Hepato-Biliary Disease in Dogs and Cats

Dr Rob Labuc BVSc MVS FANZCVSc

Melbourne, Australia

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Canine Hepato-Biliary Disorders that Practitioners see in Practice

Robert Labuc BVSc MVS FANZCVS
Melbourne Veterinary Specialist Centre
www.melbv.com.au

“I wish I could trade my heart for another liver. Then I could drink more and care less.”
Unknown

In this presentation, I will be exploring the various liver diseases of the dog and cat likely to be seen by a general practitioner, hence the awkward title above. This is to say that rare, singly reported disease entities will not occupy any particular time.

Even with information derived from history, physical examination, laboratory data, diagnostic imaging and the ’gold standard’ of histopathology, we are still often left uncertain as to what we are dealing with and how best to manage it.

This situation, along with lack of commonality in nomenclature, led to the formation in 2000 of an International Liver Standardization Group which reports to the World Small Animal Veterinary Association. This group has developed a series of guidelines culminating in the production of a book, entitled <WSAVA Standards for Histological and Clinical Diagnosis of Canine and Feline Liver Diseases> published in 2007. What is novel in this approach is that both pathologists and clinicians have banded together to develop a uniform nomenclature for liver diseases to better be able to analyze data from many varied sources.

In this schema, the diseases have been divided into the disorders of:
- Hepatic vasculature
- Biliary tract
- Hepatic parenchyma, and
- Neoplasia
It is the latter two that I will cover in more detail in this lecture.

General Background:
The acute hepatopathies include infectious diseases and toxic reactions (including drugs or medications). The chronic hepatopathies include the non-infectious inflammatory hepatopathies, copper-associated hepatitis, cirrhosis and neoplasia.

There are a number of potentially reversible hepatocytic injuries, seen microscopically, which include hepatocellular swelling, feathery degeneration, steroid-induced hepatopathy and hepatocellular steatosis (ie lipidosis). Hepatic amyloidosis is caused by deposition of reactive amyloid and is commonly associated with inflammatory disease of other organ systems.

Hepatocyte death can result from many insults, and can be seen as either apoptosis (where the hepatocytes become shrunken, intensely eosinophilic and have condensed nuclei surrounded by a non-staining halo) or necrosis. The necrosis is seen as cytoplasmic swelling and loss of integrity of the cell membrane ultimately resulting in coagulative necrosis or liquefactive (lytic) necrosis. Necrosis can be further described as focal or multifocal, confluent or bridging, massive, or piecemeal (also known as interface hepatitis).
Generally acute hepatitis is characterized by a combination of inflammation, hepatocellular apoptosis and necrosis. Depending on the age of the lesion, regeneration may also be seen. Most lesions are diffuse, and therefore diagnostic imaging studies commonly show a generalized alteration to the hepatic parenchyma. However, in some cases, there is no change seen at all.

Chronic hepatitis on the other hand is characterized by hepatocellular apoptosis or necrosis associated with a variable mononuclear or mixed inflammatory infiltrate, as well as clear evidence of regeneration and fibrosis. The proportion and distribution of these various components varies considerably depending on the disease, its age, and the species involved. Therefore, when attempting to describe the disease morphologically, there is a desire to include the activity (as determined by the degree of inflammation, hepatocellular apoptosis and necrosis) and stage (extent and pattern of fibrosis, possible architectural distortion) as well as possible aetiology.

Various toxins cause hepatopathies and may be either direct or following metabolic transformation of a non-toxic substance to a toxic metabolite by the liver. The toxins may be subdivided into fungal or plant products, drugs or chemicals. They may act in a predictable dose-dependent manner or be idiosyncratic non-dose-dependent (affecting much smaller number of animals and in a far less predictable manner). The degree of damage can vary from no morphological changes (ie biochemical only), hepatocellular swelling, steatosis, necrosis, cholestasis, inflammation and fibrosis.

Hepatic abscesses are focal or multifocal lesions that can be associated with infection or central necrosis of neoplasms. Where infectious, causative organisms include *Yersinia* spp, *Nocardia asteroides*, and *Actinomyces* spp. The route of entry may be portal umbilical veins in neonates, ascension from the biliary system, or direct contact and penetration through the liver capsule.

Hepatic granulomas may be seen with primary liver disease or as part of systemic or generalised disease. A granuloma is characterized by multifocal aggregation of activated macrophages, mostly infiltrated by lymphocytes, plasma cells and fibroblasts, and often surrounded by collagen fibres. In dogs, a granuloma may be infectious being caused by mycobacteria, systemic mycoses, opportunistic fungi, migrating nematode larvae, and schistosomiasis. Diffuse granulomatous disease can be seen in the dog associated with *Leishmania* infection and *Bartonella* spp. In cats, *Cytauxzoon felis* infection may result in granulomatous disease.

Metabolic storage diseases can cause generalised changes to the liver parenchyma and are usually associated with inherited metabolic enzyme deficiencies, although some acquired diseases have been reported. Here, the changes seen on histopathology include clear vacuoles, vacuoles with granular or hyaline material, or pigmented granules in the hepatocytes and/or Kupffer cells and macrophages. Administration of some xenobiotics (eg griseofulvin) may induce an acquired storage disease known as erythropoietic protoporphyria.
The neoplastic disorders of the liver include:

1. Hepatocellular neoplasia
   a. Nodular hyperplasia
   b. Hepatocellular adenoma
   c. Hepatocellular carcinoma
2. Cholangiocellular neoplasia
   a. Cholangiocellular adenoma
   b. Cholangiocellular carcinoma
   c. Mixed hepatocellular and cholangiocellular carcinoma
3. Hepatic carcinoids and hepatoblastoma
4. Primary vascular and mesenchymal neoplasia
   a. Includes haemangiosarcoma, lymphangioma, lymphangiosarcoma, fibrosarcoma, leiomyosarcoma, malignant mesenchymoma, osteosarcoma, rhabdomyosarcoma (all bar haemangiosarcoma are extremely rare)
   b. Myelolipoma – very rare, in felids only

**TOXIC INJURY**

**Intrinsic and Idiosyncratic Xenobiotic Hepatotoxicity**

The liver has a central role in drug metabolism and disposition, receiving 75% of its circulation directly from the splanchnic venous drainage of the abdomen. Therefore it is confronted with direct and concentrated delivery of drugs and environmental chemicals absorbed by the gut and so is susceptible to damage from these xenobiotic substances. Intrinsic hepatotoxicity results from the direct effect of the xenobiotic or its metabolite on vital cell targets (eg paracetamol). Extrinsic mechanisms or intracellular events induce the hepatic reactions to intrinsic drugs. Many of these will cause damage to zone 3 in the acinus (zone closest to terminal hepatic venule) and the response is usually necrosis without inflammation. Drug-metabolizing enzymes may in fact enhance the toxicity of some xenobiotics rather than de-toxifying them.

