INTRODUCTION

Hepatocytes have a remarkable capacity for regeneration, which means that early diagnosis and treatment have the potential to reverse disease mechanisms and improve liver function. Treatment of acute liver disease is often supportive, but treatment of chronic liver disease should always be tailored to the findings on a liver biopsy whenever possible. In the absence of biopsy diagnosis, the results of clinical pathology and diagnostic imaging can also help to generate a picture of an individual animal’s disease, and allow supportive therapy to be instigated. However, great care should be taken when administering more specific (and potentially harmful) treatments such as steroids or colchicine without a representative liver biopsy.

The aetiology of many liver diseases in dogs and cats, especially chronic diseases, is currently not well understood, so specific treatments are not possible. Non-specific treatment aimed at slowing progression can, however, make a significant difference to the quality of life and probably also the survival time. Treatment aimed at addressing clinical signs of liver disease, including ascites, gastrointestinal ulceration leading to melena and hepatic encephalopathy is also an important part of therapy. Careful dietary management to support the liver is very important too. The aims of treatment of liver disease in dogs and cats are summarised in the box below. Unfortunately, in veterinary medicine there are a lack of controlled studies on clinical efficacy and pharmacokinetics of the commonly used drugs in liver disease. As a result, many of our current treatments protocols are either derived from human hepatology, anecdotal reports or originate from low-quality veterinary clinical studies.

The aims of treatment of liver disease are:
1) Treat the underlying cause where known
2) Slow progression if possible
3) Provide an optimum environment for hepatic regeneration
4) Manage clinical signs and complications of the disease
5) ‘Above all do no harm’ - choose drugs and drug doses carefully particularly considering the possibility of hepatic metabolism and/or toxicity

FREQUENTLY USED DRUGS

1. CORTICOSTEROIDS

The most widely used anti-inflammatories in liver disease are corticosteroids, which also have immune-modulating and anti-fibrotic properties. They have a potent indirect anti-fibrotic action via reducing prostaglandin and leucotriene production from inflammatory cells and a weak direct anti-fibrotic action by inhibiting mRNA and enzymes.

In canine liver disease their primary use is in the management of chronic hepatitis (CH). There are few or no indications in the management of other canine liver diseases. In a recent study, 36 dogs with idiopathic CH were treated with prednisolone at 1mg/kg/day for at least 6 weeks (Favier et al 2013). At follow up 11 dogs were in complete remission, eight dogs had recurrent clinical signs and 17 dogs had residual disease. The use of glucocorticoids has also been reported in retrospective studies of dogs with idiopathic CH, although as it is likely that varying doses were used, and most dogs received other medications, it is difficult to draw meaningful conclusions.
In cats the main indication for corticosteroids is the treatment of lymphocytic cholangitis/ cholangiohepatitis. Again in this disease, as yet we do not fully understand the aetiology. When using corticosteroids to treat this disease in cats the dose the author generally uses is similar to that used to treat dogs. As cats tend to be more tolerant of the side-effects of corticosteroids, it is often possible to increase this dose if an adequate response is not observed.

How long should treatment continue? In humans corticosteroids are continued for at least six months beyond remission and in cases of autoimmune hepatitis, sometimes life-long. It is often difficult to assess ‘remission’ in our cases, particularly as corticosteroids induce hepatic enzymes and so confuse attempts to follow the disease clinicopathologically. Repeat liver biopsy can be very useful, although sometimes non-representative if the disease is patchy in distribution. The length of treatment therefore remains empirical and some animals remain on life-long treatment. In this situation the aim is to use a low alternate day dose.

Adverse effects of steroids in liver disease include increased protein catabolism, fluid retention, GI ulceration and risk of infections. Their use in humans with ascites, GI ulceration and encephalopathy has been shown to decrease survival time and the same is likely to be true in dogs and cats. These are patients with portal hypertension.

Azathioprine and ciclosporine have also been used as additional, or alternative, immune modulating drugs in canine CH.

**Ciclosporin in the Treatment of Canine Chronic Hepatitis**

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“Cys proved to be effective in achieving remission based on normalization of serum ALT in canine idiopathic CH. Limitations include the retrospective nature of the study, concurrent therapies given, variability of long-term follow up, and the lack of post-treatment biopsies.”

2. ANTIFIBROTICS

In addition to the anti-fibrotic action of corticosteroids, more specific anti-fibrotics exist. Colchicine, an alkaloid that binds tubulin, may be useful in some dogs with CH and moderate to marked fibrosis on biopsy, although it is not licensed for use in animals. Although it may improve survival in some human patients with advanced fibrosis, there are very limited reports of its use in dogs. If used, care should be exercised as adverse effects, including marrow suppression, anorexia and diarrhoea, are seen relatively commonly. Again, it is very difficult to judge how long to treat for and a follow up liver biopsy is necessary to assess response. The author does not use colchicine.

