There are a number of specific liver diseases unique to the cat and very different than the liver diseases observed in the dog. This is due in part to specific anatomical and metabolic differences of the cat. The following are brief descriptions and updates and newer information on common feline hepatic diseases. The clinician should however be aware that the liver pathology might also be secondary to a variety of primary non-hepatic disease conditions. This category is grouped into the classification of a reactive hepatopathy. The histology of reactive hepatopathies are nonspecific often with a variable degrees of lipidosis.

**Overview of Liver Enzymes in Cats**

In a study evaluating the utility of liver biochemistries in the diagnosis of feline liver disease found the best predictive tests for primary liver disease includes ALP, GGT, total bilirubin and bile acids. The ALT and AST are quite variable and elevations don’t always predict primary inflammatory liver disease or hepatic lipidosis. ALP is unique in cats in that the half-life is short (6 hours) and the feline liver is reported to contain only one-third the concentrations found in dogs. Consequently, increases in serum ALP with cholestasis are not expected to increase with the same magnitude as observed in dogs with similar diseases. ALP is also not induced by corticosteroids nor does it cause a steroid hepatopathy. Gamma-glutamyl transpeptidase (GGT) is a similar enzyme to ALP that increases with cholestasis and is more sensitive for feline inflammatory liver disease than ALP. Uniquely cats with idiopathic hepatic lipidosis usually have marked increases in SAP while GGT concentrations show only mild increases.

Increases in total bilirubin generally greater than 3.0 mg/dl cause clinical icterus and usually indicates primary liver disease. Biochemical increases in total bilirubin (but less than 3.0 mg/dl) can sometimes increase with secondary reactive hepatopathies and does not always indicate a primary hepatopathy is present. In the non-icteric cat abnormal bile acids are also indicators of significant liver disease or portosystemic shunting.

**Liver Diseases in Cats**

The incidence of liver disease in cats is common. When we reviewed 175 liver biopsies it was evident there were several large categories of conditions observed. Making up 87% of the liver biopsies were 4 large groups: Idiopathic and secondary lipidosis (26%), Cholangitis (25%), Neoplasia (20%) and Reactive hepatopathies (16%). Hepatic cysts are also an occasional finding in some cats and rarely cause problems. Lipidosis and cholangitis will be discussed below. Reactive hepatopathies refer to changes in the liver felt to be secondary to a primary non-hepatic disorder such as inflammatory bowel disease, hyperthyroidism and cardiac disease as examples. Hepatic neoplasia was also common. Cats are different than dogs in the fact that benign tumors and more common than malignant hepatic neoplasia. Bile duct adenomas (cyst adenomas) were the most common benign tumor and bile duct carcinoma the most common malignant neoplasia when hematopoietic tumors are excluded.

**Idiopathic Hepatic Lipidosis.** Hepatic lipidosis can occur as a primary idiopathic disease syndrome or secondary to a number of other primary disease conditions. Lipid accumulation in the liver is simply the result of nutritional, metabolic or toxic insults to the liver and the degree of lipid accumulation can be quite variable. For example, a common secondary disease associated with significant hepatic triglyceride accumulation is diabetes mellitus. This diagnosis is generally obvious (hyperglycemia and glycosuria) and the lipidosis resolves with appropriate therapy. Hepatic lipid accumulation can also result secondary to a number of other disease syndromes such as pancreatitis, starvation or other organ dysfunction. These conditions generally have less severe lipidosis than the clinical syndrome associated with idiopathic hepatic lipidosis in which there is no identifiable etiologic factor.

The etiology of idiopathic hepatic lipidosis is unknown and many theories have been put forward without substantial documentation. A current novel proposal is that there is a defect in hepatic lipid mobilization and decreased ability for hepatic fat oxidation, decreased synthesis of apoproteins and decreased lipoprotein removal from the liver. Supporting this
theory is identification of ultrastructural changes including reduction of hepatic peroxisomes, altered mitochondria and altered endoplasmic reticulum. The cause for the rapid mobilization of peripheral fat is as yet unknown. A second novel theory put forth is that the disease is a central CNS disorder causing the anorexia and the lipidosis then results. It is important to investigate any possible disorder causing anorexia and initiating the typical cascade of hepatic lipidosis.