Idiosyncratic reaction is thought to commonly involve immune-mediated mechanisms either invoking specific cell surface death receptors or involving hapten and neoepitope expression on the hepatocyte surface. The liver shows either regional or mixed zonal pattern involvement in these reactions.

As the liver has such a robust regenerative capacity the result of toxic damage varies from cell survival to apoptosis to complete cytolytic necrosis.

The appearance of the liver will vary with the toxin causing damage, but can include hepatocellular necrosis, changes consistent with toxic hepatitis, steatosis or lipidosis, and cholestasis. Xenobiotic-induced hepatic necrosis can be zonal (usually zone 3) or panlobular.
Specific Hepatic Xenobiotic Toxicities

Antimicrobials:
In dogs, the most common example is sulphonamide, where bioactivated reactive drug metabolites haptenize tissue proteins, inducing cell-mediated immunity and perhaps humoral response. These reactions can be seen within five days of initial drug exposure. Most commonly there is marked hepatic necrosis, but sometimes the lesion is a lymphocytic-plasmacytic inflammatory reaction or canalicular cholestasis.

Tetracyclines can induce hepatocellular lipid retention or fulminant hepatic failure.

Anticonvulsants:
Phenobarbital hepatotoxicity is a well-known and well-described idiosyncratic-type reaction in dogs. Phenobarbital is also well recognized as an enzyme inducer. Direct dose-related hepatotoxicity is inconsistent, occurring within months or years of initiation of therapy. Sometimes there is significant hepatic injury yet little in the way of clinical signs. Discontinuation of the drug at this stage may result in resolution. In some patients, a reduction in dose rate may improve clinical signs and laboratory parameters in some individuals, and therefore continuation of therapy is possible. The histopathology of the liver can show chronic liver injury, cirrhosis or a severe nodular vacuolar hepatopathy similar to that associated with migratory necrolytic erythema (ie hepatocutaneous syndrome). Primidone causes identical lesions, perhaps reflecting the conversion of primidone to phenobarbital. Phenytoin can also be associated with acute or chronic hepatitis, sometimes leading to death. A combination of all three of these anti-epileptic drugs increases the risk of hepatotoxicity occurring.

Diazepam:
In cats specifically, diazepam has been associated with an idiosyncratic reaction causing panlobular hepatocellular necrosis that spares the biliary epithelium. Oxazepam and clonazepam have also been implicated. Toxicity is usually recognised within the first week of treatment. Fulminant hepatic failure can quickly follow. Acute renal failure, myocardial and muscle necrosis can also occur. Recovery is possible, with supportive care and the use of N-acetylcysteine.

Oxibendazole & Mebendazole:
These paraciticides have been associated with lethal hepatotoxicity in dogs.

Methimazole:
Used for treating cats with hyperthyroidism, methimazole can cause hepatic toxicity, usually within the first month of therapy. Initially liver enzymes and bilirubin rise, but the injury is reversible with drug withdrawal. It is possible that only cats with low levels of GSH may be at increased risk as the metabolism of toxic intermediates involves GSH. Hyperthyroidism has been shown to reduce GSH concentrations in other species, so perhaps, this is a contributory factor in the cat.

Amiodarone:
Used for treatment of dilated cardiomyopathy in the Doberman pinscher, this drug has been associated with a reversible hepatotoxicity in 45% of 22 treated dogs.
Non-steroidal Anti-inflammatory Drugs:
Idiosyncratic hepatotoxicity has been reported with virtually all drugs in this group. Histologic lesions vary within and between NSAID drug classes. Hepatocellular injury and necrosis is most common, but cholestatic injury, mixed parenchymal and cholestatic injury, steatosis and granulomatous inflammation have been recognized in humans. Again, some metabolites of NSAIDs may be more toxic when hepatic GSH stores are depleted.

Aspirin and phenylbutazone are directly hepatotoxic.

Carprofen can cause idiosyncratic cytotoxic hepatotoxicity in dogs, with the severity unrelated to dose or duration of treatment. Most dogs have been on treatment for over two weeks before evidence of toxicity is seen. Occasionally, no clinical signs are observed but ALT and AST rises are modest to marked exceeding that of ALP. Renal toxicity can also occur. Withdrawal of medication and supportive care allows recovery in most dogs, but some can die. Labrador retrievers are reported to be at increased risk, however it is postulated that this could also relate to a separate predisposition to chronic hepatitis.

Paracetamol:
This hepatotoxin acts via metabolism through cytochrome P450 oxidases to a reactive metabolite. Centrilobular necrosis is the most common outcome. Conjugation of with GSH or cysteine protects the liver, so in animals deficient in these anti-oxidants can suffer lethal cellular injury. Dogs appear to have an apparent predisposition to paracetamol-induced injury as they have intrinsically low hepatic GSH concentrations. If the dog survives the initial hepatotoxicity, it can then develop haematotoxicity. The cat seems resistant to hepatotoxicity, but does develop haemolysis, methaemoglobinemia and endothelial toxicity. Treatment, apart from withdrawal of the drug includes a thiol donor to supplement cysteine and restore circulating and liver GSH. The preferred agent is N-acetylcysteine.

Lomustine (CCNU):
This is a chemotherapeutic agent shown to have a dose-dependent hepatotoxic property in the dog. In one retrospective case report, 48.8% of 206 dogs undergoing chemotherapy had ALT elevations and 1.2% suffered hepatic failure. Time to detection of toxicity ranged from 2 to 49 weeks (median 11 weeks) in another study. Cholestasis and hepatic dysfunction can also result. Despite clinical improvement following withdrawal of the drug, biochemical abnormalities and histologic lesions persisted for 4 to 38 months. Therefore, this drug can cause a delayed, cumulative, dose-related, chronic hepatotoxicity that is reversible and possibly fatal. Renal tubular injury is also possible. A metabolite of CCNU is isocyanate, and this is implicated as the mediator of toxicity through depleting cellular GSH and inactivating enzymes. Thiol supplementing nutraceuticals could possibly reduce hepatotoxicity but evidence is lacking.

Aflatoxin:
Numerous reports have described aflatoxins contaminating dog food and causing hepatotoxicity and death in many dogs. Liver aspirate cytologies showed a lipid vacuolation of hepatocytes. Histopathology showed diffuse steatosis and zone 3 parenchymal collapse. There was scattered hepatocyte necrosis and mild neutrophilic and macrophagic infiltration. Hepatic fibrosis was of variable degree, along with regenerative nodule and acquired portosystemic shunt formation. The shunt formation was preceded by diapedesis of blood.
into the intestinal lumen causing severe enteric blood loss. Some dogs were rescued with extensive and intensive supportive care however death rate is high.