3. CHOLERECTICS AND BILE ACID MODIFIERS

Ursodeoxycholic acid (ursodiol, UDCA) is a hydrophilic bile acid that displaces toxic hydrophobic bile acids and also stimulates bile flow (it is a cholerectic). These two actions reduce cell damage and oxidative stress resulting from retention of bile acids in the liver. It has also been shown to have immuno-modulatory actions by reducing immunoglobulin and interleukin production and expression of MHC-1 on hepatocytes. Recent studies show an additional anti-oxidant activity with a synergistic action with S-adenosyl-L-methionine (SAM-e) and Vitamin E. It has been used safely in many canine and feline liver cases but it is not licensed for use in small animals. It also appears to be well tolerated with no significant adverse effects reported to date.

4. ANTIBIOTICS

Antibiotics are indicated when bacterial infection is a primary cause or secondary complication of liver disease. Bacterial cholangitis is far more common in the cat compared to the dog. Bacterial infections may also be a secondary complication of many liver diseases due to decreased reticuloendothelial function. Antibiotics are also commonly used in the however a mainstay of treatment of hepatic encephalopathy.
Antibiotics should be chosen based on culture and sensitivity where possible, but often are chosen based on knowledge of likely sensitivity profile or implicated organisms. Bacteria involved are usually of enteric origin and it is particularly important to try to culture bile in ascending cholangitis cases both before and during treatment as there is a high percentage of antibiotic resistance in these cases. Antibiotics used in liver disease include ampicillin, amoxicillin, cephalaxin, fluoroquinolones and metronidazole, chose because of their efficacy against enteric organisms and concentration in bile.

Antibiotics that rely on hepatic clearance or which are potentially hepatotoxic should be avoided. These include tetracyclines, sulphonamides, chloramphenicol and erythromycin. Some caution should be exercised when using fluoroquinolones, in particular enrofloxacin, in cats.

5. ANTIOXIDANTS

These include vitamin E, zinc, silymarin (milk thistle) and SAM-e. Oxidant stress is likely to be increased in many liver diseases due to the effects of inflammation, reduced blood flow and mitochondrial damage by refluxed bile acids. Oxidation is a significant mechanism of hepatic damage, therefore antioxidant therapy is reasonable. SAM-e increases hepatic and red blood cell levels of glutathione, a potent antioxidant, and is also a critical enzyme in transmethylation, transsulfuration and aminopropylation pathways. As part of these pathways, SAM-e is essential to all cells and is particularly important in hepatocytes because of their central role in metabolism. It is widely available as a neutraceutical for dogs, sometimes in combination with silymarin.

SAM-e is particularly helpful in toxic hepatopathies in humans, such as phenobarbital-induced hepatopathy, and recent work suggests it might be helpful in chronic and acute liver diseases and in steroid hepatopathy in dogs. There is some limited experimental evidence for the use of both SAM-e and milk thistle in acute toxic hepatopathies in dogs, but little evidence available in cats.

6. COPPER CHELATORS

Copper chelators include 2,3,2-tetramine tetrahydrochloride (2,3,2-T), 2,2,2-tetramine tetrahydrochloride (2,2,2-T), penicillamine and zinc. 2,3,2-T is the more potent chelator but is not widely available in a drug formulation. Penicillamine is an alternative copper chelator, but significant adverse effects can be associated with its use. Copper chelators should be reserved for dogs in which significant copper accumulation has been identified in liver tissues, primarily those animals with copper-storage disease.

Zinc is used as prophylaxis in dogs with copper storage disease, and commercially produced hepatic support diets often contain increased zinc for this reason.

The treatment recommendations for a dog with copper-associated hepatitis are below:

- Feed a low copper diet with increased dietary zinc. Dietary management will not ‘de-copper’ the liver but will prevent further copper build up.
- Give additional antioxidants such as SAM-e and Vitamin E.
- Consider other treatments for chronic hepatitis.
- If hepatic copper levels are high or rising, consider chelation with penicillamine or 2,2,2-tetramine. Monitor blood count and serum and liver copper levels periodically if chelation therapy is used long-term and stop chelation when copper levels acceptable.
- In situations of acute hepatic necrosis and haemolysis, blood transfusions may be necessary. Consider chelation with 2,2,2-tetramine because this can chelate rapidly. Penicillamine is not helpful in the acute crisis as chelates takes weeks to months. Use other therapies as for acute hepatitis.