Affected animals generally are older obese cats that have undergone a stressful episode and with associated anorexia. There does not appear to be a breed or sex predisposition. Cats will present with an acute history of rapid weight loss (40-60% body weight over 1-2 weeks), depression and icterus. The weight loss is significant with loss of significant muscle mass while abdominal and inguinal fat stores are often spared. Typical neurological signs commonly associated with hepatic encephalopathy in the dog are uncommon. Complete anorexia, lethargy and depression may however be the result of hepatic encephalopathy. The diagnosis of idiopathic hepatic lipidosis is supported by the clinical history and laboratory findings. Icterus and marked elevations in ALP are consistent findings. ALT (SGPT) levels are generally abnormal but quite variable. GGT concentrations are only moderately elevated in these cats. Icterus with a very high ALP and normal GGT should be a clue to probable idiopathic lipidosis given appropriate clinical features. Hypercholesterolemia, hyperammonemia and abnormal bile acid levels are characteristic. Protein levels are usually normal, glucose levels moderately elevated but a few cats may actually have concurrent diabetes and recently several cats were reported to have pancreatitis and measurement of fPLI is warranted. About 1/3 of the cats have a nonregenerative anemia, hypokalemia and clotting abnormalities and about 1/2 the cats demonstrate poikilocytes in the RBC's. Severe hypokalemia, anemia or other concurrent disease (ie pancreatitis) in lipidosis cats that had a poor survival.

The liver size may be normal or enlarged on palpation or radiographically. A definitive diagnosis requires a liver biopsy or hepatic cytology. A fine needle aspirate of the liver with cytological evidence of many vacuolated hepatocytes helps support a diagnosis. Be aware that cytological diagnosis does not always correlate with histology. A needle aspirate can be performed with the cat in dorsal recumbency and a 22 g needle on a syringe directed slightly cranial and lateral to the left from the left xiphoid space. The aspirate can be stained with Diff-quick or Sudan stain. A hepatic tissue biopsy confirms the diagnosis. Care should be taken when obtaining a liver biopsy as some cats may have coagulation abnormalities.

The therapy for idiopathic hepatic lipidosis requires aggressive management. Approximately 80% or higher survival rate should be expected in cats given appropriate therapy and no underlying disease. Initial therapy requires rehydration with balanced electrolyte solutions. Replacement of potassium depletion is imperative as normokalemia improves survival. Some cats may require magnesium supplementation as well. Administration of glucose containing solutions may actually cause marked hyperglycemia in these patients. Cats also have a tendency to develop lactic acidosis and therefore lactate containing fluids (i.e. Lactated Ringers) should be avoided. The practice of adding B-vitamins to the fluids should be avoided because prolonged exposure to light in the fluid bag will inactivate them. Parenteral administration is a better option.

Adequate nutrition then becomes the most important part of the therapy for hepatic lipidosis. Since these animals are not eating forced feeding becomes necessary. In the authors experience these drugs to stimulate the appetite only produce sedation, enhance encephalopathy and rarely do cats eat their caloric needs given these drugs. Hand forced feeding may be used but it is usually difficult to supply adequate caloric support through this method and this becomes a major stress factor to the cat.

Tube feeding is the best way to administer adequate calories. Nasogastric tubes can be used but due to the small size limit the consistency of food administered and appears to be less tolerated than gastrostomy tubes. I suggests placement of an esophageal or gastrostomy feeding tube. In our practice we find that esophageal tubes to be well tolerated and having less complications than gastric tubes. One should refer to specific articles on tube placement techniques. We find the 20 French red rubber feeding tubes ideal for the esophagus.

