Excel CPD

Treatment of Liver Disease

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Introduction

Key points to remember:

- **BIG structural and functional reserve** which means you do not see clinical signs until late in disease – typically, until loss of 75% functional liver mass in chronic disease. See clinical signs earlier in acute than chronic disease as remaining hepatocytes have little time to take over functions of damaged hepatocytes.

- **BIG regenerative capacity of hepatocytes** (unlike kidney) – harness wherever possible. The usual approach to chronic liver disease in dogs is to REMOVE things (e.g. take away protein from the diet) but this can be very detrimental – we should instead think about ADDING things to support the liver (extra high quality nutrition, anti-oxidants etc).

Causes of acute liver disease in dogs

- Toxic/drug-induced e.g. phenobarbitone; carprofen (esp. Labrador retrievers); potentiated sulphonamides
- Infections e.g. Leptospira, CAV-1
- Bacterial endotoxaemia/septicaemia
- Acute hepatic necrosis in young Bedlingtons with copper storage disease
- Diffuse tumour infiltrate e.g. lymphoma

Causes of chronic liver disease in dogs (in approximate order of frequency)

- Idiopathic chronic hepatitis
- Neoplasia: primary and secondary
- Chronic progression of acute hepatopathy
- Congenital portosystemic shunts, portal vein hypoplasia
- True copper storage disease e.g. Bedlington terriers
- Lobular dissecting hepatitis in standard poodles and GSDs

Causes of acute liver disease in cats

- Suppurative/Neutrophilic cholangitis
- Toxic/drug-induced e.g. paracetamol, diazepam, phenobarbitone, potentiated sulphonamides
- Hepatic lipidosis
- Bacterial endotoxaemia/septicaemia
- Diffuse tumour infiltrate e.g. lymphoma
Causes of chronic liver disease in cats (in approximate order of frequency in UK – for North America, move lipidosis to first position)

- Lymphocytic cholangitis
- Neoplasia; primary and secondary especially lymphoma, biliary carcinoma
- FIP - associated hepatitis
- Vascular disorders; congenital portosystemic shunts and others
- Occasional toxoplasmosis
- Amyloidosis

TREATMENT OF LIVER DISEASE

INTRODUCTION

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 dogs at least, often the liver biopsy will give a diagnosis of ‘chronic hepatitis’ but give no idea of cause because of our currently limited understanding of this disease complex in dogs. However, it is important to differentiate chronic hepatitis from other causes of similar clinical signs such as non-cirrhotic portal hypertension, congenital portosystemic shunts, suppurative cholangiohepatitis and neoplasia and this is only possible with a biopsy. 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 including dietary treatment. However, more specific (and potentially harmful) treatments such as steroids or colchicine should NEVER be given without a representative liver biopsy. It is important to remember that the liver has a big regenerative capacity and so diagnosis and treatment as early as possible have the potential to result in reversal of disease mechanisms and return to normal liver function.

The aetiology of many liver diseases in dogs and cats, both acute and chronic, is currently not well understood, so specific treatments are not possible. Non-specific treatment aimed at slowing progression and treating the clinical signs can however make a significant difference to the quality of life and probably also the survival time. Careful dietary management to support the liver is also very important. Unfortunately there are also a lack of controlled studies on clinical efficacy and pharmacokinetics of commonly used drugs in liver disease. As a result, many of our current treatments protocols are either derived from human hepatology or anecdotal reports. All drugs must therefore be used carefully, particularly those (such as steroids) which also carry a significant risk of adverse effects.

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### Aims of treatment of liver disease

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

### Indications and actions of drugs commonly used in liver disease

#### 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, cephalexin, 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.

#### Anti-inflammatories

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. Corticosteroids are very rarely indicated in acute liver disease, not least because it is often associated with portal hypertension. They should be considered in the conditions shown in the box below.
In the only study documenting their use in cases of canine chronic hepatitis, given at 2.2mg/kg for 7-14 days, they resulted in a significant increase in survival time. However, the ideal dose and duration of treatment remain unknown. Immune-mediated hepatitis has not yet been convincingly shown to exist in dogs and dogs in Stombeck’s study did not behave like true autoimmune hepatitis cases in humans, in that they could be weaned off their treatment without any recrudescence of disease. Therefore, until further studies have been performed, it is the author’s opinion that lower (anti-inflammatory) doses can be used effectively with fewer side effects. The author uses a dose of 0.5-1.0mg/kg SID (dogs) or 1 mg/kg/BID (cats) reducing to 0.5mg/kg eod.