7. DIURECTICS

Ascites in liver disease is usually due to portal hypertension, and generally occurs with chronicity. However in some animals hypoalbuminaemia may contribute to the pathogenesis. If blood albumin is normal or near normal in the ascitic animal, portal hypertension is likely to exist. Portal hypertension leads to splanchnic pooling of blood with subsequent reduction in systemic arterial pressure and activation of the rennin-angiotensin-aldosterone system (RAAS). RAAS activation then leads to further fluid retention and more ascites. Spironolactone, an aldosterone antagonist, is therefore the drug of choice in ascitic patients with portal hypertension, although it can take 2-3 days to work. For this reason, spironolactone combined with a thiazide diuretic or furosemide (frusemide) can be used in an attempt to increase its
speed of action. Spironolactone also has the advantage that it does not induce hypokalaemia, which can precipitate HE (hypokalaemia allows ammonia to enter cells more easily).

8. GASTROPROTECTIVES
Portal hypertension is common in dogs with CH and leads to gut wall oedema and potentially ulceration. It can also occasionally occur in acute disease in both species. This is one of the commonest causes of death in dogs with chronic portal hypertension. Sudden GI bleeding can precipitate an acute encephalopathic crisis due to the high protein content of blood. An important method to reduce the incidence of GI tract ulceration is to ensure adequate enteral nutrition (see below), as anorexia predisposes to GI ulceration. H2 receptor antagonists, or proton pump inhibitors, are often used in the prevention and therapy of ulceration. However, there is some evidence that gastric pH is actually elevated in human CH, and moreover many ulcers are duodenal rather than gastric, so the rationale for these drugs is unclear. Traditionally, ranitidine is preferred as an H2 receptor antagonists in liver disease as it does not affect the cytochrome P450 system, and sucralfate should probably be also used.

DIETARY MANAGEMENT
Appropriate dietary management is as important as drug therapy in animals with liver disease. Each case is individual and the diet should be adjusted accordingly, so clinicians should resist the temptation to think that ‘one diet fits all’. In particular, many animals with liver disease are fed diets with inappropriate and excessive protein restriction, which may restrict hepatic regeneration and result in protein-calorie malnutrition. Specific recommendations include:
- Feed a palatable diet little and often (4-6 times a day) as many animals with liver disease may be inappetent. Frequent feeding also reduces the development of hepatic encephalopathy.
- Feed highly digestible, high quality protein in normal amounts whenever possible. Good quality commercial diets are acceptable. Suitable high quality proteins include cottage cheese, soya, chicken or fish, and these can be supplemented if weight or blood albumin decreases. Protein should only be restricted if necessary to control signs of hepatic encephalopathy. Excessive protein restriction may result in protein:calorie malnutrition and the breakdown of highly ammoniaogenic endogenous proteins.
- Animals with liver disease may have impaired carbohydrate metabolism, so a diet containing highly digestible, complex carbohydrates should be fed.
- Normal amounts of fat should be fed, although fat can be restricted if steatorrhoea develops.
- Fermentable fibre is helpful in animals with hepatic encephalopathy as it acidifies the colon and traps ammonia. It also increases nitrogen incorporation into bacteria and reduces bacterial ammonia production. Non-fermentable fibre is helpful in preventing constipation, a predisposing factor for hepatic encephalopathy.
- Zinc deficiency is common in human CH and is thought to also occur in dogs with CH. Supplementation reduces hepatic encephalopathy and decreases copper absorption from the GI tract and copper availability in the liver. Zinc may also have anti-inflammatory, anti-fibrotic and anti-oxidant effects.
- In dogs with excessive hepatic copper accumulation, primarily those with a primary copper storage disease, copper intake should be restricted. This includes not providing water from copper pipes in soft water areas.
- Fat-soluble vitamins include A, D, E, and K. Vitamin E is an antioxidant and can be supplemented in animals with liver disease. Vitamin K supplementation may occasionally be necessary if clotting times are prolonged, especially proceeding biopsy. Vitamins A and D should not be supplemented as Vitamin A can cause hepatic damage and vitamin D can cause calcification in tissues.
- Vitamin B, a water-soluble vitamin, can also be supplemented, as there may be increased loss associated with polyuria.

The effectiveness of dietary therapy should be monitored by the assessment of clinical signs and making sure that the patient maintains body weight and blood protein levels. Consideration should also be placed on the use of enteral feeding methods in the anorexic animal with liver disease.

REFERENCES

Center SA. Nutritional Support for Dogs and Cats with Hepatobiliary Disease. J of Nutr 1998;128;2733S-2746S