Liver disease is common in the cat and the finding of icterus is a frequently a clinical clue that the cat has primary liver disease. The types of liver disease as well as differences in laboratory tests for the cat are very different from disorders observed in the dog. This is due in part to specific anatomical and metabolic differences of the cat. The following includes an overview of theses differences with updates of newer information on feline hepatic disease and their treatments.

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, 51 µmol/L) or those with biochemical icterus (having only icteric serum with bilirubin ranging from 0.5 to 2.9 mg/dl). Clinically icteric cats (bilirubin > 3.0 mg/dl) likely 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 is often referred to as a reactive hepatopathy. For example, it is not unusual to find elevations in bilirubin concentrations in cats with inflammatory disease such as pyothorax, abscesses or tissue necrosis. We also found the higher the bilirubin the poorer the survival rate. Those having only mild increases in bilirubin tended to have a better prognosis however the prognosis was influenced by the underlying primary liver disease.

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 often have high elevations in both GGT and ALP. Bile acids in the cat are most useful in screening for portosystemic shunts. The ALT and AST are quite variable and reflect hepatocellular leakage from either degeneration or necrosis. These liver enzymes are less predictive of primary inflammatory liver disease than ALP and GGT (tests that reflect cholestasis). No published values exist for ALT half-life but it is presumed that ALT is much shorter (around 6 hours) than that of dogs (2.5 days). AST half-life is 77 minutes in the cat. The short half-lives may explain the variability of ALT and AST values in liver disease of cats and if marked elevations are found tend to reflect a relative acute episode. Increases in ALT alone without other enzyme elevations is often observed in cats having secondary liver involvement from some other primary non-hepatic condition for example hyperthyroidism.

**LIVER DISEASE IN CATS**

The incidence of liver disease in the cat is unknown but considered to be common. 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 (26%, both idiopathic and secondary), 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. Usually there is also a degree of secondary lipidosis associated with reactive hepatopathies. Hepatic neoplasia was also common. Cats are differ from dogs in the fact that benign tumors are 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 (ie, lymphoma) are excluded from the hepatic neoplasia group.

**HEPATIC LIPIDOSIS**

Lipidosis is common in the cat but relative uncommon in the dog. Hepatic lipidosis can occur as either a primary idiopathic 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 hepatocyte and the degree of lipid accumulation can be quite variable but 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 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. Basically any conditions leading to anorexia can also cascade into secondary hepatic lipidosis. I believe anorexic cats develop hepatic lipidosis easily. Interestingly in recent years we have seen fewer cases of the idiopathic form of hepatic lipidosis.

The etiology of idiopathic hepatic lipidosis is unknown and several 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. In the idiopathic form affected cats generally are older and obese and usually have undergone a stressful episode in the recent history followed then by a period of complete anorexia with a dramatic aversion to food. There is rapid weight loss (up to 40-60% body weight over 1-2 weeks), depression and icterus. The weight loss involves muscle mass while abdominal and inguinal fat stores often being spared. 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 levels are variable and GGT concentrations are normal or only moderately increased. Icterus with a very high ALP and normal GGT should be a clue to likely idiopathic lipidosis when appropriate clinical features are present. 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) with lipidosis has a poor survival rate. A definitive diagnosis requires a liver biopsy or presumptive diagnosis supported by a fine needle aspirate of the liver with cytological evidence of many vacuolated hepatocytes.

The therapy for idiopathic hepatic lipidosis requires aggressive management. I believe up to an 86% or higher survival rate should be expected. Initial therapy requires fluid and electrolyte replacement. Adequate nutrition next becomes the most important part of the therapy for hepatic lipidosis. Placement of 20 French red rubber esophageal feeding tube is necessary for nutritional support. The nutritional recommendations for idiopathic hepatic lipidosis are completely empirical and poorly documented. Recovery formulations providing adequate calories and protein are used. There is also no good data on the benefit of various dietary supplements. The prognosis is good with aggressive nutritional therapy and most cats recover.