**Xylitol:**
This is a sugar substitute used in cooking and confectionary. At doses exceeding 0.1 g/kg bodyweight, marked insulin release is triggered causing hypoglycaemia. At doses exceeding 0.5 g/kg, acute severe fulminant hepatic failure occurs.

Two mechanisms of liver damage have been proposed. Firstly, severe cellular depletion of ADP, ATP and inorganic phosphorous reserves leads to cellular necrosis. The other possibility is that production of high concentrations of nicotinamide adenine dinucleotide(NAD) involves the reactive oxygen species (ROS). Myonecrosis can also occur, causing elevation without concomitant elevation of urea. Hypoglycemia occurs within hours of ingestion of xylitol whilst hepatic toxicity may take 9 to 72 hours. Histology shows severe acute periacinar to mid-zonal hepatic necrosis, periportal vacuolar degeneration and mild biliary hyperplasia. Treatment involves rapid induction of emesis, followed by stabilising blood glucose. Where there is a coagulopathy identified, plasma or whole blood transfusions are indicated. It is not known if hepatoprotectants or antioxidants are of value.

**Cycad:**
The Cycad palms are natives of Australia. Most dogs ingesting any part of the plant or its seeds show gastrointestinal signs and neurological signs may follow. The seeds contain the highest concentration of the glycoside cycasin, a glycoside that is converted to methylazoxymethanol that is the active toxin. As few as one or two seeds can cause death. Clinical signs may become apparent within 15 minutes to 3 days, and last from 24 hours to 9 days. Treatment advised is as for xylitol or aflatoxin. Cytology of the liver shows hepatocytes with abnormally large nuclei, lipid vacuolation and cells with bizarre shapes. Histopathology shows centrilobular and midzonal coagulation necrosis, steatosis, and sinusoidal congestion due to collapse of the centrilobular region. Myonecrosis and coagulopathies also occur.

**Natural or Herbal Remedies:**
Although touted as being natural and harmless, some herbal remedies have been associated with hepatotoxicity. These include Chinese herbal tea, Oil of cloves, Sassafras, and Pennyroyal oil.

**Metals**
As the liver is the first organ perfused by portal circulation containing ingested minerals, this organ can become a sink for these metals if there is a problem with egress of the metal from the liver. Copper and iron play a critical role in generation of reactive oxygen species as transition metals, whilst selenium and zinc have antioxidant benefits. If copper or iron accumulate, they are known to lead to necroinflammatory liver disorders, where they enhance oxidant damage to the liver.

**Copper:**
This is a transition metal with both prooxidant and antioxidant properties. The Bedlington terrier has been well described as having an autosomal recessive trait resulting in the deletion of COMMD1 gene. Some affected dogs do not have this mutation.
However, other pure and mixed-breed dogs and a few cats also have pathologic hepatocellular copper concentrations. Serum ALT appears to correlate with the amount of damage to the liver. There is a familial tendency for hepatic copper accumulation proposed in the West Highland White terrier, yet some affected dogs never develop liver injury. It still remains unknown whether copper seen in liver disease is a causal factor, a coincidental epiphenomenon, or develops secondary to cholestasis. There is evidence that subsets of Doberman pinschers and Labrador retrievers with chronic hepatitis have histological lesions affiliated with pathological hepatocellular copper retention. In the Labrador, this may be heritable.

Copper accumulation will result in liver damage. Treatment is suggested in the following circumstances:

- Copper levels above 1500 ug/g dry liver (there is little breed variation in normal levels)
- Substantial copper deposition is focussed in zone 3 on histopathology
- Single cell necrosis affiliated with macrophages and lipogranulomas intermixed with copper-positive granules

Treatment is with chelation therapy (such as D-penicillamine or tetramine) and dietary copper restriction. Anti-oxidants and water soluble vitamins (except Vitamin C) are recommended. Oral zinc can be used as it competes for the same enterocyte carrier as used for copper and therefore reduces the uptake of copper. Zinc also induces enterocyte metallothionein, acting as a copper trap and therefore making copper unavailable for systemic absorption. However, no clinical trial evidence of efficiency is available. D-penicillamine is not to be given at the same time as zinc, as it chelates zinc instead of copper, making each treatment obsolete. Tetramine can be substituted for D-penicillamine if the latter is not tolerated.

Iron:
Approximately 80% of dogs and more than 50% of cats with chronic necroinflammatory liver disease have high tissue iron concentrations (>1500 ug/g dry liver). The iron remains within hepatic Kupffer cells, other macrophages or lipogranulomatous inflammatory foci. It remains biologically active, contributing to reactive oxygen species formation and hepatic fibrosis. Hepatocytes depleted of GSH have increased susceptibility to iron-mediated lipid peroxidation and because high hepatic iron is associated with subnormal Vitamin E availability and a reduced tissue GSH/GSSG balance, supplementation with both Vitamin E and thiol donors is recommended. Humans with hemochromatosis are treated by phlebotomy along with hepatoprotective agents and antioxidants. This condition is rare in dogs and cats, but successful treatment of iron retention in these species has been with biweekly phlebotomy. Success of treatment can be monitored with serum ferritin concentrations and serum iron indices. Chronic anti-oxidant supplements and restriction of dietary iron is also recommended.
Metabolic Diseases of the Liver

Amyloidosis:
Amyloidosis of the liver is uncommon, but may occur as part of a systemic amyloidosis. Amyloid is derived from a number of different amyloidogenic proteins associated with various disease entities. In dogs and cats, systemic amyloidosis is associated with the precursor protein amyloid A (AA), an amino terminal fragment of the acute-phase protein, serum amyloid A (SAA). When there is a chronic inflammatory, infectious or neoplastic disease process this AA accumulates. It will also occur as a familial trait. That disease in the Shar Pei and Abyssinian mainly reflects as renal disease. Familial disease affecting primarily the liver has been reported in various dogs and cats. There appears to be a unique isotype of amyloid in the Siamese suggesting a genetic cause yet again.

Diffuse hepatic amyloid deposition predisposes affected cats to having liver lobe fracture develop as a consequence of increased tissue fragility and concurrent coagulopathy. These cats may present with acute death or hypovolemic haemorrhagic shock due to massive haemabdomen. Some cases may not even show elevation of ALT. Hepatic ultrasonography initially shows a diffusely hypoechoic liver but later may show focal lesions reflecting haematoma formation. A biopsy is necessary for diagnosis, however risk should be considered due to the fragility of the liver. Cytology can show pink, amorphous amyloid fibrils next to hepatocytes with Wright-Giemsa staining.