In cats the main indication for corticosteroids is the treatment of lymphocytic cholangitis/cholangiohepatitis, also known as chronic 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 are 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. Steroids are contraindicated in the conditions shown in the box below:
Other drugs used in liver disease which have anti-inflammatory activity in addition to their other actions include ursodeoxycholic acid, anti-oxidants such as S-adenosylmethionine (SAM-e), zinc and colchicine. Azathioprine has been used in chronic hepatitis in dogs, but until an autoimmune aetiology has been definitively described in dogs, it is difficult to justify the use of either this or other immunosuppressive medications such as cyclosporine.

**Indications:**
- Where there is biopsy evidence of ongoing inflammation
- Where there is **early** fibrosis associated with an inflammatory infiltrate
- Where infectious causes have been ruled out

**Contraindications:**
- Known or suspected infectious conditions including ascending biliary tract infection
- Advanced, bridging fibrosis or non-inflammatory fibrosis. There is no evidence they slow progression and there is a high risk of serious adverse effects as previously described because of associated portal hypertension
- Ascites. Ascites in liver disease is mainly caused by portal hypertension. The use of corticosteroids in portal hypertension may precipitate GI ulceration which in turn will precipitate hepatic encephalopathy as a result of bleeding into the intestinal lumen
- Hepatic encephalopathy (HE). Corticosteroids lead to protein catabolism and the production of ammonia and other encephalopathic compounds
- Acute hepatitis. Most cases of acute hepatitis are infectious or toxic and carry a high risk of GI ulceration. Steroids should be avoided unless there is a specific and definite indication in the patient

Antifibrotics
In addition to the anti-fibrotic action of corticosteroids, more specific anti-fibrotics exist. Colchicine may be useful in some dogs with moderate to marked fibrosis on biopsy although it is not licensed for use in animals. There are no reports of its use in cats and it should be avoided in that species. It is an alkaloid that binds tubulin and has the potential to reverse fibrosis. Although it improves survival in human cirrhotic patients, there are very limited reports of its use in dogs. It should be used with care however, as adverse effects including marrow suppression, anorexia and diarrhea can occur. In the author’s experience, the most common and limiting side effect is anorexia which causes therapy to be stopped in about half of cases. Again, it is very difficult to judge how long to treat animals and a follow up liver biopsy would really be necessary to assess response.

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**Cholerectics and bile acid modifiers**

Ursodeoxycholic acid (Destolit®, Hoehst) is a bile acid modifier. It has been used safely in many canine and feline liver cases but it is not licensed for use in small animals. It is a hydrophilic bile acid that displaces toxic hydrophobic bile acids. It 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 an immuno-modulatory action 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 SAM-e and Vitamin E. Although ursodeoxycholic acid has been widely and safely in dogs, only one single case report documents its use in this species and no reports exist in cats. It was an encouraging case report, but larger studies are needed to clarify its indications and efficacy. Currently, we believe it is potentially indicated in the majority of liver diseases in cats and dogs, particularly if there is associated biliary stasis. It should be avoided in cases of complete biliary obstruction however, because of its potential to cause gall bladder rupture, although complete cholestasis is very rare in our species.

**Antioxidants**

These include vitamin E, zinc, silymarin (milk thistle) and S-adenosylmethionine (SAM-e). Oxidative damage due to reactive oxygen species (ROS) is common in many hepatopathies due to the effects of inflammation, reduced blood flow and mitochondrial damage by refluxed bile acids. Glutathione (GSH) is the main antioxidant used by the liver to protect against oxidative damage. In liver disease SAMe production is reduced and reduced levels of GSH are therefore also found in canine and feline liver disease. SAM-e is also involved in three important metabolic pathways- transmethylation, aminopropylation and transsulphuration. The use of antioxidants such as SAM-e would thus seem logical, although in general there is no clear evidence they improve quality of life or survival.

