THE LATEST UPDATE ON FELINE LIVER DISEASE

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Liver disease is common in the cat and the finding of icterus is a frequently a clinical clue that the cause is primary liver disease. The types of liver disease in the cat are very different from disorders observed in the dog, and there are also differences in laboratory tests.

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 the cat’s weak ability to conjugate compounds. It is this complex pathway that can result in icterus without evidence of significant structural liver disease. Cats with clinically icterus (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 primary non-hepatic disorders with the liver being secondarily affected.

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 alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), total bilirubin, and bile acids. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are quite variable and elevations do not always predict primary inflammatory liver disease or hepatic lipidosis, both of which cause more cholestatic (increases in ALP, GGT) than hepatocellular (increases in ALT, AST) damage. ALP is also unique in cats in that the half-life of the enzyme is short (6 hours) and the feline liver is reported to contain only one third the enzyme to ALP that increases with cholestasis and is not induced by corticosteroids nor does it cause a steroid hepatopathy. Gamma-glutamyl transpeptidase (GGT) is a similar enzyme to ALP that increases with cholestatic and is more sensitive for feline inflammatory bile duct disease than ALP. Presumably, this is because GGT is found in higher concentrations in the bile ducts than the hepatocyte where ALP predominates. Cats with cholangitis usually have higher elevations in GGT than ALP.

LIVER DISEASES

The incidence of liver disease in the cat is unknown but at Colorado State University, several large categories were observed in reviewing 175 liver biopsies and include lipidosis (both idiopathic and secondary, 26%), cholangitis (25%), neoplasia (20%), and reactive hepatopathies (16%).

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. Hepatic lipid accumulation can also result secondary to any 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 idiopathic hepatic lipidosis in which there is no identifiable etiologic factor.

In the idiopathic form, cats will present with an acute history of rapid weight loss (up to 40% to 60% body weight over 1 to 2 weeks), depression, and icterus. The weight loss is significant with loss of muscle mass while abdominal and inguinal fat stores are often spared. 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. GGT concentrations are normal or only moderately increased in these cats. Icterus with a very high ALP and normal GGT should be a clue to probable idiopathic lipidosis with appropriate clinical features.

A definitive diagnosis requires a liver biopsy or hepatic cytology. A fine needle aspirate of the liver with cytologic evidence of many vacuolated hepatocytes helps support a diagnosis. Be aware that cytologic diagnosis does not always correlate with histology. A hepatic tissue biopsy confirms the diagnosis of lipidosis but not the cause.

The therapy for idiopathic hepatic lipidosis requires aggressive management. Initial therapy requires rehydration with balanced electrolyte solutions. Administration of high glucose containing solutions and lactate-containing fluids should be avoided.

Adequate nutrition then becomes the most important part of the therapy for hepatic lipidosis. 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 a 20 French red rubber esophageal feeding tube. The nutritional recommendations for idiopathic hepatic lipidosis are empirical and poorly documented. In general, dietary fat and protein should not be restricted in these cats because calories and protein are so important in providing nutritional balance. There is also no good data on the benefit of various dietary supplements. Some suggest arginine (1000 mg/day), thiamine (100 mg/day), and taurine (500 mg/day) for 3 to 4 weeks. There is some evidence that L-carnitine supplementation (250–300 mg/day) 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. Cats with lipidosis are often cobalamin deficient and improve faster with high doses of cobalamin given 250 µg given subcutaneously (SC) weekly.

Other therapies suggested include S-adenosylmethionine (SAMe), a nutraceutical that is a naturally occurring molecule found in all living organisms that is involved in the metabolism of glutathione (GSH). The benefit of SAMe or other antioxidants in hepatic lipidosis is unknown. Another antioxidant hepatoprotectant, milk thistle or its extract silybin (available as a silybin-phosphatidylcholine combination, Marin), is also 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. To avoid these problems electrolyte abnormalities should be first corrected and then by feeding small frequent meals usually starting out with 25% of the daily calculated caloric needs and gradually increasing the diet volume over 3 to 7 days. 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.

**Feline Inflammatory Liver Disease (Cholangitis)**

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 however the histologic classification of the WSAVA Liver Standardization Group has been separated diseases into three histologic groups: neutrophilic cholangitis, lymphocytic cholangitis, and cholangitis associated with liver flukes.

**Neutrophilic Cholangitis.** This classification has previously been referred to as supplicative or exudative cholangitis /cholangihepatitis and is the most common type of biliary tract disease observed in cats in North America. Neutrophilic cholangitis is though 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. Cats 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. 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.

Therapy includes fluid and electrolyte therapy as 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 is 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 reoccurrence 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.

The CNF (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 *feline triaditis*. In a yet to be 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 older and have signs that wax and wane, and weight loss and vomiting may be present. Physical findings identify jaundice in most.

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% of the cases. Ultrasound may reveal pancreatic, bile duct, or gallbladder changes. The liver generally has a mixed echoenicity pattern with prominent portal areas. A liver biopsy confirms the diagnosis.

The primary treatment recommended is immunosuppressive therapy using prednisolone at 2 to 4 mg/kg daily and then slowly tapering over 6 to 8 weeks to 0.5 to 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 minimize the clinical signs. Based on recent observations of bacteria and around bile ducts antibiotic therapy may be
a better option. 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 as it 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 flare-ups. Approximately 50% of the cases will have a prolonged survival.

**Lymphocytic Cholangitis.** This is a very chronic inflammatory biliary tract condition that is progressive over months and years. Some describe it as being acute or chronic in nature. 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. Bacteria do not seem to be primarily involved.

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 extrahepatic 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 with chronic primary biliary cirrhosis that have a very similar histologic pattern to these chronic cases.

References are available from the author upon request.