Acute therapy involves provision of fresh blood, fresh frozen plasma and parenteral Vitamin K. However, the prognosis for cats is generally regarded as grave. Colchicine is used in humans and Shar Pei. It is has only been rarely used in cats.

Canine Hyperlipidemia:
This is a metabolic disorder, reported more commonly in Miniature Schnauzers, Shetland Sheepdogs, Briards, Beagles and severe terrier. A diffuse vacuolar hepatopathy or biliary mucocoele result.

Canine Steroid or Glycogen Vacuolar Hepatopathy:
Liver enzymes, particularly ALP, will rise within days of the administration of glucocorticoids in the dog. However there is much variation with the individual dog, different potency of different glucocorticoids and route of exposure. Ultrasonography shows diffuse or multifocal parenchymal hyperechogenicity with variable appearance of hypoechoic nodules. Unfortunately, to differentiate this from other chronic necroinflammatory or fibrosing disease, tissue biopsy is necessary.

As there is cortisol release with stress, any chronic health problem in the dog can result in vacuolar hepatopathy. Similar changes can be seen with hyperadrenocorticism (either high steroid sex hormones or high cortisol production). Vacuolar hepatopathy, in itself, has never been shown to be related to clinical signs directly.
Feline Hepatic Lipidosis:
Most systemically ill cats will develop some degree of hepatocellular fatty vacuolation due to the fact that this species is so predisposed to accumulating triglycerides. This accumulation only becomes problematic when it becomes severe. A normal feline liver contains fat that makes up <5% of total organ weight. In HL, the liver may double or triple in weight! Fat accumulation is the result of the hepatic synthesis of triglycerides exceeding their dispersal or use. Overnutrition augments this fat accumulation, so obesity predisposes to the development of HL. When an obese cat becomes anorexic, fatty acid release from all peripheral adipose stores challenges the liver's ability to utilise and disperse them. Hormones and blood glucose also influence the balance of lipolysis and storage of triglycerides. Therefore, stressed cats (catecholamines, corticosteroids) or unregulated diabetics are more likely to develop HL. Other factors involved may include deficiencies of GSH, Vitamin B\textsubscript{2} and L-carnitine.

Cats of any age may be affected. A key feature is that there is a dramatic rise in ALP, moderate rise in transaminases and minimal change to GGT. Ultrasonography typically shows a liver that is hyperechoic and enlarged. Liver aspirates show profound hepatocellular lipid vacuolation, with >80% of hepatocytes severely affected. One should be mindful of the possibilities of concurrent pancreatitis, pancreatic neoplasia, cholangiohepatitis, biliary obstruction and biliary tree neoplasia as these can lead to secondary HL.

Treatment is aimed at identifying any underlying disease and addressing it. Supportive care is important to lead to recovery. If recovery occurs, it is rare to have HL recur. Treatment can take weeks to months of assisted alimentary and metabolic support. A recovery rate of 85% is expected. The most important aspect to therapy is to have the cat ingest a high protein diet that provides adequate caloric density. Oesophagostomy or gastrostomy tubes are typically used. Nasooesophageal tubes can be used in the initial stages. Care must be taken to avoid hypophosphatemia associated with a re-feeding syndrome recently described. Anti-emetic and pro-motility medications are of benefit. Fluid therapy is provided until alimentation is being achieved. Electrolytes and soluble vitamins (B and K) are also added. L-carnitine and taurine may be of benefit. Ursodeoxycholic acid is not recommended as there is evidence of biliary obstruction. It may also worsen taurine deficiency, cause cellular toxicity and promote formation of lithocholic acid which itself is hepatotoxic. Antioxidant supplementation with Vitamin E and n-acetylcysteine has also been recommended.

Infections

Enteric flora can enter the portal venous system by transmural migration, but are usually killed or removed by the Kupffer cells (macrophages) of the liver, migrating macrophages or neutrophils. Locally produced IgA also assists. Some bacteria are eliminated in the bile. Conditions that predispose the liver to infection include obstruction to bile flow, impaired hepatic perfusion, oxidant damage, compromise of immunocompetence, increased translocation of enteric organisms, migrating parasites and iatrogenic factors.

Primary hepatocellular infections, particularly abscesses, are uncommon. An abscess may arise where there has been trauma, ascending biliary infection, or ischemia due to the presence of a tumour or thromboembolic disease. If immunocompromised, the patient is at greater risk. If there are multifocal abscesses and microabscesses, they are likely to have arisen along vascular or lymphatic distribution, or perhaps ascending along the biliary tract.
Septic peritonitis and abdominal effusion may be seen if an abscess bursts. Ultrasonography detects the presence of discrete focal hepatic parenchymal lesions along with peritoneal effusion. If a gas-forming organism is present, the gas will create a brightly reflective surface. Aspirates from either an hepatic lesion or abdominal effusion are likely to demonstrate neutrophils in various stages of degeneration as well as bacterial organisms. Both aerobic and anaerobic cultures of blood, urine, hepatic aspirates or bile may be positive. Polymicrobial infections typically occur with anaerobic infection, with approximately 50% of solitary abscesses in dogs being polymicrobial. As anaerobes are difficult to culture, if a variety of bacteria are seen on cytology, assume it is an anaerobic infection. Anaerobes may potentiate infection with other organisms, so therapy should be continued even if no organisms are cultured. Always look for underlying disease and manage this if detected. Adenocarcinomas and adenomas are common underlying cause of hepatic abscessation in the dog (ie non-infectious).

Good initial therapy is achieved with a potentiated-penicillin combined with fluoroquinolone or aminoglycoside. Anaerobic spectrum can be provided if the penicillin is replaced with metronidazole or clindamycin. (n.b. decreased the metronidazole dose if there is icterus or decreased hepatic function).

The abscess can be drained percutaneously with sonographic guidance. This can help to confirm the diagnosis, stabilise the patient for surgery if that is indicated, and it may be an effective form of treatment. Risks include contamination of the abdomen and therefore one should be prepared to have surgical intervention.

Management of multiple abscesses or microabscessation is with medical treatment alone using intravenous antibiotics and general supportive care. Antibiotics should be continued for some months.

Systemic infectious diseases affecting the liver include infectious canine hepatitis (CAV-1), but is rare due to effective immunization protocols. Virulent calicivirus has been associated with disseminated hepatocellular necrosis with mild inflammatory infiltration.

