use is considered. The reader is encouraged to refer to the references for further detail of these and other hepatobiliary diseases.

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# READER QUESTIONS AND ANSWERS

1 **TRUE OR FALSE?**
Glucocorticoids (prednisolone) can be safely given to all dogs with chronic hepatitis.

2 **TRUE OR FALSE?**
Oxidation is a significant mechanism of hepatocellular damage.

3 **TRUE OR FALSE?**
It is important NOT to restrict patients eating highly digestible good quality protein if they do not suffer from hepatic encephalopathy.

4 **TRUE OR FALSE?**
Ascites in patients with chronic hepatitis and normal blood protein levels is usually due to the development of portal hypertension.

5 **TRUE OR FALSE?**
Copper chelators should be prescribed to all dogs with chronic hepatitis.

ANSWERS: 1: FALSE, 2: TRUE, 3: TRUE, 4: TRUE, 5: FALSE