SAM-e, which increases hepatic and red blood cell glutathione levels, is widely available as a neutraceutical. SAM-e is particularly helpful in toxic hepatopathies in humans, such as phenobarbital-induced hepatopathy, and recent work in small animals suggests it:

- Prevents oxidative damage due to acetaminophen toxicity in cats and dogs
- Minimises liver enzyme increase in dogs treated with lomustine
- Mitigate some pro-oxidant systemic and hepatic effects of prednisolone

There is also evidence for the efficacy of Silybin (silibinin, milk thistle) as a hepatoprotectant - primarily in acute experimental models of toadstool toxicity in dogs (improved survival, reduced liver enzyme). Experimentally, it has been shown to:

- Scavenge free radicals

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- Increase levels of GSH
- Protect against oxidative stress
- Stimulate bile flow and production of hepatoprotective bile acids
- Have anti-inflammatory activity

Two products contain both SAMe and silybin and the products have been shown to be absorbed well in active form, namely Denamarin (Protexin) and Zentonil Advance (Vetoquinol). The bioavailability and biological effect of a stable salt of SAMe (in Denamarin) has been documented in healthy cats, cats with cholangiohepatitis and dogs with steroid-induced vacuolar hepatopathy. Results demonstrated that it was adsorbed, significantly increased concentrations of SAMe and GSH and improved tissue redox status.

Vitamin E has been shown to be an effective anti-oxidant in canine liver disease and levels are reduced in hepatocytes in copper storage disease, so these would also be cases in which to use anti-oxidants. Zinc also has anti-oxidant activity. Note, however, that not all antioxidants are necessarily innocuous in liver disease- for example ascorbate may increase liver damage by accumulating iron, so it is best to avoid supplementing Vitamin C.

**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 available in a drug formulation. 2,2,2-T is available but not in the UK. Penicillamine is an alternative copper chelator, but significant side-effects can be associated with its use. Penicillamine is not helpful in an acute crisis however as chelation can take weeks to months. Zinc is generally used as prophylaxis in dogs with copper storage disease, and commercially produced hepatic support diets often contain increased zinc for this reason.

**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. 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. Commercially produced hepatic support diets may be too low in protein, especially for cats, and again protein supplementation may be necessary. These liver diets have other beneficial features such as increased zinc and B-vitamins, so in practice, dogs with liver disease may either be fed a commercial liver diet with extra high quality protein supplementation or

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alternatively may be fed another high quality, digestible diet such as a diet marketed for intestinal disease. Suitable high quality proteins for liver disease (i.e. with all the essential amino acids and also digestible) include cottage cheese, chicken or fish. The effectiveness of dietary therapy should be monitored by the control of clinical signs and checking that the patient maintains body weight and blood protein levels. General recommendations for dietary management of dogs and cats with liver disease are summarised below:

<table>
<thead>
<tr>
<th>Palatability: Feed a palatable diet little and often (4-6 times a day) as many animals with liver disease may be anorexic. A good diet is essential for optimising hepatic regeneration and hepatic function. Little and often feeding minimises hepatic work and signs of encephalopathy</th>
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<tbody>
<tr>
<td>Protein: Highly digestible, high quality protein should be fed in normal amounts wherever possible. Protein should only be restricted if necessary to control signs of hepatic encephalopathy. If anything, most dogs with liver disease have increased protein requirements. Supplementation with a high quality protein source such as cottage cheese could be considered, particularly when using a commercial hepatic diet. Monitoring of serum albumin can be useful to allow adjustment of dietary protein levels. <strong>All cats with liver disease should be fed unrestricted amounts of high quality protein</strong>, and cats with hepatic lipidosis should be fed as high a protein diet as possible.</td>
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<tr>
<td>Carbohydrate: Dogs with liver disease have impaired carbohydrate metabolism. Highly digestible, complex carbohydrates should be fed. Cats are no adapted to use carbohydrate as their primary energy source and are less able to utilise dietary carbohydrate than dogs so the primary consideration in cats is good protein rather than high carbohydrate diet</td>
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<tr>
<td>Fat: Feed normal amounts but only reduce if steathorrhoea develops</td>
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<td>Fibre: Fermentable fibre is helpful in animals with hepatic encephalopathy as it acidifies the colon and so traps ammonia. It also increases nitrogen incorporation into bacteria and reduces bacterial ammonia production. Non-fermentable fibre is also helpful in preventing constipation, a predisposing factor for hepatic encephalopathy. Lactulose is a synthetic disaccharide that acts as a soluble fibre. Cats are not well adapted to increased dietary fibre, which can increase taurine requirements and reduce nutrient digestibility.</td>
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<tr>
<td>Minerals: Zinc deficiency is common in humans with chronic liver disease and is thought also to occur in dogs and possibly in cats. Supplementation reduces encephalopathy and reduces copper absorption from gut and copper availability in the liver. It may also have anti-inflammatory, anti-fibrotic and anti-oxidant effects. There are no specific recommendations for zinc in cats</td>
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<tr>
<td>Copper: increased concentrations of copper can be seen in some liver diseases and so its intake should be restricted. This includes not feeding water from copper pipes in soft water areas</td>
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<td>Fat soluble vitamins: Vitamin E is an antioxidant and can be supplemented in liver disease at a dose rate of 400-600IU/day in medium-sized dogs. Vitamin k supplementation may occasionally be</td>
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necessary if clotting times are prolonged, especially proceeding biopsy. Vitamin K should be given by the parenteral route in this situation. Vitamins A and D should not be supplemented. Vitamin A can cause hepatic damage and vitamin D supplementation can cause calcification in tissues.