**Neoplasia**

Tumours of the liver and biliary system in the dog and cat may be primary or metastatic. Primary tumours are less common. The tissue of origin can be hepatocellular, bile duct, mesenchymal or neuroendocrine.

Cats more commonly have benign tumours whilst dogs typically have malignant tumours. The peak age of diagnosis is 10 to 12 years, although it is interesting to note that malignant tumours in the cat typically occur in younger cats. Female dogs seem predisposed to biliary carcinoma whilst male dogs and cats seem to suffer hepatic cellular carcinomas. Some evidence exists that hepatocellular carcinoma is predisposed by prior chronic hepatitis in the dog and biliary carcinoma is predisposed by prior chronic cholangitis in the cat.

Tumours may be massive, nodular, or diffuse in distribution. Discrete massive tumours carry the best prognosis as they are most often resectable.
In older dogs, it is not uncommon to see a **benign nodular hyperplasia** associated with vacuolar hepatopathies. These are of great nuisance value, as histopathological biopsy is the only means of differentiating these innocuous lesions from significant pathology.

**Biliary cystadenomas** can be seen as single or multifocal tumours that are considered benign in older cats. However, if located in the porta hepatis, can lead to malignant behaviour through obstruction to vasculature or the biliary system. In younger cats, one may see polycystic disease affecting the liver with or without renal involvement.

Primary hepatic tumours tend to metastasize to the regional lymph nodes, then lung and peritoneum in the dog, whilst in the cat, the pattern is to spread to the peritoneum. The exceptions to this in the cat are biliary tumours that may extend to the pancreas. Far less commonly affected sites are the brain, spinal cord, bone, kidney, adrenal gland and spleen.

Secondary metastases to the liver are common in both dogs and cats, and are regarded as more common than primary tumours. Lymphoreticular neoplasia is seen in the liver in dogs and cats, and represents the largest proportion of hepatobiliary neoplasia in the cat.

Many dogs and cats with hepatic neoplasia may be free of clinical signs (25% and 50% respectively) at the time of diagnosis. Often the only finding is a palpable cranial abdominal mass or hepatomegaly. Where symptomatic, the usual signs of liver disease are present, including peritoneal effusion and hepatic insufficiency causing hypoglycaemia or hepatic encephalopathy.

Haematology is usually the non-specific change typical of liver disease. Lymphoma may show with circulating lymphoblasts, whilst with mast cell tumours, peripheral eosinophilia may be seen.

Clinical pathology is non-specific as well. It is noted that alpha-fetoprotein (AFP) may increase in dogs with hepatocellular carcinoma, lymphoma, chronic hepatitis or rapidly regenerating liver disease. Therefore measuring its levels may help with monitoring response of disease to treatment.

If ascites is present, cytological assessment of the fluid may assist with diagnosis.

Diagnostic imaging is the most useful non-invasive technique for detection of mass lesions and extent of metastasis. Radiography may show evidence of hepatomegaly and displacement of other abdominal organs. It may also occasionally detect dystrophic mineralisation of masses. Pulmonary metastases are detected on lung radiographs.

Abdominal ultrasonography has a variable sensitivity to detect neoplasia (reported to vary from 20 to 84%). This can be dependent on equipment quality, operator skill and type of tumour. However, there is no reliability in differentiating various patterns of generalised liver parenchymal change or even focal lesions. Of the tumours, lymphoma shows the greatest variation in appearance, being able to mimic any other lesion or appear like perfectly normal tissue. Other pathology that can have similar sonographic appearance to neoplasia includes haematoma.

CT or MRI may provide additional information on tumour staging and planning for surgery.
Definitive diagnosis still requires some form of biopsy, from simple fine needle aspirate biopsy cytology through to surgical resection of the tumour. Lymphoma, mast cell tumours and carcinomas can often be comfortably diagnosed by cytology alone. Error still does occur, so careful interpretation is necessary. All forms of biopsy carry the risk of haemorrhage, however FNA biopsy carries the least.

The treatment options and prognosis varies with type, location and extent of neoplasia. If neoplasia is focal or restricted to a liver lobe, surgical resection remains the best therapy. If the tumour involves the porta hepatis, resection is not feasible. Otherwise, with adequate supportive care, up to 80% of the liver can be resected. During surgery, do not to assume any additional nodules are metastatic disease, as many benign nodular diseases can co-exist with neoplasia. Where haemabdomen has occurred, subtotal resection of mass lesions can still be life-sparing by stopping further bleeding. If biliary obstruction has occurred, biliary diversion surgery is indicated, otherwise cirrhosis will occur within 6 to 8 weeks.

The best prognosis is associated with focal canine hepatocellular carcinoma in dogs and benign tumours in the cat. Following surgical resection of hepatocellular carcinoma (HCC) in the dog, MST is 377 days. Tumours with poorest prognosis include biliary carcinoma in the dog and malignant tumours in the cat. Biliary carcinoma carries a high metastatic rate in dogs (56 to 88%) and cats (67 to 78%). Surgical resection for this tumour is difficult.

In cats, the benign tumours such as biliary adenoma and myelolipoma should still be resected as they may undergo later malignant transformation or eventually involve other vital structures such as vessels and biliary tract.

Post-operative chemotherapy has been shown to be of some benefit in dogs with haemangiosarcoma. Other tumours that can be controlled with chemotherapy are canine mast cell tumour and lymphoma. Radiation is not an option for liver tumours as the liver is exquisitely sensitive to its effects. Newly reported means of therapy include percutaneous injection of alcohol and chemoembolization. However, data on their use in small animals is lacking.

**Canine Inflammatory Hepatic Disease**

**Chronic hepatitis (CH):**
Previously this has been known as chronic active hepatitis or chronic lobar hepatitis. This term covers all diseases that are chronic, ie longer than 4 to 6 months and show apoptosis or necrosis of hepatocytes associated with inflammatory infiltrate (may be mixed, but usually lymphoplasmacytic). Typically CH will progress to fibrosis and cirrhosis. If a cause is known, it is included in the term as an adjective, but is otherwise understood to be idiopathic. Severity can also be described (ie mild, moderate or severe).

Various causes include heavy metals such as copper, drugs or infectious agents. There are also familial tendencies which now include the Doberman pinscher, Bedlington terrier, West Highland white terrier, Cocker spaniel, Dalmatian, Skye terrier, standard poodle, Labrador retriever, German shepherd dog, Scottish terrier, English springer spaniel and beagle. These
dogs are typically 4 to 7 years of age when affected. Sex predilection is variably reported. However minor variations occur with each breed.