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 has been somewhat confusing but using the histological classification of the WSAVA Liver Standardization Group this complex has is separated into three important 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 from bacterial translocation from the gastrointestinal tract. In the acute neutrophilic form (ANF), the lesions are exclusively neutrophilic or suppurative but over time it is thought that some cases may progress to a chronic neutrophilic form (CNF) with a mixed inflammatory pattern containing variable numbers of neutrophils, lymphocytes and plasma cells.

In the ANF coliforms (predominately E. coli) are frequently cultured from the liver or bile. Inflammation can also extend into the hepatic parenchyma causing a cholangiohepatitis. Cats with this syndrome tend to be younger (~3-7 years) and present with illness usually a week or less in duration. They may have evidence of a fever, anorexia, vomiting or lethargy. A leukocytosis may be identified on the CBC. The ALT/AST and ALP/GGT are usually increased but quite variable and cats are
frequently icteric. Ultrasound should be performed to rule out pancreatitis, biliary obstruction or other intra-abdominal disorders. In some cases we will perform an ultrasound-guided cholecystocentesis for cytology and culture. It is generally considered to be a safe procedure and may provide important diagnostic information. A liver biopsy is required for histology and will confirm the diagnosis. The liver biopsy should always also 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 and temporary stent placement should be considered. Concurrent pancreatitis may be diagnosed with an elevated feline PLI and pancreatic ultrasound changes.

Inflammatory bowel disease (IBD) is diagnosed by presence of GI signs, intestinal ultrasound changes and/or an intestinal biopsy showing chronic inflammation.

Therapy first includes fluid and electrolyte replacement if needed. Antibiotics are also a critical part of the therapy in ANF. Culture and sensitivity of the liver or bile will drive antibiotic selection. Without a positive culture I would consider the likelihood of E. coli or other enteric aerobe (i.e., enterococcus). Ampicillin, ampicillin-clavulanic acid, cephalosporins and aminoglycosides have been suggested as likely effective antibiotics. Ampicillin or ampicillin-clavulanic acid is often my choice because of the likelihood of E. coli and the fact that both antibiotics are concentrated in the bile. It is recommended that affected cats be treated for at least 1 month or even longer with antibiotics as a short duration of therapy may result in reoccurrence of clinical signs. Ursodeoxycholic acid (Ursodiol 10-15 mg/kg/day) is also recommended. Abdominal discomfort and vomiting may be associated with hepatobiliary pain and buprenorphine 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.

In a recent study using FISH analysis we identified the presence of bacteria in 2/3 of the cases having the CNF. The most common bacteria identified was E. coli followed by enterococcus. Historically the CNF was treated with corticosteroid therapy but in light of our findings we recommend if cultures are negative that antibiotic therapy be instituted prior to corticosteroid therapy. Remainder of the management is similar to the acute form. It has been argued that many cases do not improve until corticosteroids are given. Steroid improvement may be due to the fact many cats also have concurrent inflammatory bowel disease and/or chronic pancreatitis. One study found 83% of affected cats had inflammatory bowel disease (IBD) and 50% had concurrent chronic pancreatitis. The association of the three together has been referred to as “feline triaditis syndrome”. IBD is generally treated with corticosteroids and diet and clinical improvement may actually be due to the IBD therapy.

The pathogenesis of the triaditis syndrome is not well delineated. Possibly the common channel theory where the pancreatic ducts and bile ducts join before entering the duodenum could explain ascending bacteria. Also unique to the cat is the high bacterial concentration in the proximal small bowel. With concurrent IBD there is the likelihood of increased enteric bacterial translocation to the liver and pancreas. In a yet unpublished FISH study we also found approximately 1/3 of cats
with moderate to severe acute or chronic pancreatitis to have bacteria in the pancreas. Cats with concurrent pancreatitis may also have increases feline pancreatic lipase immunoreactivity (fPLI) and or ultrasound changes.

So in summary, when ever possible cats suspected of having cholangitis should have hepatic biopsies but also hepatic and biliary cultures, pancreatic biopsies and small intestinal biopsies.