Water soluble vitamins: Vitamin B should be supplemented as there can be increased loss in liver disease associated with polydipsia-polyuria. Vitamin C should not be supplemented.

**Treating specific clinical signs of liver disease**

Treatment aimed at addressing clinical signs of liver disease is an important part of therapy. In most cases this will be in addition to some of the other treatments discussed above. Occasionally, in some disease such as end-stage cirrhosis for example, this will be the main aim of treatment as the disease has progressed too far for the use of anti-inflammatories or anti-fibrotics.

**Ascites**

Ascites in liver disease is usually due to portal hypertension, although in some animals hypoalbuminaemia may be important in its pathogenesis. The development of ascites due to portal hypertension in cats with liver disease is very uncommon. Blood albumin should therefore be measured first, and if this is low, increasing dietary protein levels may be all that is required to control the ascites. A high biological value protein such as cottage cheese should be used for this purpose. Other methods to increase blood albumin include the use of canine plasma or human albumin solutions, but these are usually not necessary except in acute cases.

If blood albumin is normal or near normal in the ascitic dog, 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 accumulation of 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 (Aldactide®, Pharmacia) or furosemide (frusemide) can be used in an attempt to ‘speed-up’ its onset 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). High sodium foods should be avoided. Therapeutic paracentesis should only be performed if the ascites is life threatening, which is very uncommon. Removal of the ascites can result in a precipitous drop in blood albumin followed by rapid reformation of the ascites; a concurrent plasma or albumin transfusion should therefore also be given if paracentesis is performed.

**Gastrointestinal ulceration**

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Portal hypertension is common in dogs with chronic liver disease and leads to gut wall oedema and potentially ulceration. This is one of the commonest causes of death in dogs with chronic portal hypertension. Sudden gastrointestinal bleeding can precipitate an acute encephalopathic crisis due to the high protein content of blood. These animals can become very encephalopathic while the blood is still in the gut before melaena is evident clinically, so the cause of the deterioration may not be clinically apparent.

The use of potentially ulcerogenic drugs (e.g. corticosteroids or non-steroidals) should therefore be avoided wherever possible. If such drugs are necessary, or the dog has evidence of gastrointestinal bleeding, they should be used cautiously after warning the owner of adverse effects to look out for and withdrawn immediately if there is any evidence of bleeding. Sucralfate should be used concurrently to try to protect against ulceration although there is little evidence this helps. It is also vitally important that the dog keeps eating as anorexia also predisposes to GI ulceration. H$_2$ blockers may also be used in addition to sucralfate although there is some evidence that gastric pH is often elevated in chronic liver disease and many ulcers are duodenal rather than gastric, so the need for H$_2$ blockers is unclear. Traditionally, ranitidine was preferred as an H2 blocker in liver disease as it does not affect the cytochrome P450 system. However, there are specific circumstances where cimetidine, the H2 blocker currently licensed in dogs, can be specifically indicated. For example, in toxic hepatitis such as paracetamol toxicity, suppression of drug metabolism by P450 enzymes can be helpful.

