Laboratory testing
A sick cat may become icteric (jaundice) without having primary liver disease. This is because of the complexities of bilirubin metabolism combined with cat’s weak ability to conjugate compounds. Normal hepatic bilirubin metabolism must go through several steps in the hepatocyte before excretion into the bile. This metabolism can be affected by inflammatory cytokines or endotoxins and from nutritional alterations due to mobilization of free fatty acids delivered to the liver or from protein deficiencies resulting from catabolic conditions. Cats also have inherent low concentrations of glucuronyl transferase, an enzyme required to convert bilirubin to water-soluble form prior to hepatic excretion. It is this complex pathway that can result in icterus without evidence of significant structural liver disease. We recently reviewed 180 cats having elevated bilirubin concentrations and cases were grouped them into those clinically icteric (bilirubin>3.0 mg/dl) or those with biochemical icterus (having only icteric serum with bilirubin ranging from 0.5 to 2.9 mg/dl). Cats with clinically icteric (bilirubin > 3.0 mg/dl) most often have primary hepatobiliary disease when hemolytic disease is ruled out. Cats having biochemical icterus (bilirubin < 3.0 mg/dl) do not always have primary hepatobiliary disease and many have other non-hepatic disorders with the liver being secondarily affected with what I refer to as a reactive hepatopathy.

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. ALP increases with hepatic cholestasis. ALP is unique in cats in that the half-life of the enzyme is short (6 hours compared to 72 hours in the dog) 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 do they 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. Presumably this is because GGT is found in higher concentrations in the bile ducts than the hepatocyte where ALP predominates. Uniquely cats with idiopathic hepatic lipidosis usually have marked increases in ALP while GGT concentrations show only mild increases. Cats with cholangitis usually have higher elevations in GGT than ALP. Bile acids in the cat are most useful in screening for portosystemic shunts.

Liver disease in cats
In an unpublished review of 175 consecutive liver biopsies performed on cats at Colorado State University several large categories were observed. Making up 87% of the liver biopsies were 4 groups: Lipidosis (both idiopathic and secondary, 26%), Cholangitis (25%), Neoplasia (20%) and Reactive hepatopathies (16%). Hepatic cysts are also an occasional finding in some cats but rarely cause problems. Lipidosis and cholangitis were the most common conditions and will be discussed below. Reactive hepatopathies refer to changes in the liver that occur secondary to a primary non-hepatic disorder such as inflammatory bowel disease, hyperthyroidism and cardiac disease as a few examples.

Hepatic lipidosis
Hepatic lipidosis can occur as either 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 and the process is reversible. 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 associated with anorexia and weight loss such as pancreatitis, inflammatory bowel disease or other major organ dysfunction. These secondary conditions generally have less severe lipidosis than the clinical syndrome associated with idiopathic hepatic lipidosis in which there is no identifiable etiologic factor. Lipid accumulation is more unique to cats than dogs, in other words cats get lipidosis easily from many conditions.

The etiology of idiopathic hepatic lipidosis is unknown and many theories have been put forward without substantial documentation. One 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. The cause for the rapid mobilization of peripheral fat however is as yet unknown. A second novel theory speculated by some is that the disease is a primary central anorexia disorder with resultant lipidosis. In any event it is important to investigate all possible secondary conditions leading to anorexia and initiating the typical cascade of hepatic lipidosis. One study reported on a number of cats with acute pancreatitis resembling the idiopathic form of hepatic lipidosis.

In the idiopathic form affected animals generally are older and obese cats that have undergone a stressful episode in the recent history followed by a period of complete anorexia. There does not appear to be a breed or sex predisposition. Cats will present with...
an acute history of rapid weight loss (up to 40-60% body weight over 1-2 weeks), depression and icterus. The weight loss is significant with loss of 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 in part the result of hepatic encephalopathy. These cats generally have a total aversion to any type of food.