The nutritional recommendations for idiopathic hepatic lipidosis are completely empirical and poorly documented. There are numerous reports in the literature suggesting various diets (with a variety of protein and fat content recommendations) and various dietary supplements. There is evidence that L-carnitine supplementation in cats may protect against hepatic lipid
accumulation and consequently may be an appropriate dietary adjunct for patients with liver disease. Carnitine is required for transport of long chain fatty acids into the mitochondria for subsequent oxidation and energy production. A deficiency of carnitine may lead to impaired mitochondrial function. It appears that carnitine deficiency could result in chronic liver disease and that supplementation may help protect against encephalopathy, hypoglycemia, and subcellular damage. Studies have however failed to show carnitine deficiency in cats with hepatic lipidosis. Suggested dose is 250-300 mg/day. Supplementation is reported to be associated with better survival rates, however this is poorly documented.

The author also believes that stress plays a major role in this disease process and the sooner a patient can be stabilized and sent home away from the hospital environment the better. Most owners generally can manage tube feeding the cats at home. The tube should not be removed until the cats are voluntary eating adequate calories on their own. Tube feeding often averages about 4-6 weeks.

Considerable interest and research is being directed at various nutrient supplements and at this time the recommendations are only speculative or anecdotal. Some suggest arginine (1000 mg/day), thiamine (100 mg/day) and taurine (500 mg/day) however if feeding an adequate diet this should not be required. Some suggest L carnitine (250 mg/day) supplementation and there may be some benefit in this supplementation though not well documented. Other supplements suggested include zinc, fish oil, and potassium. There is also evidence to suggest many cats with hepatic lipidosis have cobalamin deficiency. Studies found cobalamin (vitamin B12) was depleted in many cats with lipidosis. Experimental cobalamin deficiency results in lethargy, anorexia and weight loss. Anecdotal reports suggest cats improve faster with high doses of cobalamin given 250 µg SQ weekly. Serum cobalamin levels can be determined to document the deficiency.

Other therapies suggested include S-Adenosylmethionine (SAMe) Denosyl SD4 (Nutramax) is a nutraceutical that is a naturally occurring molecule found in all living organisms involved in the metabolism of glutathione (GSH). GSH participates in many metabolic processes and plays a critical role in detoxification mechanisms of the cell. Depletion of hepatic GSH can indirectly cause toxic effects in these cells by increasing oxidative stress. Exogenous administered SAM has been shown to increase intracellular GSH levels in hepatocytes and prevents GSH depletion when exposed to toxic substances thus acting indirectly as an antioxidant. SAMe is also important in hepatocyte membrane integrity and function. The suggested dose is 100 mg/day. The benefit of SAMe or other antioxidants in hepatic lipidosis is unknown. Another antioxidant hepatoprotectant is milk thistle or its extract silybin (Marin™), a safe hepatic support therapy.

The prognosis is guarded however has markedly improved with aggressive nutritional therapy and treating secondary complications. It is reported that about 2/3 of the cats with hepatic lipidosis survive with such therapy. There is a need for good controlled studies evaluating various therapies. Weight reduction appears to be essential in prevention as obesity plays a role in this disease.

**Feline Inflammatory Liver Disease (Cholangitis).** Cholangitis is an inflammatory disorder of the hepatobiliary system. It appears to be a disease complex that may be concurrently associated with duodenitis, pancreatitis, cholecystitis and/or cholelithiasis. The terminology is somewhat confusing and pathologists describe the condition differently. Based on the histological classification of the WSSAV Liver Standardization Group this complex has been separated into three histological groups; acute neutrophilic (suppurative) cholangitis, chronic neutrophilic (mixed inflammatory infiltrates) cholangitis, and lymphocytic cholangitis. It is probable that the neutrophilic acute and chronic forms of cholangitis represent different stages of one disease.

**Acute Neutrophilic (Suppurative) Cholangitis.** This is an acute neutrophilic inflammation of the portal triads and bile ductules. It is thought to be the result of an ascending bacterial infection. Usually coliforms (E. coli) are cultured from the liver or bile. Inflammation can also extend into the hepatic parenchyma causing a cholangiohepatitis. There is in some cats an association of pancreatitis, cholelithiasis or even biliary obstruction.