**Hepatic encephalopathy**

Hepatic encephalopathy (HE) is most commonly seen in dogs and cats with congenital portosystemic shunts (PSS) but is also seen in animals with portal hypertension and acquired PSS. Ammonia, mercaptans, short chain fatty acids and other compounds are all involved in the genesis of HE. The most important cause of HE is elevated ammonia and therefore treatment recommendations are aimed at minimising blood ammonia levels. It is important to remember that the elevated ammonia does not JUST come from the GI tract but can also come from breakdown of endogenous protein (muscle) if the animal is in negative nitrogen balance. Excessive dietary protein restriction can therefore be counterproductive in some cases (Shawcross and Jalan 2005). Acute encephalopathic crises are relatively rare, but require intensive management. Treatment recommendations are summarised below.
**Summary of treatment of acute encephalopathic crises.**

| Identify, remove and treat any precipitating causes such as gastrointestinal bleeding, constipation, metabolic alkalosis, hypokalaemia, azotaemia or inflammatory disease |
| Nil by mouth for 24-48 hours |
| Intravenous fluids- crystalloids (some say to avoid lactated ringers (Hartman’s solution)) |
| Avoid/treat hypokalaemia - measure potassium regularly and supplement fluids as necessary especially in cats |
| Avoid/treat hypoglycaemia as this can cause irreversible brain damage and seizures. Measure blood glucose frequently and supplement fluids as necessary |
| Warm water/lactulose enemas to remove any source of ammonia from the faeces. Can be followed by a neomycin retention enema |
| Ampicillin iv to protect against bacteraemias |
| Gastroprotectants if evidence of gastrointestinal bleeding – iv ranitidine (avoid cimetidine as this is metabolised by the liver). Oral sucralfate only once the animal is able to swallow |
| Commence feeding of a high quality diet little and often after 24-48 hours. Continue with long term treatment of HE as discussed below |
| Use a low dose propofol infusion if fitting (1mg/kg bolus followed by 0.1-0.2 mg/kg/min infusion-to effect). Intravenous diazepam can be tried first but tends to be less effective in these cases |

Most animals have lower grade waxing and waning signs such as hyperactivity and/or depression, pacing, circling, ataxia, central blindness and hypersialosis (especially in cats). Management recommendations for these patients include:

- Traditionally, dietary management has revolved around protein restriction to reduce ammonia absorption from the colon. However, more recently it has been questioned whether colonic ammonia absorption is really significant, except in dogs on poor quality diets with poorly digestible protein. On good diets, there should be no protein remaining undigested in the colon and the most significant source of gut ammonia is likely to be glutamine metabolism by small intestinal enterocytes which is unavoidable. Endogenous ammonia production is also probably important and inflammatory mediators can also be encephalopathic. Excessive protein restriction should therefore be avoided however, as this may result in the breakdown of highly ammoniaogenic endogenous proteins. A high quality, very digestible protein should be fed little and often in normal amounts. Monitor the effectiveness of treatment by regular weighing, body condition scoring and checking blood albumin levels. Increase protein levels in diet if blood protein levels fall or the dog looses weight. The author’s choice of a supplementary protein source in these cases is cottage cheese.

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• Long term antibiotics to control gut flora and thus reduce protein breakdown in the gut. Ampicillin, amoxicillin or metronidazole are suitable choices.
• Lactulose as a fermentable fibre source to reduce the production and absorption of ammonia and speed gut transit.

The true efficacy of both antibiotics and lactulose have recently been questioned in man and there are no studies in dogs to support or reject their use. Anecdotally, they seem to help some dogs whereas others are managed life long without them. The author recommends that clinicians ‘titrate’ their use in individual cases based on clinical response until further information is available.

**Treating some specific liver diseases**

**Acute hepatitis**

Acute hepatitis is uncommon and is usually caused by acute infections or toxins (see earlier). It carries a poor prognosis in dogs and cats but there is potential for complete recovery if the animal can be nursed through an acute crisis. The treatment involves non-specific intensive management and is outlined in the table below:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Description</th>
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<tbody>
<tr>
<td>Treat the cause if known: e.g. antibiotics for leptospirosis, stop hepatotoxic drugs, N-acetylcysteine for paracetamol toxicity</td>
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<tr>
<td>Diet: Nil <em>per os</em> until vomiting ceases then a palatable low fat diet. <strong>Do not restrict protein</strong> as this may inhibit hepatocyte regeneration</td>
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<tr>
<td>Anti-oxidant support during recovery, particularly for toxic liver damage where glutathione depletion is present- Vitamin E and SAM-e</td>
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<tr>
<td>Intravenous fluid support. Dextrose saline usually best. Monitor serum potassium and supplement to fluids as necessary. Monitor renal output carefully- maintain urine output, but do not over-infuse as this may worsen ascites. Avoid central catheters unless coagulation status known</td>
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<tr>
<td>Measure blood glucose every few hours as this can become very low in acute hepatitis</td>
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<tr>
<td>Treat hepatic encephalopathy</td>
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<tr>
<td>Treat any gastrointestinal ulceration</td>
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<tr>
<td>Control vomiting. Note that the anti-emetic medication maropitant (Cerenia®, Pfizer) is contraindicated in animals with liver disease</td>
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<tr>
<td>Treat any ascites with spironolactone ± furosemide or a thiazide diuretic</td>
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</tr>
<tr>
<td>Antibiotics: consider use in all cases to protect against infectious complications and to reduce gut flora to reduce HE. Should definitely be used in dogs with pyrexia and other evidence of infectious complications. Use broad spectrum agents safe for use in liver disease such as ampicillin, amoxicillin, metronidazole and fluoroquinolones. Use iv in the acute stages</td>
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Copper storage disease in Bedlington terriers

