Feline Inflammatory Hepatic Disease

Liver disease is a common clinical finding in the cat with hepatic lipidosis, chronic inflammatory disease (cholangitis), neoplasia and hepatocellular necrosis (toxic or drug-related conditions) occurring most frequently. A recent study, based on liver biopsy data, have identified cholangitis is the second most common category of liver disease in cats after hepatic lipidosis. This document will discuss only liver disorders associated with cholangitis.

In 2006, the World Small Animal Veterinary Association (WSAVA) Liver Standardization Group published a simple classification scheme that differentiated inflammation of the bile ducts (cholangitis) into 4 categories: neutrophilic cholangitis, lymphocytic cholangitis, destructive cholangitis and chronic cholangitis associated with liver flukes.

While less commonly diagnosed, infectious hepatobiliary disease is an important differential diagnosis. There is overlap in defining infectious from inflammatory hepatobiliary disease, especially with neutrophilic cholangitis. There are many primary hepatic infectious diseases that have been shown to result in secondary inflammation. Signalment, clinical signs, laboratory data and diagnostic imaging can aid the clinician in differentiating inflammatory liver disease forms of liver disease such as infectious and neoplastic conditions, as well as hepatic lipidosis. However, the clinician cannot rely solely on these diagnostics modalities to definitively diagnosis feline liver disease. Cytology and/or histopathology have an essential role in diagnosing feline liver disorders.

Neutrophilic cholangitis (NC) is common in the cat and less common in dogs. Two forms have been recognized: acute neutrophilic cholangitis (ANC, predominate neutrophilic infiltration) and chronic neutrophilic cholangitis (CNC, having a mixed cellular infiltrate of neutrophils, lymphocytes and plasma cells). Ascending intestinal bacterial infectious has been proposed as the pathogenesis for both ANC and CNC. CNC may represent a later stage of the same disease process, possibly triggered by persistent infection or inflammation. On histopathology neutrophils and other inflammatory cells are observed within bile duct lumen. If the inflammation extends in to the hepatic parenchyma the diagnosis is cholangiohepatitis (CH).

Physical examination findings often are identical in cats with either ANC or CNC and may include fever, dehydration, icterus, abdominal pain and hepatomegaly. The majority (55%) of cats demonstrate peripheral neutrophilia. Reports have suggested that cats with the acute form more often exhibit neutrophilia (50%) than cats with the chronic form (30%). Less often band neutrophils, neutropenia and anemia also may be present. Common laboratory findings include increased serum activity of alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyltranspeptidate (GGT), alkaline phosphatase (ALP) and hyperbilirubinemia. However, it is not uncommon for cats with NC to have no increases in serum liver enzyme activities. It is also uncommon to identify signs of hepatic dysfunction such as hepatic encephalopathy, abnormal coagulation parameters, hypoalbuminemia, decreased blood urea nitrogen (BUN) and hypocholesterolemia. Apart from the frequency of neutrophilia, laboratory findings generally do not differentiate between ANC and CNC.

Radiographs rarely are useful in making a diagnosis of NC. Interestingly, recent reports suggest that most cats with cholangitis for any form have normal sonographic findings, which include liver size, echogenicity, and biliary system. When sonographic changes are present they
include hepatomegaly, hyperechoic hepatic parenchyma, dilated common bile duct (>4 mm) and echogenic gallbladder contents. Unlike in canine patients, identifying gallbladder debris in the cat cannot be assumed to be an incidental finding.

Enteric bacteria may be cultured from bile or liver of cats with cholangitis, especially ANC. *Escherichia coli* alone or, less often, in combination with other organisms is most often cultured from the bile of these cats. Other cultured organisms include *Enterococcus* spp., *Bacteroides* spp., *Clostridia* spp., *Staphylococcus*, and α-hemolytic *Streptococcus* spp.

Cats affected with cholangitis often have comorbidities with pancreatitis and inflammatory bowel disease (IBD) being most frequent. Concurrent inflammation in the liver, pancreas and small intestines of cats is commonly referred to as *feline triaditis syndrome*. Early reports describing feline triaditis found that 83% of cats with cholangitis also had histologic evidence of IBD and 50% had concurrent chronic pancreatitis. Feline triaditis is speculated to be due to the *common channel theory*, according to which the pancreatic ducts and bile ducts joint as a common duct before entering the duodenum. If a cat vomits due to IBD, intestinal contents may be forced past the duodenal papilla and enter both the pancreatic and common bile ducts resulting in infection/inflammation of both the pancreas and biliary system.