Cats with this syndrome are usually young (~3-5 years) and present with acute illness usually a week or less in duration. They may have evidence of a fever, anorexia, vomiting or lethargy. A leukocytosis is generally identified on the CBC. The ALT and ALP are increased but variable and these cats are frequently icteric. Ultrasound should be performed to rule out
pancreatitis and biliary obstruction. In some cases we will perform an ultrasound-guided cholecystocentesis for cytology and culture. A liver biopsy is required for histology and will confirm the diagnosis. The liver should be cultures too. If obstruction is identified surgery becomes indicated to decompress and flush the biliary system. I always try to avoid surgical diversion surgeries unless it is the last resort.

Therapy for these cats first includes fluid and electrolyte therapy if needed. Antibiotics are a critical part of the therapy as well. Ampicillin, cephalosporin and metronidazole have been suggested as effective antibiotics. Unless a culture and sensitivity says otherwise ampicillin is my choice because of the likelihood of *E. coli* and the fact that it is concentrated in the bile. It is recommended that cats be treated for at least 1-2 months with antibiotics. Short duration of therapy may result in reoccurrence of clinical signs. Ursodeoxycholic acid (Actigall 10-15 mg/kg/day) should be used as well.

**Chronic Neutrophilic Cholangitis.** Chronic (neutrophilic, mixed or lymphocytic-plasmacytic) cholangitis may be the result of progression of the acute neutrophilic cholangitis. In the chronic stage the liver lesions are associated with the presence of a mixed inflammatory infiltrates in the portal areas consisting of neutrophils, lymphocytes and plasma cells. Possibly fibrosis, ductular proliferation or extension of inflammation into the hepatic parenchyma can occur as well. There is also a direct relationship between chronic cholangitis and inflammatory bowel disease and chronic pancreatitis. One study found 83% of affected cats had inflammatory bowel disease and 50% had concurrent chronic pancreatitis. The association of the three together has been referred to as triaditis (see below). Possibly the common channel theory where the pancreatic ducts and bile ducts join before entering the duodenum explain this triad of clinical signs. Ascending bacteria initiate the acute disease and then over time it becomes chronic. In a recent abstract presented at the ACVIM Forum in 2009 we reported that many >60% of the cats having chronic neutrophilic cholangitis had bacteria in the liver associated with portal areas and specifically bile ducts based on non-culture methods using FISH immulogic staining for bacteria. The most common bacteria included *E. coli* and *Enterococcus*.

Affected cats are usually middle aged or older and have a long duration of signs being weeks to months. Presenting complaints are often vomiting, lethargy and anorexia. Signs may wax and wan and weight loss may be present. Physical findings identify jaundice in most, possibly hepatomegaly and rarely abdominal effusion.

The laboratory findings are variable. Most cats are icteric and there are variable increases in ALP/GGT or ALT/AST. Hyperglobulinemia is observed in over 50% if the cases. Ultrasound may reveal pancreatic, bile duct or gallbladder changes. The liver generally has a mixed echoegnicity pattern with prominent portal areas. Cats with concurrent pancreatitis may have increases feline pancreatic lipase immunoreactivity (fPLI). A liver biopsy confirms the diagnosis.

The primary treatment involves immunosuppressive therapy using prednisolone at 2-4 mg/kg daily and then slowly tapering over 6 to 8 weeks to 0.5-1 mg/kg given once or every other day. This therapy does not appear to resolve this chronic disease but generally slows the progression and minimizes the clinical signs. A course of antibiotic therapy for several weeks is administered for the possibility of a bacterial component. Icterus, very high serum bile acids and biliary cholestasis are the norm. Since high concentrations of hydrophobic bile acids are toxic to hepatocytes and biliary epithelium reducing toxic bile acids is reasonable. Ursodeoxycholic acid is a nontoxic hydrophilic bile acid that when administered changes the bile acid milieu. Ursodeoxycholic acid (10-15 mg/kg/day) is nontoxic and suggested for these cats. This drug will increase bile flow, change bile acid concentrations to less toxic concentrations, reduce inflammation and fibrosis and improve liver enzymes. Observations by some believe that ursodeoxycholic acid may actually be more beneficial than corticosteroids.