This disease is a primary copper storage disease, and appears to be due to a defect in the transport of copper from the hepatic lysosomes to the biliary tree. Recent work has identified the gene involved to be COMMD1 (formerly MURR1), although the exact function of the protein it encodes remains unknown. It is inherited as an autosomal recessive trait and up to 60% of Bedlington Terriers in some countries have been affected in the past, although the incidence is reducing with genetic testing and selective breeding. The Animal Health Trust in the UK offers a genetic test based on identifying the defective gene, COMMD1, for identifying affected dogs.

It has also suggested a primary copper storage disease in Dalmatian dogs and some West Highland white terriers and Labrador retrievers. Anecdotally, Dalmatians with copper storage disease have been reported in the UK whereas to the author's knowledge, no cases of copper storage disease have been reported in UK Labrador retrievers. Many other breeds of dog can show secondary hepatic copper deposition in chronic liver diseases, but this accumulation is usually peri-portal and thought to be secondary to cholestasis. This distinction is important as copper chelation is needed in primary copper storage disease but is probably unnecessary in secondary disease.

In spite of the increased awareness of the disease and the availability of genetic testing, middle-aged Bedlingtons still present with chronic hepatitis as a result of copper accumulation. This is easily prevented by feeding by feeding a restricted copper diet from early life. It is obviously important not to put a growing Bedlington terrier on a veterinary diet formulated for liver disease, because although low in copper, they are also low in protein so not appropriate for growth. A number of maintenance dog foods are low in copper and these would be safer for a growing puppy. Care should also be taken to avoid high copper tit-bits such as liver, kidney, shellfish, cereals, chocolate and legumes. Avoid tap water in soft water areas because of copper in the pipes.

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 including ursodeoxycholic acid.
- 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.

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Canine chronic hepatitis
It is important to initiate therapy as early as possible in canine chronic hepatitis to try to inhibit fibrosis and cirrhosis. While specific and effective measures are not proven for canine chronic hepatitis, even non-specific and supportive treatments may lead to marked improvements in the quality of life. Consideration should be given to:

- Diet: A palatable high quality protein diet supplemented with zinc, B Vitamins and anti-oxidants should be fed. Do not restrict protein intake excessively unless signs of HE. Monitor serum albumin and adjust protein intake accordingly. Feed little and often to reduce hepatic work.
- Ursodeoxycholic acid is probably beneficial in animal with CH
- Anti-oxidants (SAM-e and vitamin E) are probably warranted in all cases
- Consider prednisolone if there is significant inflammation especially if this is associated with early fibrosis.
- Consider antibiotics if there is a significant neutrophilic component to the inflammation or there is an ascending infection.
- Treatment of ascites with spironolactone ± furosemide or a thiazide diuretic.
- Treatment of HE with antibiotics, diet and lactulose (see above).

Congenital portosystemic shunts
Congenital portosystemic shunts (PSS) can be surgically treated, although some dogs and cats also respond well to long term medical management. Prior to surgical treatment, all animals should first be ‘stabilised’ with medical management. Medical management resolves around therapies aimed at aimed at minimising hepatic encephalopathy (see previously).