An immune-mediated mechanism is implied as a correlation between the number of CD3+ lymphocytes and chronic hepatitis in dogs has been found. Both ANA and antibodies to liver membrane proteins are occasionally reported, but this is a non-specific finding. In the Doberman, MHC class II antigen expression has been found on hepatocytes from affected dogs but not controls.

The boxer and Anatolian shepherd have also had copper associated with their form of CH - but these have been single case reports. In the Bedlington terrier, there is inability to excrete copper into the biliary tract, so causing formation of reactive oxygen species (ROS) which causes the hepatitis and ultimately cirrhosis. It is known that copper can accumulate secondary to the presence of inflammation, cholestasis and increased dietary copper intake, but the amount is relatively minor. Normal dogs usually have <400 ug copper/g hepatic tissue dry weight (or ppm), whilst copper-associated CH sees copper concentrations >2000 ug Cu/g liver. This finding suggests that the copper causes the inflammation. Copper toxicosis is suggested if copper first accumulates in zone 3 of the acinus (ie centrlobular). Some affected dogs also have concurrent Fanconi syndrome.

Iron can also accumulate in the liver of dogs with hepatic disease. Normal concentrations are 400 to 1200 ppm, whilst levels up to 7680 ppm have been found in dogs with hepatitis. The iron tends to accumulate in Kupffer cells and other macrophages rather than hepatocytes. Nonetheless, this may aggravate pre-existing hepatic damage.

Another possible cause of CH in the dog is α1 antitrypsin where its accumulation in hepatocytes may lead to hepatocyte death as in humans. As these cells die, mononuclear cells are attracted and they produce more α1 antitrypsin. Even though seen in higher concentration in dogs with CH or cirrhosis, whether it is a cause or effect remains unanswered.

Clinical signs of CH vary dramatically because this is such as slow and insidious disease. For that reason, sometimes dogs presenting with what appears to be acute onset of signs are already in advanced and near-end-stage disease. Where cirrhosis is present, signs include lethargy, depression, anorexia, vomiting, weakness, weight loss, polyuria/polydipsia, ascites, and diarrhoea. Icterus is however uncommon, whilst seizures, bleeding and fever are rare. When not in hepatic failure, signs tend to be vague, with often just lethargy, weight loss, anorexia, and/or vomiting. Occasionally, this disease can be detected early with fortuitous blood testing finding elevations of ALT and low albumin. Even though clinically normal, disease may still be well advanced, but compensated. It is interesting that migratory necrolytic erythema rarely coexists with CH, even though West Highland white terriers and Cocker spaniels seem predisposed to both diseases. Myopathy can also be associated with CH.

ALT is the most consistently elevated liver enzyme, often 5 to 18 times normal, whilst elevations in ALP will be more modest. If cirrhosis develops, these enzymes may moderate as there is less viable liver tissue. Hypoalbinuminema or hypocholesterolemia may reflect reduced hepatic function. Further evidence of reduced hepatic function may be low BUN and elevated serum bile acids. Hypoglycemia is fortunately rare, but is associated with a poor
prognosis. Prolongation of coagulation times have been reported in 10 to 60% of dogs with CH. The prolonged PT may be prognostic, as can be thrombocytopenia.

Radiography is of little assistance in diagnosis, unless ascites or microhepatica is detected. In a similar way, ultrasonography is also of limited assistance as changes are typically non-specific, unless obvious microhepatica, nodularity of the liver with cirrhosis or ascites are present. Development of ascites carries a poor prognosis. Acquired portosystemic shunts may be present, and rarely, ‘target’ lesions are observed in the liver.

Definitive diagnosis requires histopathological assessment of the liver. No ideal method of biopsy collection has been identified. As a warning, in one study, core needle biopsies missed histological changes seen in surgical biopsies in 52% of biopsies in 124 dogs and cats.

Histopathology shows hepatocellular apoptosis or necrosis, particularly piecemeal necrosis or interface hepatitis (interface between parenchyma and connective tissue) and inflammation (mixed, but primarily lymphocytic and plasmacytic). Necrosis eventually extends between portal areas and to central veins (bridging necrosis). Hydropic change, vacuolar change typical of steroid hepatopathy, is common and may reflect the chronic stress occurring. Regeneration, regenerative nodules and bile duct proliferation are common. In advanced CH there is fibrosis and may lead to cirrhosis. Rarely, there is portal thrombosis. Copper may be present, seen with special stains, or measured.

Therapy is aimed at the underlying cause if one is identified. Otherwise, it is the use of supportive care, anti-inflammatories, and anti-oxidants that are the mainstays of therapy. Reducing or preventing fibrosis and treating hepatic encephalopathy may be necessary.

Inflammation is reduced with the use of glucocorticoids. They also inhibit fibrosis and stimulate appetite. Copper absorption may also be reduced, this making the patient feel better. The corticosteroids seems to work better with animals with less advanced disease and may not assist the severely affected. Prednisolone tends to cause less side effects than dexamethasone. Although the steroids induce further elevation of ALP, monitoring ALT may show improvement in the hepatitis. Where steroids are ineffective or cause adverse effects, azathioprine or cyclosporine can be considered.

Antioxidant therapy is indicated. Vitamin E is cheap, safe and may have potential benefit. S-adenosyl-L-methionine, silymarin and ursodeoxycholic acid are indicated, but only the latter has shown clinical efficacy.

If copper is shown to be present at levels greater than 2000 ppm of liver, copper chelation therapy should be considered. D-penicillamine is the initial drug chosen. Repeat liver biopsies can track effectiveness. This drug also has anti-fibrotic and anti-inflammatory effects. Trientine (or tetramine) is another chelator that can be considered.

Orally administered zinc can help displace copper and reduce intestinal absorption of copper. Care is needed as excessive doses can cause haemolytic anaemia. Diets low in copper would seem indicated, however effectiveness remains unknown.
Fibrosis and Cirrhosis:
Any severe or chronic hepatic insult can lead to fibrosis and cirrhosis. Once hepatocellular necrosis occurs following inflammation, the space created is filled with more inflammatory cells. Following hepatocellular necrosis, instead of hepatocytes and biliary epithelium regenerating, the release of lysosomal proteases and radicals leads to the attraction of Ito cells that produce collagen. Fibrosis results and this alters the extracellular matrix so that hepatocytes growing on this are functionally altered.

So, where there has been acute massive necrosis or CH, fibrosis is a common result. Fibrosis, as it progresses, can lead to bridging of connective tissue from central vein to portal triad. Cirrhosis is when this bridging fibrosis causes permanent distortion, regenerative nodules and porto-central vascular anastomoses. If the fibrosis cuts across the acinar zone, micronodular cirrhosis results. If the fibrosis surrounds the bile ducts, biliary cirrhosis results. Fibrosis leads to inability of vessels and sinusoids to expand, and therefore resistance to blood flow is increased. This impairs perfusion and oxygenation, leading to decreased hepatocyte function.