The disease is slow and progressive often scattered with flair ups. Approximately 50% of the cases will have a prolonged survival. The final stage of this disease complex is biliary cirrhosis having extensive fibrosis and bile duct proliferation that may end with liver failure associated with ascites and hepatic encephalopathy.

**Mild Lymphocytic Portal Hepatitis.** This is a common incidental histological finding observed in older cats. It is thought to be a nonspecific inflammatory reaction (probably from intestinal inflammation) and does not progress. The mild inflammation is limited to the portal triad and does not progress beyond the limiting plate of the triad. It is reported to be a finding
in 82% of the cats over 10 years of age. Liver enzymes are quite variable or can be normal. Icterus is uncommon. There is no specific therapy is required for this condition.

**Lymphocytic Cholangitis.** This is an uncommon condition apparently more common in Europe. It is characterized by a consistent moderate to marked infiltration of small lymphocytes in and restricted to the portal areas, often associated with variable portal fibrosis and biliary proliferation. There may be lymphoid aggregates, obliteration of bile ducts and biliary hyperplasia and fibrosis or bridging portal fibrosis. The etiology is unknown. It is postulated this condition is the result of immune mediated mechanisms based on immunologic studies performed in some cats. This disease appears to be very chronic associated with weight loss, anorexia and variable icterus. Ascites and hepatic encephalopathy may occur. The enzymes are variable but hypergammaglobulinemia is common. In one study prednisolone had no effect on the disease and those authors suggested ursodeoxycholic acid might be more beneficial. The long-term prognosis is guarded.

**Complications of Cholangitis Syndromes.** The following are conditions often observed with the cholangitis cases. Bile sludge and or cholioliths often occur with inflammatory biliary tract disease. Thick inspissated bile or cholelieths are thought to be the result of deconjugation of the normally soluble conjugated bilirubin from the action of bacterial enzymes or inflammatory products present in the biliary tree. The certain bacteria such as E. coli are capable of producing the enzyme beta glucuronidase that can deconjugate bilirubin resulting in pigment precipitation. Cholelieths in cats are primarily bilirubin pigment stones that contain various amounts of calcium and other precipitates. Some cholelieths may be radiopaque if enough calcium is incorporated in the cholelieth. Primary cholesterol cholelieths as occur in humans do not naturally occur in cats or dogs. Bile sludge or cholelieths may block bile flow and can cause complete obstruction. Obstructive cholelieths should be removed surgically. Occasionally a clear viscous fluid devoid of bile pigments is seen in the gallbladder of some cats thought to be the result of severe intrahepatic cholestasis and reabsorption of intraductal bile.

Bile sludging is best managed by treating the primary cholangitis, treating any biliary tract infection, and by the use of choleretic agents to increase the flow of bile. Ursodeoxycholic acid (Actigall®) should be prescribed. Corticosteroids have a similar effect on bile flow and may also be useful. Complete obstructions may require surgery and in rare conditions a cholecysto-duodenostomy or cholecystojejunostomy is required. Cholecystitis is inflammation of the gall bladder and occurs frequently in the cholangitis syndrome. Radiographically gas within the gall bladder may be observed due to bacterial fermentation. Characteristic thickening of the gall bladder wall may be seen with ultrasound examination. Rarely is there the need for a surgical cholecystectomy if the primary disease is adequately identified and treated.

Feline triaditis is a syndrome that has been observed in many cats having cholangitis. This condition is associated with a concurrent chronic cholangitis-cholangiohepatitis, chronic pancreatitis and duodenitis. Since the common bile duct and pancreatic ducts join a common channel before they enter the duodenum extension of inflammation and luminal contents in both directions is common. Chronic fibrosing pancreatitis with ductal inflammation and nodular hyperplasia is reported frequently with inflammatory biliary disease in the cat. Some of these cats to also have lymphocytic-plasmacytic infiltrates within the duodenum (IBD) as well. Each part of the triad alone can have a similar clinical presentation often associated with chronic intermittent vomiting, lethargy, and anorexia. Liver enzymes are variable and pancreatic amylase and lipase concentrations are not helpful however fPLI levels may be abnormal.