Suppurative cholangitis
Suppurative (acute/neutrophilic) cholangitis occurs more commonly in cats than in dogs. It presents usually as an acute disease with signs of malaise, inappetence, vomiting, pyrexia and jaundice. Blood tests reveal the presence of a leucocytosis with neutrophilia, increased ALT, GGT and TBIL. Ultrasonography sometimes reveals abnormalities of the gall bladder wall or content but again a liver biopsy is required for a definitive diagnosis.
As it is usually caused by an ascending bacterial infection from the gut, treatment involves antibiotics. If possible these should be based on culture and sensitivity, usually from a sample of bile taken from the gall bladder at laparotomy or ultrasound-guided fine needle aspiration. However, failing that antibiotics which are safe in liver disease and have a broad spectrum of activity against gut bacteria are selected. *E.coli* is frequently encountered, so therapy should use an antibiotic with
action against this organism. Other organisms reported are all of gut origin and include *Enterococcus spp.*, *Klebsiella spp.*, *Clostridium spp.*, faecal *Streptococcus spp.*, *Corynbacterium spp*, and *Bacteroides spp*. Suitable examples include penicillin's, cephalosporin's and fluoroquinolones. However, it should be appreciated that a significant number of isolates show antibiotic resistance and some will develop resistance during therapy. This underlines the important of obtaining a culture and sensitivity of bile wherever possible and or repeating it during treatment if the response is poor. Antibiotic treatment should continue for a minimum of four weeks. In addition it is advisable to use ursodeoxycholic acid to encourage bile flow. Dietary therapy should revolve around using a high quality protein diet. There is no real reason to use a specific hepatic diet in this condition as these may be too protein restricted and in fact, since this is predominantly a septic disease, critical care diets would be more appropriate.

**Lymphocytic cholangitis**

This is again predominantly a disease of cats, although it is occasionally recognised in dogs. It is thought that it may have an immune-mediated aetiology, although this has not been proved. This form of cholangitis behaves very differently from the suppurative form. There is no acute onset of the disease and many cases progress slowly for 6 months to several years. Lymphocytic cholangitis occurs quite regularly in cats and in the UK there is a clear predisposition in Persians. Cats with this disease have variable signs but generally remain relatively bright (compared to the suppurative disease) and have variable appetite, vomit occasionally and gradually lose weight. Occasionally cats have ascites or jaundice. Blood tests reveal increases ALT and bile acids in most cases and nearly all cats have increased globulins.

Current advice for treatment resolves around immunosuppressive doses of steroids, gradually reducing, combined with ursodeoxycholic acid. There is disagreement about the use of antibiotics but, while the aetiology remains uncertain their use would seem wise. Dietary management in cats involves the use of high a quality, normal protein level
Hepatic lipidosis occurs in both cats and dogs but is most clinically significant in cats. Hepatic lipidosis can be primary (idiopathic) or secondary to other conditions such as pancreatitis or diabetes mellitus. Primary lipidosis is a disease of cats seen most commonly in North America, although it is also recognised in the UK. It causes a high mortality unless treated aggressively. It is most commonly recognised in previously obese cats which have become anorexic, although it can also occur in ‘thin’ cats. It causes acute liver failure due to the swelling of hepatocytes and the mortality is high unless the animal is intensively treated. Although the pathophysiology remains incompletely understood, the primary cause is anorexia and lack of protein combined with stress. Clinical signs are related to the acute loss of hepatic function together with hepatocyte swelling causing intra-hepatic cholestasis. Affected cats typically become markedly jaundiced and show hepatic encephalopathy usually manifesting as marked depression and anorexia. The diagnosis involves demonstration of hepatocytes swollen with lipid, together with ruling out any underlying cause as far as possible. FNA of the liver is usually sufficient to make a diagnosis. Blood results demonstrate marked elevation in hepatocellular and cholestatic enzymes. A hallmark of HL in cats is a very high ALP with a disproportionately low GGT. Most cats also have elevated TBIL. Radiographs and ultrasound usually reveal hepatomegally and the liver appears hyperechoic.