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 and quite variable in magnitude of elevation. GGT concentrations are only moderately increased in these cats. Icterus with a very high ALP and normal GGT should be a clue to probable idiopathic lipidosis given with appropriate clinical features. Hypercholesterolemia, hyperammoniemia and abnormal bile acid levels are characteristic. 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. Finding severe hypokalemia, anemia or other concurrent disease (ie pancreatitis) in lipidosis cats has a poor survival rate.

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 xyphoid space. The aspirate can be stained with Diff-quick or Sudan stain. A hepatic tissue biopsy confirms the diagnosis of lipidosis. 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. I believe up to an 80% or higher survival rate should be expected in cats given appropriate therapy and no underlying disease is present. Initial therapy requires rehydration with balanced electrolyte solutions. Replacement of potassium deficits is imperative as normokalemia improves survival. Some cats may also require magnesium supplementation as well. Administration of glucose containing solutions may actually cause marked hyperglycemia in these patients and result in a refeeding syndrome (see below). 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 also be avoided because their 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. Force-feeding or appetite stimulation is generally not adequate to meet caloric needs and tube feeding is the best way to administer adequate calories. Nasogastric tubes can be used but due to the small size feeding is limited to liquid diets and they are less tolerated than larger tubes. I suggests placement of either 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 is some evidence that L-carnitine supplementation in cats may protect against hepatic lipid accumulation (at least in weight reduction studies in cats) and consequently may be an appropriate dietary adjunct for cats with lipidosis. 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 have 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 not well documented.

There is also new evidence to suggest many cats with hepatic lipidosis have or will develop cobalamin deficiency. Experimental cobalamin deficiency results in lethargy, anorexia and weight loss – the signs observed with lipidosis. Anecdotal reports suggest cats improve faster with high doses of cobalamin given 250 µg SQ weekly. Serum cobalamin levels should first be determined to document the presence of a deficiency.

Other therapies suggested include S-adenosylmethionine (SAMe) a nutraceutical that is a naturally occurring molecule found in all living organisms and is involved in the metabolism of glutathione (GSH). GSH participates in many metabolic processes and plays a critical role in detoxification mechanisms of the cell. SAMe is also important in hepatocyte membrane integrity and function. The suggested dose is 100 mg/day. Another antioxidant hepatoprotectant is milk thistle or its extract silybin (available as a silybin-phosphatidylcholine combination, Marin™), is a safe hepatic support therapy.

The prognosis must be guarded however with aggressive nutritional therapy many if not most cats recover. Several complications that can occur with therapy include a re-feeding syndrome and vomiting. The re-feeding syndrome is associated with the development of an often life-threatening electrolyte disturbances that occurs within 24 to 48 hours of enteral feeding. If vomiting occurs I will sometimes use maropitant (Cerenea™) or other antiemetics. Maropitant is metabolized by the liver and the dose I use in cats with hepatic lipidosis is lower (0.25- 0.5 mg/kg SQ q 24 h) with my normal cat dose being 1.0 mg/kg SQ q 24 h. We have also used
mirtazapine (Remaron™) a tetracyclic antidepressant that has both antiemetic and appetite stimulant effects (approximate dose is 1/8 of a 15 mg tablet every 3 days) with encouraging preliminary success.

When the cat is consuming adequate calories without the need for tube supplementation the feeding tube can be removed. Tube feeding may extend for up to 4-6 weeks. A failure to respond to traditional hepatic lipidosis therapy should signal the need to investigate the likelihood of an underlying condition in the patient.

**Inflammatory liver disease**
Cholangitis is an inflammatory disorder of the hepatobiliary system. It is 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 WSAVA Liver Standardization Group this complex has been separated into three histological groups; neutrophilic cholangitis, lymphocytic cholangitis and cholangitis associated with liver flukes.

**Neutrophilic cholangitis**
This classification has previously been referred to as suppurative or exudative cholangitis /cholangiohepatitis and is the most common type of biliary tract disease observed in cats in North America. Neutrophilic cholangitis is thought to be the result of biliary tract infection ascending from the gastrointestinal tract. In the acute neutrophilic form (ANF), the lesions are exclusively neutrophilic or suppurative but over time it is thought that cases may progress to a chronic neutrophilic form (CNF) having a mixed inflammatory pattern containing variable numbers of neutrophils, lymphocytes and plasma cells.