As mentioned before, preventing fibrosis is an important goal to the long-term management of CH. Prednisolone, azathioprine, penicillamine, zinc and Vitamin E may inhibit or delay fibrosis. Colchicine, increases collagenase activity and may be used if severe fibrosis already exists. However, like so many of these treatments, there is limited information to support its efficacy.

Infectious Canine Hepatitis and Chronic Hepatitis:
Canine adenovirus 1 (CAV-1) has been found in some dogs with chronic hepatitis. PCR gives only a low percentage of positive results. No cause and effect relationship has been found. Some authors propose that the viral infection initiates a self-perpetuating form of chronic hepatitis.

Lobar Dissecting Hepatitis:
In this disease, the inflammatory cells are found diffusely throughout the hepatic lobule rather than being restricted to periportal regions. Collagen and reticulum fibres are seen dissecting around small groups or single hepatocytes - ie dissecting. Even though copper is found in the liver, it appears to be secondary rather than a cause. Mainly neonates and young dogs are affected (11 month mean in one study). Ascites is the most common presenting sign, and liver enzymes are elevated. There may be a breed predilection in Standard Poodles. A similar change has been reported in the cat.

Drug-Associated Hepatitis:
As discussed earlier, hepatitis can occur with many drugs, but a few a particularly associated with fibrosis. Included are trimethoprim/sulphonamide, phenobarbital, diethylcarbamazine-oxibendazole, amiodarone, and carprofen, but even here, the inflammation is relatively mild and does not result in an appearance resembling CH. Some individuals however do have severe inflammation.

Cholangiohepatitis:
This is defined by mixed periportal (zone 1) inflammatory infiltrates with inflammation usually extending through and into the bile ducts. Cytology and culture should be performed to rule out ascending bacterial infection. ALT, ALP and bile acids tend to be higher than seen with
CH, but overlap in values prevents differentiation on laboratory tests alone. Drugs have also been implicated occasionally. Perhaps antibiotic therapy is indicated here.

**Acidophil-Cell Hepatitis:**
This is a probable viral, transmissible disease reported in the UK. In the acute phase there is little inflammation but CH and cirrhosis may be sequelae. Biopsy is required for diagnosis, with acidophil cells with angular shape and acidophilic cytoplasm seen throughout the parenchyma.

**Leptospirosis:**
Acute renal failure is the typical presentation but depending on serovar, hepatitis can also be present. Histopathology in the acutely infected dog shows oedema and congestion with occasional mild neutrophilic and eosinophilic infiltrates. Various studies have identified evidence of Leptospirosis in dogs with various forms of hepatitis, including CH.

**Granulomatous Hepatic Inflammation:**
This is an uncommon disease characterised by multiple discrete and sharply defined nodular infiltrates consisting of aggregates of macrophages (sometimes with epithelial cells). Surrounding the nodule can be lymphocytes and plasma cells. The lesions can be focal, multifocal or diffuse. Inciting causes include bacteria (*Nocardia, Mycobacterium, Rhodococcus, Borrelia, Bartonella*), fungi (histoplasmosis, coccidioidomycosis), and parasites (*Hepatozoon, Heterobilharzia*). Non-infectious causes include drug reaction, lymphangiectasia, histiocytosis or histiocytic neoplasia, lymphosarcoma, immune-mediated inflammation, and copper-associated inflammation. Finding a cause may be difficult, and in one report, less than 50% were identified with a cause, so many if not most, are idiopathic.

Clinical signs vary. Culture, serology and PCR is indicated when this reaction is found on histopathology. If a cause cannot be found, it still may be wiser to treat with anti-infective agents before trialling immunosuppressive drugs.

**Leishmaniasis:**
This infection of dogs seldom presents with signs of hepatic disease. Whilst biochemical changes are occasionally found, histologic changes are common. Most infected dogs have granulomatous or pyogranulomatous portal infiltrates. Amastigotes are commonly found.

**Babesiosis:**
Anemia and fever are the typical clinical signs, however non-suppurative hepatitis has been reported.

**Feline Inflammatory Liver Disease**
The basis of Liver Standardization Group classification of feline inflammatory liver disease has been on the major inflammatory cell type seen on biopsies. Either the neutrophil or the lymphocyte is the major cell seen, and therefore three distinct forms are recognised: lymphocytic cholangitis, neutrophilic cholangitis and cholangitis associated with liver fluke. These forms also tend to have differences in their presentation and management, making for easier clinical case management – however this is still not a perfect scheme.
The cholangitis complex is regarded as the most common hepatic disease of cats where hepatic lipidosis is not highly prevalent.

Cholangitis is now the preferred term as hepatic parenchymal involvement in the inflammation is not a consistent feature, and is only an extension of the primary cholangitis. In fact, primary hepatic parenchymal inflammation is regarded as being quite rare in the cat.

**Neutrophilic Cholangitis:**
Obviously, the dominant inflammatory cell is the neutrophil, found within the bile duct lumen and/or epithelium. This inflammation can be subdivided into acute and chronic phases.

In the acute phase, the limiting plate may be disrupted with neutrophils spilling out into the portal areas. If it extends to hepatic parenchyma, abscessation may occur. Periportal necrosis is common and bile ducts show necrosis and degeneration. Depending on the phase of the disease, fibrosis will be found in various extent.

In the chronic phase, there will be fibrosis and bile duct proliferation, whilst the inflammatory reaction becomes more mixed. There can be marked variation in the distribution of lesions, from few portal tracts to diffuse hepatic change.

Mild pancreatitis commonly accompanies neutrophilic cholangitis – reported in the majority of cases clinically and in 50% of a retrospective pathological study. Inflammatory bowel disease also was been diagnosed in up to 83% of cats with cholangitis in the same pathological study. In the IBD, the inflammatory reaction was predominantly lymphocytic and plasmacytic, however in some cases a neutrophilic component was present.

This finding has led to the coining of the term ‘triaditis’ and perhaps reflects a common cause to these entities. Neutrophilic cholangitis is believed to be caused by ascending bacterial infection along the biliary tract. Generally, bacteria can be recovered from samples of bile, and typically reflect a mixed population of common gut flora. In some cats, *Helicobacter* may play a role.

It has been proposed that IBD may predispose to ascending infection from the bowel along pancreatic and bile ducts (joined before entering the duodenum) into the pancreas and liver respectively. In triaditis, it is the cholangitis that is regarded as the predominant feature with pancreatitis and IBD being complications.