Specific therapy involves feeding the cat a high protein diet. Cats will often not eat by themselves and require placement of a gastrotomy tube, sometimes for several months. Treatment recommendations for cats with hepatic lipidosis are shown below:

- Treat any identifiable underlying cause
- Combine this with nutritional support via a gastrostomy tube or eosophagostomy tube for 4-6 weeks. A naso-oesophageal feeding tube can provide some temporary feeding support prior to GA for placement of a more permanent tube. Feed a high protein diet (such as intensive care diets or concentration diets). Some authors advocate the additions of extra nutrients such as taurine, vitamin B or carnitine, although there is no firm evidence this is necessary.
- HE may occur and should be managed by little and often feeding rather than reducing protein intake. Ampicillin and lactulose should also be used if this occurs.
- Anti-emetics and pro-motility agents such as ranitidine and metoclopramide may be necessary if the cat is vomiting or has delayed gastric emptying with reflux of food up the feeding tube
- I.V. fluid support in the early stages and careful monitoring of blood glucose and potassium are essential. There is no evidence that adding insulin to the fluids helps in non diabetic cats with lipidosis and in fact it increases the risk of serious hypokalaemia and hypophosphataema.
Drug toxicity

Almost any drug can cause liver disease by either dose-related or idiosyncratic mechanisms. Most cases of drug toxicity result in acute hepatitis, although this can progress to chronic hepatitis with fibrosis and cirrhosis, particularly when the drug is administered chronically. Some of the more commonly implicated drugs include paracetamol, diazepam, phenobarbitone, primidone, potentiated sulphonamides, tetracyclines and carprofen particularly in Labrador retrievers.

The treatment for a suspected drug reaction should involve removal of the offending drug and supportive therapy as above. In addition, more specific treatments exist for certain toxicities including:

- **Paracetamol** (acetaminophen): The antidote is N-acetylcysteine which binds the toxic metabolite and increases the glucuronidation process. SAM-e may also be beneficial as it can replenish glutathione which inactivates the toxic metabolite.

- **Diazepam**: Acute fulminant hepatic necrosis with a high mortality has been associated with repeated oral administration of diazepam to cats. All reported cases had been receiving diazepam orally for at least five days with total daily doses ranging from 1.25 to 2.5 mg. Five of 11 cats became lethargic, ataxic, and anorectic within 96 hours of initial treatment. All cats became jaundiced during the first 11 days of illness. Unlike phenobarbitone, diazepam does not induce hepatic enzymes in normal animals; therefore a key finding is a sudden dramatic increase in hepatic enzymes, particularly ALT. In the above case series, serum biochemical analysis revealed profoundly high ALT and AST activities. Ten cats died or were euthanatized within 15 days of initial drug administration, and only 1 cat survived. Treatment involves immediate and complete withdrawal of the drug and aggressive support as outlines above.

- **Potentiated sulphonamides**: These drugs can cause a variety of adverse reactions by both dose-related and idiosyncratic mechanisms. One of the manifestations of sulphonamide hypersensitivity is acute hepatopathy, and it can occur in as little as 5 days of treatment and is an idiosyncratic, not dose-related, phenomenon. Clinical signs and treatment are as for other cases of acute hepatitis and the drug must be withdrawn immediately. In addition, it has been suggested that N-acetylcysteine (a glutathione precursor also indicated for paracetamol toxicity) is helpful.
- **Phenobarbitone**: Chronic phenobarbitone administration has been associated with an acute hepatic necrosis and also chronic hepatitis and cirrhosis in dogs. Toxicity is uncommon but hepatic enzyme induction is very common. The potential for hepatotoxicity may be increased by concurrent medication with other drugs requiring hepatic metabolism so this should be avoided if possible. It is important to monitor blood levels regularly as many dogs that develop hepatotoxicity have serum concentrations at, or above, the therapeutic range and have been on the drug for >5 months. If seizures are not controlled at a high blood concentration the addition of another drug which does not require hepatic metabolism should be considered (potassium bromide or gabepentin). If hepatotoxicity does occur, if possible the drug should be withdrawn or the dose significantly reduced. Reductions in phenobarbitone dose of between 25% and 100% have been shown to be sufficient to resolve toxicity in most cases. In addition, SAM-e appears to be particularly useful in phenobarbitone toxicity as it is a precursor for antioxidant and detoxifying systems in the liver.

A different subset of dogs with phenobarbitone toxicity present with superficial necrolytic dermatitis (hepatocutaneous syndrome) in the absence of other signs of hepatic failure. The liver appears very different on examination from those of dogs with phenobarbitone-induced hepatitis, and is described as having a ‘Swiss cheese’ appearance on ultrasound. The mechanism for phenobarbitone-induced superficial necrolytic dermatitis is unknown but it may be due to induction of excessive amino acid metabolism in the liver and therefore peripheral (skin) deficiency. It has therefore been recommended that these cases be treated with amino acid supplementation in the form of an i.v. infusion or egg white.