The ANF 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. 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. An elevated feline PLI would support concurrent pancreatitis. A liver biopsy is required for histology and will confirm the diagnosis. The liver should always be cultured because of the relationship of bacteria and cholangitis. If obstruction is identified surgery becomes indicated to decompress and flush the biliary system. However, I always try to avoid surgical diversion surgery of the biliary system unless it becomes 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, ampicillin-clavulanic acid,cephalosporins and metronidazole have been suggested as effective antibiotics. Unless a culture and sensitivity says otherwise ampicillin or ampicillin-clavulanic acid are my choice because of the likelihood of E. coli and the fact that both are concentrated in the bile. It is recommended that cats be treated for at least 1 month or even longer with antibiotics. Short duration of therapy may result in recurrence of clinical signs. Ursodeoxycholic acid (Actigall 10-15 mg/kg/day) should be used as well. Abdominal discomfort and vomiting may be associated with hepatobiliary pain and buprenorphine (Buprenex™) should be administered.

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 “feline triaditis”. 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 yet published study we have identified over 50% of affected cats to have evidence of bacteria in and around bile ducts of these cats suggesting that resident bacteria may be responsible for the chronic inflammation.

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 may minimizes the clinical signs. A course of antibiotic therapy for several weeks is administered for the possibility of a bacterial component and in light of our yet unpublished study more aggressive antibiotic therapy may be indicated. 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 and in fact may be even more beneficial than corticosteroids. This drug is reported to increase bile flow (choleresis), change bile acid concentrations to less toxic concentrations, reduce inflammation and
fibrosis and improve liver enzymes. Liver support therapy such as SAMe, Silybin or other antioxidants may be of benefit in the long term management.

The disease is slow and progressive often scattered with periodic 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.

**Lymphocytic cholangitis**

This is a condition (severe lymphocytic portal hepatitis, progressive lymphocytic cholangitis or nonsuppurative cholangitis) is described as a very chronic inflammatory biliary tract condition that is progressive over months and years. Some describe it as being acute or chronic in nature. This disorder appears to be more common in European cats than in cats in North America. The pathology of the liver is characterized by a consistent moderate to marked infiltration of small lymphocytes predominately restricted to the portal areas, often associated with variable portal fibrosis and biliary proliferation. The later stages result in considerable distortion of liver architecture. The bile ducts can also become irregular with dilation and fibrosis. In some cases lymphocytic infiltrates in the portal areas may be confused with well-differentiated lymphocytic lymphoma. It is postulated that lymphocytic cholangitis could be the result of immune mediated mechanisms based on preliminary immunologic studies while others have found DNA fragments of Helicobacter pylori in the bile of some cats suggesting bacterial involvement in the pathogenesis of the disease. We have found bacteria to be less commonly associated with this condition using special fluorescent stains for enteric bacteria.

This syndrome as a slowly progressive chronic disease continuing over months and years. It is often first identified in cats under 4 years of age and Persian cats appear to be over-represented, suggesting a possible genetic predisposition. The most common clinical features observed late in the disease include ascites, jaundice, and hypergammaglobulinemia (in almost all cases). In advanced cases, ultrasonographic examination often demonstrates dramatic changes intra and extra-hepatic bile ducts with marked segmental dilations and areas of stenosis that may lead the operator to believe there is an obstruction. Ascites and hepatic encephalopathy occur late in the disease as a result of acquired portal hypertension and hepatic dysfunction.

The treatment for the chronic lymphocytic cholangitis involves using anti-inflammatory or immunosuppressive therapy in addition to supportive therapy as described with neutrophilic cholangitis. Some report lymphocytic cholangitis had a better response when treated with ursodeoxycholic acid than with corticosteroids. This finding may not be completely unexpected because ursodeoxycholic acid has been shown to have a positive treatment effect in humans having chronic primary biliary cirrhosis having a very similar histologic pattern to these chronic cases.

**References**