Definitive diagnosis of NC requires a liver biopsy or biliary cytology and positive culture. Cytologic examination of fine-needle liver aspirate showing suppurative inflammation may help support the diagnosis, but liver aspiration cytology does not have good correlation with histopathology, especially with inflammatory liver disease. Because liver aspirates are often highly blood contaminated it can be very difficult to determine if the source of the neutrophilic inflammation comes from the blood or liver tissue itself. If possible, a percutaneous ultrasound-guided gallbladder aspirate for both cytology and culture should be performed along with liver biopsies. Suppurative inflammation and bacteria may be observed in the bile cytology and is diagnostic for NC. Biopsy techniques include ultrasound-guided needle biopsy, laparoscopy, or laparotomy.

Treatment for ANC is focused on antibiotic therapy, which is ideally based on culture and sensitivity results. With negative cultures or empiric therapy an antibiotic should be chosen based on the most likely organisms present. Choices should be appropriate for gram-negative aerobes and need good penetration in the hepatic and biliary systems. Cephalosporines, amoxicillin, or amoxicillin-clavulanic acid are appropriate choices for empiric therapy. A fluoroquinolone would be another good recommendation and metronidazole may be added to extend the spectrum to anaerobes. Treatment should extend 4-6 weeks with most cats improving clinically in a week with the appropriate antibiotic therapy.

If biopsy results indicate a large presence of lymphocytic and plasmacytic inflammation in conjunction with neutrophilic inflammation corticosteroid can be considered. Also, corticosteroids can be considered if response to antibiotic therapy is poor or incomplete.

Cats with ANC frequently present acutely ill and require aggressive supportive care. Common electrolyte abnormalities include hypokalemia and hypophosphatemia. If coagulation abnormalities are present vitamin K₁ (0.5 to 1.5 mg q12h SC or IM) is recommended, especially before liver biopsy. Many cats that present with acute signs of NC require pain management with buprenorphine being an ideal analgesic for these patients. Antiemetics such as maropitant (*Cerenia*), administered at 1 mg/kg a24h SC or IV help return these patients to eating and also has some visceral analgesic properties that will help patients with concurrent pancreatitis.
Drugs used for chronic management, in addition to antibiotics, include ursodeoxycholic acid (Ursodiol, Actigal, 10 to 15 mg/kg q24h PO) and silybin in combination with SAMe (Denamarin, 90 mg SAMe and 9 mg silybin). Ursodiol has several positive effects on the biliary system including, amelioration of damage to cell membranes caused by retained toxic bile acids and improvement of biliary secretion of bile acids (choleresis).

**Lymphocytic cholangitis (LC)** is a chronic disease that affects the biliary system and is generally more slowly progressive. Histologic lesions include lymphocytic inflammation directed at bile ducts. Initial studies suggest that LC may have an immune-mediated etiology. Other studies have failed to find an infectious cause for LC.

Clinically cats with LC tend to be older than cats with NC. A median age of 11.5 years, with a range of 4 to 11 years, has been reported. Presenting clinical signs include vomiting, lethargy, anorexia and weight loss, which are similar to cats with NC. Clinical signs in LC cats tend to wax and wane often over several months. LC cats tend to have leukocytosis less frequently (33%) than cats with NC. Similar to that of cats with NC, many cats with LC tend to have increases in ALP, ALT, AST and total bilirubin with variable increases in GGT. Sonographic changes in liver and biliary system do not differ from those with NC, but cats with LC were less likely to have concurrent pancreatic changes detected sonographically.

Treatment of cats with LC is similar to that of cats with NC, except that corticosteroids usually are given to control the inflammatory component of the disease. Antibiotic therapy is initiated while awaiting liver biopsy, bile cytology and culture results. Corticosteroids are started if results show LC. Prednisolone at 1 to 2 mg/kg q24h is started initially. Prednisolone has better oral absorption than prednisone in the cat making it the drug of choice. It is recommended to taper the dose by 50% every 2 weeks until 0.5 mg/kg q24 is reached. It is recommended to check a serum chemistry and determine clinical response before each taper. Ideally treatment decisions are based on repeat liver biopsies. Median survival time was estimated at 755 days in one study of 26 cats with LC and prednisolone therapy was associated with better survival compared to prednisone. Cats on long-term corticosteroids must be monitored for signs of diabetes mellitus or congestive heart failure. In severe cases with incomplete response to corticosteroids treatment with chlorambucil can be added to the treatment protocol.

References: