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Liver and Pancreatic Disease Mini Series

Session Two: What's Gone Wrong and How Can I Help Fix It?

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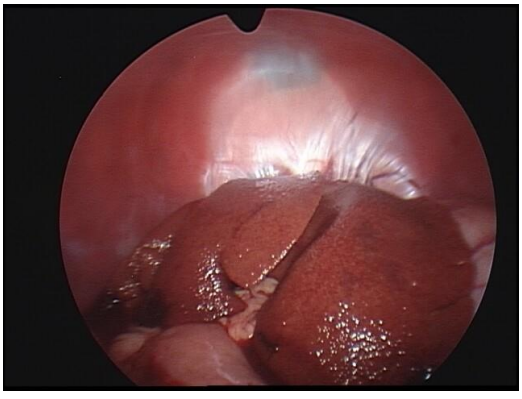

Session 2: Hepatic disease

Liver disease: what's gone wrong and how can I help fix it?
The second of the sessions in this mini-series focuses on diseases of the liver and will follow the WSAVA liver standardization group classification that was published in 2006. This groups liver diseases into vascular disorders, parenchymal disorders, neoplasia and lastly disorders of the biliary tract (which will be covered in the final session alongside pancreatic diseases). The session will also include discussion of some of the complications of liver disease including the management of ascites, hepatic encephalopathy and coagulopathies.

Hepatic vascular disorders
The WSAVA standardization group categorised vascular liver disease into one of 3 broad groups. Congenital portosystemic shunts (which may be intra or extrahepatic and are usually single vessels, although rare multiple vessels have been reported), portal vein hypoplasia which can occur with and without portal hypertension (portal vein hypoplasia without portal hypertension used to be referred to as microvascular dysplasia) and disturbance to flow leading to portal hypertension and the formation of secondary acquired shunts.

Congenital portosystemic shunts are anomalous vessels that form vascular communications between the portal and systemic circulations, thus allowing portal blood to bypass the liver. Roughly two thirds of congenital portosystemic shunts are extrahepatic, and these are most commonly seen in small breed dogs, with breed predispositions reported in Yorkshire Terrier, Maltese Terrier, Havanese Terrier, Dandie Dinmont and Pug. The other third of portosystemic shunts occur within the hepatic parenchyma and are most common in large breed dogs, with Irish Wolfhound, Labrador and Golden Retriever, Australian Shepherd and Australian Cattle Dog reported as predisposed. Portosystemic shunts are also reported in cats, although much less commonly than dogs. Apparent breed predispositions include the Domestic Short Hair and Oriental breeds.

Portal vein hypoplasia is congenital condition of the liver in which the portal circulation is undeveloped. This can occur either with or without portal hypertension. Portal vein hypoplasia without portal hypertension was previously called microvascular dysplasia and describes shunting of blood into the systemic circulation within the liver itself. This occurs on a microscopic level within blood vessels within the hepatic lobules allowing blood to bypass the hepatic sinusoids. Several breeds appear predisposed including Yorkshire terriers and Cairn terriers [in which an autosomal mode of inheritance is suspected. The condition can occur in isolation or in association with the presence of congenital portosystemic shunts and has rarely been reported in cats.

Portal vein hypoplasia with portal hypertension was previously called non-cirrhotic portal hypertension and occurs due to severe under development of the portal vasculature, which leads to increase portal pressure and hypertension. The increase in portal pressure leads to embryonic veins being recanalised, allowing the development of multiple acquired portosystemic shunts. Portal vein hypoplasia with portal hypertension has rarely been reported in cats.

Disturbance of flow that lead to an increase in portal are either the result of severe parenchymal liver disease such as cirrhosis or increase flow within the portal vein as seen with hepatic arterio-venous malformations. Severe parenchymal disease leading to fibrosis obstructs the flow of blood through the hepatic sinusoids resulting in portal hypertension and the development of acquired portosystemic shunts. Very rarely hepatic arterio-venous malformations are documented. In dogs and cats these are congenital malformations with connection of the hepatic arterial circulation to the portal vein. This leads to portal hypertension, and the subsequent development of multiple acquired portosystemic shunts. Acquired arterio-venous malformations have been documented in people secondary to surgery or trauma, but these can have not yet been document in companion animals.

Congenital portosystemic shunts are the most common cause of hepatic encephalopathy in cats and dogs, however all vascular conditions that lead to portal blood entering the general circulation have the potential to lead to signs of hepatic encephalopathy and these signs may be acute or chronic in nature, varying from vague listlessness and lethargy, through to acute seizures. Signs may have been present since birth but in some cases signs of a portosystemic shunt may not have become evident until later in life and some shunts are picked up incidentally. Both dogs and cats may have a history of unusual behaviour [pacing, head pressing staring into space], depression or seizures. Often these signs are worse post parandially. Gastrointestinal signs such as vomiting and diarrhoea are uncommon, but haemorrhagic diarrhoea is occasionally seen, especially if there is an elevation in portal pressure. Inappetance is relatively common and cats with hepatic encephalopathy will often salivate profusely. Polyuria and polydipsia are commonly reported, although sometimes this is subtle in nature. The presence of ammonium biurate calculi and urinary tract infections can lead to signs of dysuria and stranguria.

On physical examination most animals with hepatic vascular disorders are in poor body condition. Enlarged kidneys is often seen in animals with portosystemic shunts, the reason and consequences of this are unclear and probably not of clinical significance. Cats with congenital portosystemic shunts often have copper coloured irises. Unless there is portal hypertension the presence of ascites is uncommon. Jaundice is usually only see if there si severe hepatic dysfunction (e.g. in cirrhosis). A soft heart murmur which appears flow-related in origin may be heard. It is usually soft, systolic and has a point of maximal intensity over the left ventricular outflow tract. The haemodynamic effects caused by turbulence in hepatic arterio-venous malformations can lead to dilation or aneurism formation. This turbulence can occasionally be heard as a bruit or murmur on abdominal auscultation.

Haematology often reveals a mild anaemia with the cells often microcytic and hypochromic in nature. This thought to be the result of alterations in iron metabolism as a result of the shunting vessel. Target cells are also commonly seen due to disruptions in cholesterol metabolism. Congenital vascular disorders such as congenital portosystemic shunts rarely lead to significant liver enzyme elevations; however liver enzymes will be elevated with liver disease and marked elevations in bilirubin may also be seen. Signs of hepatic dysfunction are common. Roughly half of dogs with congenital portosystemic shunts have hypoalbuminemia, with two thirds have a reduction in urea; this pattern of findings is also common in cats. Between a third and a half of dogs with portosystemic shunts will have biurate crystals. Mild elevations in UPC ratio are also commonly seen which are likely to reflect mild glomerular disease. Elevated post-prandial bile acids are reported as 100% sensitive for hepatic vascular anomalies. However they are poorly specific and do not differentiate vascular disorders from other cases of hepatic disease. Fasting ammonia or post parandial ammonia levels (taken at 6 hours) are less sensitive for detecting vascular disorders but can be useful when animals cannot be fed or when bile acids are difficult to interpret e.g. in Maltese terriers. Ammonia tolerance tests are more useful, however giving ammonia is contraindicated in dogs that are showing signs of hepatic encephalopathy.

Ultrasonographic evaluation of the liver is good way of evaluating the blood supply to the liver, however the technique is dependent on the skill of the operator and the ability of the machine. Evaluation of the presence of portosystemic shunts depends on their location, with shunts with in the liver tissue being easier to identify. Visualisation of extra hepatic portosystemic shunts depends on their location and identification can be complicated by the presence of gas with in the small intestine. Hepatic parenchymal changes are usually fairly apparent on ultrasonography, however should not be present with congenital portosystemic shunts. Sever parenchymal disease will lead to hepatic changes and this is usually obvious as changes in echotexture and a nodular appearance. Evaluation of hepatic size is more difficult on ultrasound however most vascular disease will be associated with a small liver. Evaluation of the portal vein will allow identification of blood flow and measurement of portal pressure. Arterial malformations are usually identified easily due to their high pressure flow on Doppler ultrasound and secondary shunts usually appear as a tangle of vessels, which are most commonly seen near the right kidney.

Computed tomography with contrast to allow evaluation of the portal vasculature is more accurate in identifying portosystemic shunts. This can be a very useful technique in evaluating shunts with a tortuous course (e.g. portal azygous connections) or in large breed or obese dogs where the quality of abdominal ultrasound is reduced. CT angiography is also necessary for the closure of intrahepatic portosystemic shunts by interventional radiology (see later). Scintigraphy, performed by following radioactive tracers placed in the colon or injected into the spleen through the portal system, have been used to document portosystemic shunts. This allows documentation of the presence of a shunt and estimation of the shunting fraction, but is difficult due to the restrictions on handling radioactive materials, thus is rarely performed in the UK.

Medical therapy focuses on the treatment of hepatic encephalopathy [see later] and whilst surgery is possible for congenital portosystemic shunts and arteriovenous malformations, medical management is the only option available for portal vein hypoplasia and shunts that have formed secondary to liver disease. The long term outcome for dogs with congenital portosystemic shunts with medical management is good with a recent study showing no difference in survival between medically and surgically managed cases. Logically surgery, especially if there is a large shunting fraction should return normal liver anatomy and should be considered where finances allow, however if this is not possible many dogs with low volume shunts may manage very well on medical management alone.

Surgery aims to restore the normal blood supply to the liver, allowing the liver to develop and grow with its increased blood supply. Complete shunt ligation is uncommon [around 1 in 5 dogs with intrahepatic shunts and 1 third to a half of dogs with extra hepatic shunts] as a result a variety of surgical techniques have been described to allow gradual occlusion of flow through the portal vein. These include the placement of ameroid constrictors [these are rings that contain a resin with swells gradually over a number of days], hydraulic occluding devices, staged surgical banding and cellophane banding in an attempt to cause fibrosis leading to more gradual occlusion over the longer term.

Surgical mortality rates reported are very variable, with cats having higher rates of complications compared to dogs and those the intrahepatic shunts being more difficult to occlude. In dogs mortality rates of 2-20%, complication rates of 9-50% and a good to excellent outcome in 80-85% of patients with extra hepatic portosystemic shunts have been reported. For dogs with intrahepatic shunts these figures are slightly less good [mortality rates of 15-25%, complication rates of 30-50% and a good to excellent outcome in 55-85% of patients]. In cats reports document complication rates of 40% and a good outcome in 60-70%. Rates of surgical complications appear to be lower with strict 3-4 week periods of medical management prior to surgery; attenuation of a congenital shunting vessel should not be viewed as an urgent procedure, although there are situations were liver function is markedly reduced leading to systemic consequences (oedema and ascites) - in these cases it is probably that the liver disease is multifactorial and concurrent portal vein hypoplasia is often present.

Given the difficulty of identifying intrahepatic portosystemic shunts, dissecting them and ligating them, recently a new interventional radiology technique of percutaneous transjugular coil embolization has been described. Under fluoroscopy access to the shunt is gained using long wires and catheters through a sheath placed in the jugular vein. Contrast is then injected into the caudal vena cava and the shunting vessel at the same time to allow identification of the anatomy. Once the shunting vessel has been identified a stent is placed across the junction of the shunt with the caudal vena cava. This has been measured previously form CT evaluation and should span the opening by around 2cm on either side of the shunt's opening. Thromboembolic coils can then be placed into the entrance of the shunt and these are caught against the stent. Over time the coils thrombose and there is a reduction in blood flow. This is a much less invasive technique compared to open surgery, although the implants are expense. Long term outcome appears similar at this stage to that of open surgery although there are fewer potential procedural complications.

Outcome in dogs with portal vein hypoplasia is less well described. One case series reported 92% of dogs with portal vein hypoplasia without portal hypertension had a good long term outcome with most dying of diseases unrelated to the liver. Dogs portal vein hypoplasia and portal vein hypertension had less favourable outcomes with 44% reported to have a good long term outcome in one report, however many of these the dogs in the non-survivor group were euthanased at the point of diagnosis, so long term outcome is difficult to determine ad there may be a favourable response to medical therapy. Animals that have acquired portosystemic shunts have poor prognoses due to the underlying liver disease. Animals with arterio-venous malformations may have a good outcome if surgery is successful; however there is a fair risk of operative complications and some malformations are not resectable. The prognosis of medical management alone for this condition is unknown.

There are main potential complications post shunt ligation, thankfully most are mild and easily treated or avoided. Portal hypertension can occur from too aggressive constriction of the shunting vessel at surgery or if a gradually occlusive devise is used such as an ammeroid constrictor or cellophane band, that this has become thrombosed or kink after placement. Usually ascites is the first clinical sign accompanied by abdominal pain, gastrointestinal ulceration and haemorrhage [which may be severe enough to be life threatening]. If mild ascites is present then this may just be tolerated, however if there is more severe change it may be that surgery and removal or adjustment of the device is needed.

It is also possible that signs of hepatic encephalopathy may worsen after surgery and there are multiple reasons why this may occur. These include: hypokalemia, hypovolemia, acidosis, hypoglycaemia, coagulopathies and sepsis. Seizures are also relative common post shunt ligation, as well as blindness, especially in cats [45% in one case series]. These can be immediate or develop over the 7 days after surgery. Careful monitoring for signs of recurrent hepatic encephalopathy, which may develop as a result of failure of shunt occlusion, development of secondary acquired shunts due to portal hypertension or microscopic shunting (portal vein hypoplasia, previously referred to as microvascular dysplasia).

Seizures can be difficult to control and a propofol infusion or loading with levetriacetam (Keppra) is suggested. The pre-operative administration of levetriacetam has also been shown to reduce the frequency of seizures reported post-surgery. Cat should be taken with cats being administered a propofol infusion due to the risk of Heinz body anaemia. With intractable seizures, the administration of dexamethasone should be considered (0.1mg/kg) as some dogs have a good response; the reasons for this are unclear. Increased intra-cranial pressure may also develop in some dogs manifested by severe neurological signs, a Cushing's reflex and the presence of papilloedema. Mannitol infusion should be given (0.5-1g/kg over 10-20 minutes and the response evaluated and infusions repeated as needed.

Medical management of hepatic encephalopathy is important prior to and following surgery [see notes below]. The optimum period for medical management following surgery is unclear, however following surgery medication is usually maintain for a 4-6 week prior before evaluation of hepatic parameters and hepatic imaging where appropriate. Once liver function is improved medication is gradually withdrawn, with antibiotic therapy stopped first, followed by lactulose 4-6 weeks later and dietary changes after a further 4-6 weeks. It is important to note that post prandial bile acid concentrations are frequently elevated in dogs following PSS surgery, especially in intrahepatic portosystemic shunts where complete occlusion is rarely seen. The elevation in bile acids in these cases rarely correlates with outcome and oftern dogs with intrahepatic portosystemic shunts have very good long term prognoses with a significant reduction in shunting fraction. Where patients have significant elevations in bile acids or there are signs of hepatic dysfunction on biochemical analysis (e.g. persisting low levels of albumin, cholesterol and BUN) then further evaluation should be performed, with consideration of further attenuation of the shunt where appropriate.

Hepatic parenchymal disorders

Chronic hepatitis

Chronic hepatitis the most common liver disease in dogs but is rarely seen in cats. Its aetiology is poorly understood condition. The distinction between acute and chronic hepatitis is made on hepatic biopsy and is assessed by the presence or absence of significant fibrosis. Due to the fact that patients with chronic hepatitis may suffer periodic flare ups of their disease the management of patients with both acute and chronic hepatitis is considered together. Left untreated the fibrosis will progress to cirrhosis leading irreversible changes within the liver architecture and death.

The pathogenesis of chronic hepatitis is poorly understood. There are many theories and influences on the development of the condition and these include: genetic influences, which are currently poorly defined, however certain breeds are predisposed to chronic hepatitis, and within certain breeds, there appears to be a gender predisposition (e.g. female Dobermans, male Cocker Spaniels). Metabolic defects such as excessive copper accumulation is a recognised cause of chronic hepatitis in certain breeds such as the Bedlington Terrier and Dalmatian {see later for more information of Copper-associated hepatitis]. Excessive iron accumulation has been seen in approximately 80% of dogs and 50% of cats with various chronic hepatopathies. Iron accumulation is usually a secondary consequence rather than a cause of the chronic hepatitis, it is important as iron has both a pro-inflammatory and pro-fibrotic effect. Autoimmunity may play a role and Dobermans with chronic hepatitis have alterations in hepatocyte MHC II expression compared to healthy Dobermans. Increased circulating concentrations of anti-nuclear antibodies (ANA) and anti-liver membrane antibody have also been shown in some dogs. There is some evidence that dogs with CH occasionally respond to immunosuppressive doses of prednisolone. Infectious agents also play a role with bacteria ascending the biliary system leading cholangiohepatitis in dogs [see session 3]. A recent study looking for evidence of Adenovirus, Parvovirus, Leptospirosis or human hepatitis A, C and E infection in dogs with a variety of chronic hepatopathies did not show any convincing evidence that these infectious agents play a role in the development of canine chronic hepatitis. Many drugs and toxins (e.g. phenobarbitone) can cause hepatitis

Most dogs will be diagnosed in middle age (4-7 years old) and will often present with very vague signs such as inappetence, GI disease, lethargy, occasionally PU/PD. Jaundice and ascites relatively uncommon. Often this presentation is quite late in the disease course making therapy difficult as often there is great than a 70% reduction in liver function before clinical signs develop. Canine chronic hepatitis is recognised in wide variety of dog breeds including cross breeds but papers consistently document increased incidences in certain specific breeds, which include: American and English Cocker spaniels (males more than females), West Highland White terriers (no apparent sex predisposition), Skye terriers (no apparent sex predisposition), Dobermans (strong female predisposition) and Labrador retrievers (female bias).

Blood work may show elevations in ALT as well as elevations in other enzymes. Occasionally there are elevations in bile acids and bilirubin. Hypoalbuminemia is present in about 40% of dogs with chronic hepatitis and 75% of dogs where the chronic hepatitis has progressed to cirrhosis. As a result low albumin may be associated with a poor prognosis.

Diagnostic imaging usually reveals non-specific changes, but is useful to assess liver size, the portal vasculature, the biliary system and evidence of nodular change suggestive of possible cirrhosis. A liver biopsy is essential for the diagnosis of chronic hepatitis as it not only allow diagnosis, but establishment of prognosis [the degree of fibrosis and damage present] and guides therapeutic decisions (for example is there a significant accumulation of copper present). Changes seen can be very variable and initially consist of necrosis of varying severity, associated with mild to moderate infiltrates of lymphocytes and plasma cells. May have occasional neutrophils but a predominately suppurative infiltrate would suggest an infectious aetiology. In later stages, evidence of cirrhosis (fibrosis, biliary hyperplasia, nodular regeneration) will predominate.

Where possible the identification and removal of an underlying cause will be the most effective treatment strategy for example addressing copper levels (see below) or removing medication e.g. switching therapies from phenobarbitone to potassium bromide. For animals presenting with an acute exacerbation of their illness, or those in a crisis, intravenous N-acetly-cysteine may be beneficial. Fluid therapy and correcting hypoglycaemia and electrolyte imbalances is important as well as treating hepatic encephalopathy if present.
Antacids are useful to protect the gastric and intestinal mucosa, especially if portal hypertension is present. Feeding the patient early and with a good quality diet is essential. Protein should only be restricted in patients with hepatic encephalopathy.

In chronic cases supportive therapy is recommended however there is limited evidence to support clinical decision making. Diet, SAM-e, ursodeoxycholic acid and other anti-oxidants should all be considered. The use of prednisolone as chronic therapy is controversial and there is limited evidence for and against its use. It may be of some benefit to some individual patients and breeds (English Springer Spaniels) and should only be considered once all potential underlying causes have been excluded. When monitoring a dog receiving prednisolone, be aware that concentrations of ALKP and to a lesser extent, GGT will increase whereas concentrations of ALT should decrease (but likely not normalise).

Copper-associated hepatitis
In normal animals copper is stored within lysosomes of the hepatocytes. In animals with an inborn error of copper metabolism, copper accumulates within the hepatocyte cytoplasm. Copper accumulation results in the generation of oxidants, which in turn causes hepatocyte necrosis and consequent inflammation. Copper can accumulate due to cholestasis resulting from any form of hepatopathy, however it is generally accepted that hepatic copper accumulation in excess of 2000ppm [dry matter weight] as measured by atomic absorption analysis is very unlikely to be a secondary effect and is compatible with a primary copper accumulation.

Copper associated hepatitis has been most extensively studied in the Bedlington Terrier, although has been reported in a large number of other breeds, including the Doberman, West Highland White Terrier, Skye Terrier, Labrador and Dalmatian (especially in the USA and Canada). It is important to remember however, that non-copper associated hepatopathies can also occur in those breeds. Copper-associated hepatitis in the Bedlington Terrier is associated with a mutation in the COMMD-1 / MURR1 gene. It is very likely that other genes are also involved, as the association between this specific mutation and the presence of copper accumulation in Bedlington's varies depending on the population being studied. In general copper accumulation occurs from 6 months of age and dogs start to show signs of copper associated liver disease between 4-7 years old. After 7 years or so, hepatic copper accumulation starts to decline, possibly because of replacement of hepatocytes with fibrous tissue.

Blood tests may reveal elevations in ALT, reflecting hepatocyte damage and death; this will then progress to signs associated with chronic hepatitis as discussed above. Occasionally hepatocyte necrosis has been reported in which large amounts of copper can be released into the blood stream, leading to haemolytic anaemia and renal failure. Histological assessment of the liver uses rubeinic acid staining to document the presence and location of iron within the liver. This pattern of iron accumulation can help to determine if the disease is primary or secondary to underlying inflammation. Where possible liver should be submitted for more accurate assessment of iron levels and atomic absorption is the preferred method. A genetic test for the COMMD-1 / MURR1 defect is available for screening in Bedlington terriers.

A diet with a low copper content may be helpful in dogs with chronic hepatopathy to prevent secondary copper accumulation. However when extensive copper accumulation has occurred chelating agents should be considered. D-penicillamine is the most commonly used therapy and chelated extracellular copper is excreted in urine. This leads to translocation of stored iron from the liver and a gradual depletion of the copper stored. This is normally a gradual process and D-penacillamine is normally given for months to years. D-penacillamine can irritate the gastrointestinal tract, most commonly leading to vomiting.

As a result the drug is best given in food. Trientine is another chelating agent used and works similarly to D-penacillamine. It may be more effective and is used in dogs which cannot tolerate administration of D-pencillamine. Administration of zinc induces the expression of metallothionein in enterocytes which causes copper to be bound within enterocytes. Copper remains within the enterocytes, which is eventually sloughed and excreted in the faeces, ultimately reducing the amount of copper absorbed.

Zinc should be administered 1-2 hours before food and should not be used with other chelating agents as the agents will chelate the zinc preferentially rather than the copper. The use of zinc will help prevent disease as it is not useful in reducing store copper from within the liver.

Lobular dissecting hepatitis

Lobular dissecting hepatitis is an inflammatory hepatitis of young dogs (average age of affected animals is around 1 year). It has been reported in several breeds, but standard Poodles are over-represented. Histopathology reveals diffuse fibrosis disrupting the normal hepatic architecture, along with mild to moderate mononuclear cell infiltrates. The cause is unknown and it is though the lobular dissecting hepatitis may have several causes with the lobular dissecting hepatitis reflecting the response of the juvenile liver to insult, rather than being a diagnosis in its own right. Treatment recommendations are similar to those for chronic hepatitis. The prognosis is generally very guarded, although occasional patients have been exceptions to this rule.

Vacuolar hepatopathy

This condition is defined but the accumulation of glycogen or fat within hepatocytes and is usually associated with steroid excess or the accumulation of hormones having steroid like effects e.g. progesterone. Typically this change is seen in association with hyperadrenocorticism, or animals receiving exogenous steroid therapy such as prednisolone or anabolic steroids. Concurrent systemic disease such as diabetes will also lead to vacuolar changes. Blood test usually lead to an increase in ALKP which is disproportionally larger than the other liver enzymes. There is rarely evidence of hepatic dysfunction, although in severe cases this can occur. On ultrasound evaluation the liver is usually hyperechoic (due to the fat or glycogen infiltration) and nodular hyperplasia is often present concurrently, which can mimic the changes seen in neoplasia. Screening for underlying metabolic conditions such as hyperadrenocorticism by performing an ACTH stimulation test would be suggested. Vaculolar change is usually readily diagnosed on fine needle aspirate and usually resolves if the underlying condition is treated.

Hepatic lipidosis

Hepatic lipidosis can be seen in dogs and cats, however is a much more clinically significant problem in cats. It is a syndrome characterised by severe hepatocellular lipid accumulation, leading to intrahepatic cholestasis and impaired liver function and whilst very serious is potentially reversible with appropriate treatment. The remainder of this section will focus on feline hepatic lipidosis.

Feline hepatic lipidosis may occur as a primary event, or may be secondary to another disease process; underlying conditions such as cholangiohepatitis, neoplasia, gastrointestinal disease, pancreatitis or endocrine disorders are identified in over 50% of cats. Primary (or idiopathic) lipidosis is most commonly seen in North America, although it is rarely seen in the United Kingdom. It is most commonly seen in obese cats that undergo a period of stress or anorexia and is associated with high levels of mortality, In comparison to cats with secondary hepatic lipidosis, those with primary idiopathic hepatic lipidosis are usually younger, have higher ALKP/bilirubin levels, absence of hyperglobulinaemia, normal GGT and a better survival rate. An initiating acute pancreatitis is common, and if present carries a worse prognosis. Secondary lipidosis is the commonest from seen in the United Kingdom and is most commonly seen in cats that are thin.

The pathogenesis of hepatic lipidosis is not well understood, however the proposed mechanisms include metabolic changes associated with starvation and obesity, androgenic release during illness or stress, protein and nutrient such as taurine and relative carnitine deficiency. The balance of triglyceride lipolysis and accumulation is modulated by blood glucose concentrations, hormonal, neural and pharmacologic mechanisms. The activity of hormone sensitive lipase (promoting lipolysis) and lipoprotein lipase (promoting fat uptake) directly regulates fat metabolism. Noradrenaline, adrenaline, growth hormone, glucagon, corticosteroids and thyroxine all increase hormone sensitive lipase, whereas insulin inhibits it. Since cats readily release catecholamine when stressed, stress may therefore exacerbate hormone sensitive lipase activity, and as a result promote lipolysis.

Furthermore, in starvation hormone sensitive lipase increases and lipoprotein lipase decreases, favouring hepatocellular fat accumulation. Studies have also documented disturbances in the regulation of appetite, resulting in inappropriate anorexia.

Clinical signs are often initially vague consisting of progressive lethargy and anorexia, sometimes accompanied by intermittent vomiting. As the disease progresses, signs of acute liver failure develop with jaundice and signs of hepatic encephalopathy such as depression and ptyalism. Diagnosis is based initially on clinical history, physical examination, laboratory findings, ultrasonography and cytology of aspirates revealing swollen heptaocytes containing lipid and the exclusion of other causes where possible. Definitive diagnosis can be made by histopathology of liver biopsies once the cat is stabilised, but may not be needed as cytology is sufficient in most cases and a definitive diagnosis should not delay treatment. Diagnostic imaging often reveals hepatomegaly and with diffuse hyperechogenicity seen on ultrasound. This is not a specific finding for lipidosis however, since clinically normal obese cats and those with hepatic lymphoma may also have hyperechoic hepatic parenchyma.