**Lymphocytic Cholangitis**

This condition (severe lymphocytic portal hepatitis, progressive lymphocytic cholangitis or nonsuppurative cholangitis) is described as a very chronic inflammatory biliary tract disorder that is progressive over months and years. Some describe it as also being acute 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. We have found bacteria to be less commonly associated with this condition using special fluorescent stains (FISH) for enteric bacteria.

The syndrome is usually chronic progressing over months to years. The clinical features are often similar to the neutrophilic form but advanced disease can result in ascites, jaundice, and hypergammaglobulinemia (in almost all cases). In advanced cases, ultrasonographic examination may demonstrate 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 (prednisolone) and/or immunosuppressive therapy (I frequently use chlorambucil in severe cases) in addition to supportive therapy as described with neutrophilic cholangitis. 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 and may be a helpful adjunct therapy.

**Triaditis Syndrome**

The term "triaditis" is used to describe concurrent inflammation of the pancreas, liver and small intestines and is based on histological conformation. However, the specific conditions that constitute the diagnosis of triaditis include any inflammatory process within these organs but is most often is associated with a combination of pancreatitis, cholangitis and inflammatory bowel disease (IBD). Triaditis has been reported in 50-56% of cats diagnosed with pancreatitis and 32-50% of those with cholangitis or inflammatory liver disease.

Although there appears to be a direct association between the three organ involvement, the etiology and pathophysiology of this syndrome is yet unknown. Likely causes of inflammation include bacterial infection, immune mediated or idiopathic mechanisms. When all three organs (liver, pancreas and intestine) become inflamed it becomes triaditis. Because the etiology of this syndrome is unknown it is difficult to know
how to best treat it. Since it is likely several etiologies are responsible and the specific therapies are also variable and will different from case to case.

**Bacterial Theory.** One theory for triaditis is that both acute and chronic pancreatitis could be the result of an extension of ductular inflammation from the biliary system. This is because the common bile duct and pancreatic duct both merge into a common channel before entering into the intestine. It is possible bile and enteric bacteria from the common channel enter both the pancreatic duct and common bile duct and are responsible for both inflammatory liver and pancreatic changes. With the theory of ascending bacteria from the intestine bacteria may be responsible for both cholangitis and pancreatitis. It is known that cats also have on the order of 100 times higher concentrations of bacteria in the proximal duodenum than do dogs or humans (dogs $10^3$ cfu/g vs cats $10^5$ to $10^8$ cfu/g). High enteric bacterial concentrations coupled with inflammatory changes in the intestine would be a likely source of bacterial seeding either via the common channel or through intestinal translocation with hematogenous seeding. In either case IBD would likely potentiate bacterial movement.

FISH analysis (fluorescence in situ hybridization [FISH] using a 16S rDNA probe that recognizes a specific class of enteric bacteria) is a non-culture method staining technique for bacteria. In a published study we found through FISH analysis that enteric bacteria was present in liver tissues of 69% of the cats having a chronic or acute inflammatory liver disease. The most common bacteria identified in the livers with cholangitis are *E. coli* and *Enterococcus*. In yet another, but yet unpublished study, we used FISH to examine the pancreas of cats with either acute or chronic pancreatitis and found a relatively high frequency of bacteria in that organ (35% or 11/31 cases). Infection was most prevalent in cats with moderate to severe acute or chronic pancreatitis. The localization and type of intra-pancreatic bacteria suggests translocation of enteric bacteria. The most common organisms identified were *E. coli*, *Streptococcus* spp and *Enterococcus* spp. Further, an experimental pancreatitis study in cats clearly demonstrated that *E. coli* translocated from the intestines into experimentally induced acutely inflamed pancreas as well as into the liver and gallbladder supporting the intestinal translocation theory. These findings have substantial implications for the diagnosis and management of cats with pancreatitis.