This disease is more commonly seen in middle-aged and older cats. They usually present as acutely ill cats, often being anorexic and pyrexic. Vomiting is common. Icterus is also common, mainly due to intrahepatic cholestasis. Abdominal pain may be present.

Clinical pathology shows evidence of hepatopathy, but does not distinguish this from lymphocytic cholangitis. Diagnostic imaging also shows no distinct differentiation, however increased echogenicity and evidence of obstruction to the extra-hepatic biliary tract may be seen. Cholelithiasis is commonly encountered.

Histopathology is necessary for definitive diagnosis – this can be from fine needle aspirate, through to core biopsy or wedge biopsy. Surgically collected biopsies allow concurrent examination of the pancreas and bowel, as well as giving opportunity to biopsy these organs.
and re-establishing bile flow if obstructed (either through manipulation or surgical redirection).

Treatment involves use of a broad-spectrum, bactericidal combination, such as potentiated-penicillin, fluoroquinolone, cephalexin and metronidazole. Corticosteroids should be avoided, however may have some benefit in assisting re-establishment of bile flow through reducing inflammation and fibrosis. They should not be used without concurrent antibiotic use.

Cholecystectomy or cholecystoduodenostomy may be necessary in some cases where inspissated bile is present. Surgical risk is high, but prognosis is reasonable if survived! So surgery should only be performed where absolutely necessary.

Supportive care includes the use of fluid therapy, nutrition, and choleretics (such as ursodeoxycholic acid). Vitamin K is indicated if there is clotting dysfunction. There is no evidence of whether SAMe is of benefit.

Prognosis appears to be reasonable, with many cats living for more than a year after diagnosis and successful treatment. Recurrence can occur and can be soon after initial treatment. If surgery is required to re-establish bile flow, prognosis appears to be worse. Concurrent triaditis complicates the management and prognosis. Consideration is given to use of immunosuppressive (for pancreatitis) or anti-inflammatory (for IBD) doses of corticosteroids and dietary change.

Lymphocytic Cholangitis:
A predominantly lymphocytic infiltrate is seen restricted to the portal areas, often with variable portal fibrosis and biliary duct proliferation. Lymphocytes centred around bile ducts or present in the biliary epithelium are not a consistent feature, nor is there usually any infiltrate within the lumen of the bile ducts, and no epithelial degeneration. Solitary plasma cells and eosinophils may be present. Sometimes neutrophils are seen. Fibrosis is also variable, but can become severe in chronic disease. Initially the fibrosis is restricted to a septal or monolobular pattern, with bridging fibrosis between portal areas. Prominent nodular hyperplasia frequently eventuates. The vasculature may become disrupted, with a prominence of small vessels seen on the liver surface.

Lymphocytic portal hepatitis is possibly a distinct entity or may be part of lymphocytic cholangitis. This is a mild, non-specific reaction commonly seen in older cats and found as an incidental finding. In one survey, 29/30 cats older than 15 years had this change. However, some cats with clinical signs of liver disease have had this change seen on histopathology. Yet, again, reports of pancreatitis and IBD have accompanied lymphocytic portal hepatitis, but do not seem particularly related to lymphocytic cholangitis.

An immune-mediated mechanism is suspected with lymphocytic cholangitis with the predominant lymphocyte being CD3+ T-cell. There are also IgA+ plasma cells and MHC class II expression by a variety of immune cells. Antibodies against liver cell components have not been identified. Some have postulated that an inciting cause triggers initiation of lymphocytic cholangitis, and with progression, clinical signs then develop. It also possible that lymphocytic cholangitis represents the chronic stage of an earlier neutrophilic cholangitis. But the weight of evidence still maintains these two diseases as separate entities.
This disease seems to be less common than the neutrophilic form and typically is seen in cats less than 4 years of age. There is a predisposition in Persian cats. Icterus and ascites are the two main presenting signs, with icterus being the most common. Some cats may just show weight loss despite an apparently good appetite. Hepatomegaly may be palpated. Pyrexia is unusual. Mesenteric and sometimes superficial lymph nodes may be enlarged. Hepatic encephalopathy may occur in chronic cases. As clinical signs may be so mild, there can be a delay before diagnosis is made.

Ascitic fluid may be thick with a high protein content (mainly globulins), being clear to yellow and a low cellular content.

Hepatomegaly may be detected on radiography and ultrasonography. Echogenicity of the parenchyma may be increased.

Biopsy is required for diagnosis. FIP is an important differential diagnosis due to the type of ascitic fluid present, as is lymphoma due to the lymph node enlargement. Reliable differentiation requires histopathology.

Treatment is based on use of corticosteroids at immunosuppressive doses. Use of other agents has little clinical data to support their use. In Europe however, it was reported that corticosteroids had no significant effect on the disease. There are no controlled studies in the use of colchicine. Choleretics, SAMe and nutritional support may be helpful. Abdominoceotesis may be considered when ascites is severe, otherwise use of diuretics and ACE-inhibitors may be useful.

Prognosis would appear to be reasonable, with most cats responding to therapy. Mean survival in 25 cats was 37 months. Prognosis may be better for cats with icterus rather than ascites. Some individuals may need to remain on prolonged therapy, or repeated therapy.

**Mixed Inflammatory Infiltrates:**
Some cats with inflammatory liver disease show a mixture of both neutrophil and lymphocyte infiltration. Bile duct proliferation with epithelial degeneration and necrosis is seen. The inflammatory infiltrate occurs within the lumen of the bile ducts, differentiating this from lymphocytic cholangitis. The Liver Standardization Group suggests that this is usually a chronic form of neutrophilic cholangitis, but in some cases may be an acute episode of neutrophilic cholangitis superimposed on a pre-existing lymphocytic cholangitis.

The clinical signs tend to be mild and waxing-waning, with gradual weight loss. Treatment poses a problem as it is not known whether to use antibiotics or corticosteroids. One recommended approach is to treat with antibiotics first, whilst waiting for bacterial cultures. If positive, antibiotics are continued for 4 to 6 weeks, and if there is not clinical recovery, corticosteroids are used. If the culture is negative, the antibiotics are continued for 2 to 3 weeks, but glucocorticoids are used simultaneously.
Cholangitis associated with Liver Fluke (Platynosomum sp):
This parasite does not appear to be in Australia or New Zealand. Infection occurs following ingestion of raw freshwater fish or amphibians by the cat. The flukes migrate to the liver causing dilation of bile ducts with papillary projections and periductal and portal fibrosis. A mixed, mild to moderate inflammatory infiltrate may be present within bile ducts and portal areas. Flukes and eggs are present but rarely seen within bile ducts. Parasiticides are the treatment administered.

References:
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