The most common laboratory findings include hyperbilirubinaemia and elevations in ALT and ALKP (often more than 5-fold) without significant elevations in GGT. In comparison, cats with inflammatory liver diseases would be expected to have elevations in GGT and serum globulins. Absence of jaundice does not exclude hepatic lipidosis since liver enzyme elevations and histological evidence of hepatic lipidosis occur before cholestasis. Bilirubinuria also precedes increases in serum bilirubin and may be a useful marker of early cholestasis since the presence of any bilirubin in the urine is always an abnormal finding in cats. Cats with lipidosis are also often hypokalaemia and hyperglycaemia. Haematology is often unremarkable, although poikilocytosis may be evident. Haematology should however be monitored during treatment, in addition to serum biochemistry, as hypophosphatemia can occur with refeeding, which may result in haemolytic anaemia. A mild to moderate non-regenerative anaemia of chronic disease can also develop.

Coagulopathies are common in cats with hepatic disorders, including hepatic lipidosis. Commonly this results from vitamin K deficiency, but may also be caused by reduced production of clotting factors by the liver, or less commonly a consumptive coagulopathy. Vitamin K deficiency occurs secondary to anorexia and malabsorption resulting from cholestasis, with subsequent lack of intestinal bile salts to aid in absorption of fat and fat soluble vitamins.

Successful treatment of cats with hepatic lipidosis requires aggressive nutritional support as soon as possible. Most cats will require enteral assisted feeding for several weeks and often longer, and therefore oesophagostomy or gastrostomy tubes are the method of choice. Naso-oesophageal tube feeding can be useful for the first few days, until the cat is stable enough to undergo anaesthesia for the placement of a longer term feeding tube. In contrast to dietary management of other liver diseases, a high protein diet is required to treat hepatic lipidosis, unless the cat is initially showing signs of hepatic encephalopathy. Cats with lipidosis should be feed 60-80kcal/kg/day. Intravenous fluid therapy is essential and careful monitoring and management glucose, potassium and phosphate levels are especially important.

Additional treatment with L-Carnitine (250mg/day for potential effects in increasing mitochondrial fatty acid oxidation), taurine (250mg/day to prevent deficiency) and vitamin E (50mg/day as an antioxidant) once daily and subcutaneous vitamin B1 (100mg), vitamin K (2mg to prevent vitamin K deficient coagulopathies) twice daily for 3 days and vitamin B12 (250µg twice weekly) are also recommended, since early provision of these is thought to improve clinical outcome, although as yet there is no firm evidence for this.

Other treatments that are often required include anti-emetics and pro-motility drug. Gastric stasis is common and aggressive treatment may be required with constant rate metoclopramide infusions (1-2mg/kg/day) and/or pro-kinetics such as ranitidine.

Careful monitoring and frequent reassessment of haematological and biochemical parameters is essential to ensure improvement is occurring, and to monitor for complications such as hepatic encephalopathy, hypokalaemia, hypophosphatemia and subsequent haemolytic anaemia. Prompt treatment is required should any of these complications occur. Additional treatment may also be required for any underlying disease if another disease process is identified following initial stabilisation. If cats recover from hepatic lipidosis, no long term consequences should be seen.

Hepatic neoplasia

Primary hepatic tumours (hepatocellular, biliary epithelial, mesenchymal or neuroendocrine in origin) are uncommon and much less frequent in companion animals compared to man [0.6-1.5% of all tumours in dogs and 1-2.9% of all tumours in cats]. Due to the good vascular and lymphatic supply to the liver and its reticuloendothelial function, metastatic neoplasia is more common than primary tumours in both cats and dogs; common examples include lymphoma, mast cell tumours, histiocytic sarcoma and tumours that metastasis from the gastrointestinal tract e.g. pancreatic tumours. It has been reported that around a third of all non-hepatic neoplasia will metastasise to the liver. The most common primary hepatic neoplasms in dogs are hepatocellular carcinomas and in cats, biliary carcinomas, reflecting the high degree of biliary tract disease seen in feline patients. Benign tumours are more common than malignant tumours in cats, whereas malignant tumours outnumber benign tumours in dogs. Neoplasia is usually seen in older animals [average age 10 – 12 years]. No convincing sex or breed predilection in either species has been reported, with the exception of canine biliary carcinoma which is seen more often in females.

The clinical signs of hepatic neoplasia are often non-specific and include abdominal pain, vomiting and inappetence. Jaundice is possible and seen particularly in animals with biliary neoplasia. Occasionally haemorrhage from the mass may lead to haemoabdomen, especially in animals with haemangiosarcoma. It is not uncommon to see animals with hepatic neoplasia with no signs at all.

Elevations in liver enzymes and bile acids are commonly seen but are not specific for heaptic neoplasia. Mild anaemia and a mild neutrophilia are also seen. Elevations in bilirubin are uncommon and are usually associated with biliary carcinoma. Hypoglycaemia can occur with very large tumours and can lead to paraneoplastic signs [weakness and collapse]. These can be benign such as hepatoma or malignant such as hepatocellular carcinoma; other than pathology there is no reliable method of distinguishing benign from malignant tumours.

Diagnostic imaging is helpful however it is important to remember that ultrasonographic appearance of a mass cannot easily differentiate between benign and malignant masses. Radiographs may show gross hepatomegaly and are often the starting point of evaluation, however ultrasound is more useful in evaluation the location and invasion of hepatic masses. Ultrasonography is dependent on the operator and the machine available, Hepatic masses may be hypo or hyper echoic texture and there are no specific echogenicity changes that define specific tumour types. If the tumour is obstructing the biliary system this is likely to be visible on ultrasound evaluation. Metastasis of malignant hepatic tumours usually first occurs to the peritoneum and local lymph nodes with the lungs being less common and seen later in the disease course. Advanced imaging such as MRI and CT are used for surgical planning with MRI having the ability to discriminate between some tumour types. CT will also give higher accuracy with evaluation of possible pulmonary metastasis.

As discussed previously it is important to be aware of the limitations of sampling techniques, however fine needle aspiration may be useful in diagnosing metastatic neoplasia (e.g. lymphoma, mast cell tumour) and may occasionally help in diagnosing primary hepatic neoplasia. Tru-cut biopsies are more accurate than cytology in diagnosing hepatic neoplasia though are associated with potential risks. If there is no evidence of metastasis and the tumour appears relatively easy to resect tissue sampling is not normally performed before mass removal.

Surgery is the best treatment option for most hepatic neoplasms and with solitary and resectable tumours, is usually very effective. Usually surgery involved lobectomy and requires a good deal of surgical skill as well as good understanding of the hepatic anatomy. In the absence of a definitive surgery, chemotherapy is unlikely to be effective, as hepatic tumours are generally not sensitive to chemotherapy; with the exception of some metastatic tumors for example lymphoma and mast cell tumour.

Hepatocellular carcinomas have three distinct phenotypes in dogs; solitary (or historically called massive) which arise in one lobe and form 61% of hepatocellular carcinomas reported, multi-nodular involving several lobes (29%) and diffuse describing involvement of all liver lobes (10%). Metastatic rates vary from 5-60%, with the lowest rates reflecting solitary hepatocellular carcinoma, the highest rates to the diffuse phenotype. Patient survival is heavily dependent on the phenotype and its ease of surgical resection. The results of surgical resection of solitary tumours are usually excellent, although a complication rate of nearly 30% has been reported (mostly minor haemorrhage post-surgery) but results are frequently excellent in the solitary / massive form. Following attempted surgical excision, the reported complication rate is 28% (most complications being minor haemorrhage) and the peri-operative mortality rate reported at approximately 10%, with most animals dying of massive haemorrhage. This is considered a high figure and now surgical stabling devises and trasnsfusion medicine has advanced the figure is likely not so high. Neoplasms within the right lobes are more difficult to excise than those on the left, given the close proximity of the vena cava. Following excision, recurrence rates are low (less than 10%) and one study showed mean survival times for a group of dogs following complete excision of greater than 4 years (with most dying of diseases other than hepatic neoplasia) compared to animals not having surgery with a mean survival of 270 days (with most dying due to progressive disease).

Biliary carcinomas or adenocarcinomas are usually highly malignant, with metastases reported in approximately 80% of cases at time of diagnosis. In cats however, adenomas are more common than malignant tumours. Surgery is recommended if there is no evidence of metastases and good survival times have been reported if there is complete resection. Surgery is complicated by the fact that biliary neoplasia commonly arises very close to the porta hepatis, making excision technically challenging.

A new technique has been developed recently for focal but unresectable tumours called hepatic chemoembolization. This is an interventional radiology technique which allows selective administration of chemotherapy and embolic agent directly to the local artery supplying the tumour. This gives drug concentrations 10-50 times higher than seen with systemic administration, with reduced blood supply further enhancing the effects of the chemotherapy (hepatic tumours take the majority of their nutritional and oxygen supply from the hepatic arterial supply (80% hepatic artery, 20% portal supply) compared to the normal liver is primarily reliant on the portal circulation (80% portal supply, 20% hepatic artery)). This technique has been used in man with fair outcomes and has recently been reported in several canine patients. CT evaluation is needed for planning and it is challenging to access the specific artery with a very fine micro-catheter. This is done via access to through the femoral artery and driving a fine catheter through the aorta to the celiac artery and then into the selected hepatic branch. Once in position chemotherapy is administered (usually carboplatin or doxorubicin) and then the artery is occluded with PVA spheres (300-500µm in diameter). The tumour will then shrink in size over the following 4-6 weeks, treatment is generally well tolerated, however inflammation secondary to tumour necrosis can lead to pyrexia and lethargy; generally these signs are transient and respond well to NSAIDs.

Benign nodular hyperplasia (BNH)
This is a benign condition of the liver that leads to the formation of grossly visible nodular changes within the liver tissue and can cause confusion with other more sinister causes of nodular disease for example neoplasia and cirrhosis. The cause of benign nodular hyperplasia is unknown, however nutritional factors such as protein restriction have been suggested to play a part. The incidence increases with age with studies showing 70-100% of dogs 14 years or older having evidence of BNH; but it rarely occurs in cats. BNH is often associated with mild increased in ALKP which is usually mildly elevated (2-3 times the reference interval).

However is some cases marked and more dramatic increases are seen with elevations greater than 10-20 times the reference interval. A mild elevation in ALT is usually seen associated with cellular regeneration, however bile acids and other liver function markers are usually normal. The nodules are not always visible on ultrasound and may have a very similar appearance to the surrounding parenchyma. A biopsy is needed for definitive diagnosis and a surgical wedge is preferred where possible. No treatment is usually suggested although hepatic antioxidants could be suggested, alongside review of the animals nutritional status.

Consequences of hepatic disease

Hepatic encephalopathy
Hepatic encephalopathy (HE) is a complex syndrome which describes neurological signs relating to hepatic insufficiency. Gastrointestinal flora produce many compounds which have been implicated in HE such as ammonia, short chain fatty acids, mercaptans, skatoles and indoles. These substances cause neurotoxicity and alter brain neurotransmitter balance leading to altered neurological function.

Treatment

1) Correct fluid balance, acid base imbalances and electrolytes
The type and rate of fluids given depends on the clinical presentation and degree of hypovolaemia present. Classically lactate containing solutions, such as Hartman's, have been avoided. Acid base imbalances should be assessed if possible; metabolic acidosis from lactic acidosis is most likely and should resolve with appropriate fluid management. Hypokalaemia may precipitate, and worsen HE, and should be supplemented if present.

Serum Potassium	Amount KCl to add to 250ml 0.9% NaCl
<2 mmol/l	20 mmol
2 -2.5 mmol/l	15 mmol
2.5 – 3 mmol/l	10 mmol
3 – 3.5 mmol/l	7 mmol

2) Correct hypoglycaemia
Hypoglycaemia is commonly associated with hepatic insufficiency and can both precipitate and potentiate hepatic encephalopathy. Parenteral glucose supplementation can be given as a bolus (1-5ml of 20% glucose over 5-10 minutes) or as a 2.5-5% infusion

3) Antibiotics
Antibiotics are used to reduce the gastrointestinal bacterial load and reduce toxin production. Hepatic insufficiency due to portosystemic shunting can be associated with low grade systemic bacteraemia, due to portal blood missing the RE cells in the hepatic sinusoids. Commonly suggested antibiotics are ampicillin (10-40mg/kg TID) and Metronidazole (10mg/kg BID).

4) Lactulose
Lactulose (1-4-β-galactosidofructose) is hydrolysed in the colon to organic acids which act in a number of ways. Firstly the acidic environment leads to ammonia forming ammonium ions with in the colon. This traps ammonia ions in the gut as ammonium (in contrast to stark contrast to ammonia) can not cross the gut wall.

The acid environment also beneficially alters the populations of gut flora. Secondly lactulose acts to decrease gut transit time by producing osmotic diarrhoea. Oral lactulose should be given at a titrated dose in order to produce 2-3 soft stools a day (starting doses are suggested at 0.1-0.3ml/Kg BID and should be reduced if diarrhoea is seen and increased if constipated). In severe HE lactulose enemas should be given (20ml/kg of 30% lactulose solution) as a retention enema.

5) Diet

A moderately restricted protein diet is needed, with good digestibility. Most of the caloric intake should be in the form of carbohydrate and fat.

Good commercial prescription liver diets fulfil these criteria; however cottage cheese can be added to increase protein content. Meat and egg produces should be avoided.

6) Treatment of seizures

Animals with severe HE may develop seizures. These should be controlled whilst the underlying cause is addressed (antibiotics, lactulose enemas, addressing fluid balance, electrolytes, etc). Whilst benzodiazepines are commonly used to control seizuring patients, they appear less effective in hepatic encephalopathy. Propofol infusions or phenobarbitone loading may be more appropriate; however care must be taken due to reduced hepatic function in these patients. Recently levetriacetam (Keppra) has been suggested as the drug of choice and administration has been shown to reduce the risk of seizures post-surgery for dogs with porto-systemic shunts.

Coagulopathies

Coagulation defects have been reports in a fairly high proportion of dogs with liver disease[between 66-93% depending on the study], with prolongation of aPTT being the most common abnormality reported. Defects in coagulation may arise as the result of a number of different mechanisms. They may be the result of reduced coagulation factor production, either as the result of reduced hepatic mass [e.g. cirrhosis] or where there is diffuse hepatic disease [e.g. hepatic lipidosis].They may also result from a lack of vitamin K absorption, through biliary duct obstruction. Here the vitamin K dependant coagulation factors [II, VII, IX and X] are reduced, although clinically this is not commonly documented, it may be in part due to the insensitivity of PT and aPTT in measuring coagulation times. Coagulation status [platelet numbers and coagulation times] should be measured prior to any surgery or liver biopsy and where coagulation defects are documented vitamin K should be supplemented and coagulation times repeated in 48 hours. Where more marked changes or active bleeding is documented transfusion with fresh frozen plasma or a whole blood transfusion may need to be considered.

Gastrointestinal ulceration

Gastrointestinal ulceration in dogs with liver disease may occur due to a combination of coagulopathy and portal hypertension causing gastrointestinal mucosal damage. These features are seen in combination most commonly in dogs with portosystemic shunts and in animals with portal hypertension due to cirrhosis, periportal fibrosis or thrombosis. If ulceration is suspected then antacid therapy with an H2 antagonist (e.g. cimetidine, ranitidine or famotidine) should be considered, with consideration that although cimetidine is the licensed product in the UK, awareness of the likely effect of cytochrome P450 inhibition on drug metabolism, which affect therapeutic levels of treatments given.

Portal hypertension and ascites

Ascites may occur in liver disease due to either low oncotic pressure or due to portal hypertension. In both instances treating the underlying cause is suggested, however support may need to be given in the short term. Oncotic support may be provided in the form of colloid infusion, with larger starch molecules more suitable for this purpose than gelatins. Colloids should not be given if portal hypertension is present as they will worsen the ascites; in these cases spironolactone may help due to the volume of fluid present.