**Immune-mediated Theory.** Cats having chronic lymphocytic pancreatitis or lymphocytic cholangitis invasive bacteria are less commonly visualized. With the combination of lymphocytic (chronic) pancreatitis, lymphocytic or mixed lymphocytic and neutrophilic cholangitis and lymphocytic plasmacytic enteritis may all be a consequence of an immune-mediated process rather than active bacterial infection. In people and experimental animals autoimmune pancreatitis and cholangitis are recognized as extra-intestinal complications of IBD, with immune attack frequently directed against bile and pancreatic ducts. Immune mediated damage may either be a consequence of immune responses against bacteria (that may or may not have established an active infection) that cross-react with host tissues with resultant innocent by-stander immune responses in the intestines, liver and pancreas, or immune attack directed against host antigens unmasked by tissue damage. In further support for an immune etiology are human studies demonstrating that a variety of autoantigens have been implicated again suggesting that immune responses to translocated bacteria, perhaps facilitated by a leaky gut, and may promote an immune inflammation in a susceptible individuals. We also know feline IBD when not dietary or antibiotic responsive often improves with immunosuppressive therapy supporting again a possible the immune theory. At this point there are no reliable clinical tests to detect an immune response.

**Diagnosis.** The definitive diagnosis involves histopathology from each organ. It is important when ever doing an exploratory surgery for a biopsy of intestine, pancreas or liver that all three organs should be carefully inspected and biopsied even if they appear normal because triaditis is so common. Evidence of liver disease is based on identification of elevations in liver enzymes and or total bilirubin. Liver ultrasound findings in cats are quite variable and many affected livers can appear normal. Abnormal ultrasound changes in cholangitis include prominent portal areas, duct distention and thickened gallbladder wall. In some cases bile duct obstruction can occur from duct inflammation, cholelithiasis or thick
bile sludge. Surgical flushing or even temporary stent placement may be required in these cases. I will also always culture the liver biopsy and bile that has been obtained from a gallbladder aspirate. A presumptive diagnosis of pancreatitis includes an elevated serum pancreatic lipase immunoreactivity test (fPLI) and abdominal ultrasound showing abnormal pancreatic changes. In one study the fPLI sensitivity is reported to be 67% and the specificity of the fPLI to be 91%. Ultrasound will detect anywhere from 35 to 67% of cats with pancreatitis. Pancreatic biopsies are safe and easy to perform either at surgery or via laparoscopy. I also now culture most of my pancreatic biopsies as well. Intestinal disease is often diagnosed based on signs of GI disease (vomiting or diarrhea) and ultrasound changes in the bowel with mucosal thickening or loss of layering. Some cats may also have decreased folate of cobalamin (B₁₂) serum concentrations with triaditis. Intestinal biopsies confirm inflammatory intestinal disease and are obtained via endoscopy or surgery. It is ideal to biopsy each segment of the small intestine because the IBD can be regional. Further, the most common area for GI T-cell lymphoma is the ileum that must be reached endoscopically via colonoscopy.

**Treatment Considerations.** Since the etiology of feline triaditis is unknown it is almost impossible to make absolute treatment recommendations. The first step in the therapy should be directed to the organ that is thought to be primarily responsible for the clinical signs. Because we believe that both bacterial and immune-mediated theories are possible one should use all the clinical information available to help direct the course of therapy.

**Inflammatory Bowel Disease (IBD).** The etiology of IBD is unknown. Possibly dietary constituents, bacterial causes or an abnormal immune response are all thought to be likely etiologies. Lymphocytic plasmacytic enteritis frequently responds to dietary modification with an antigen restricted (novel protein) or a hydrolyzed diet. Refractory patients typically escalate to diet plus antimicrobial therapy using enteric antibiotics such as tylosin (15 mg/kg bid), metronidazole (7-10 mg/kg bid) or amoxicillin. If the patient fails to respond to more conservative therapy then I will then institute anti-inflammatory therapy using prednisolone (1-2 mg/kg q 24h with gradual dose reduction based on response). Often B₁₂ supplementation is required (250 µg SQ weekly). Concurrent low-grade small T-cell intestinal lymphoma can respond well to therapy with chlorambucil (2 mg PO given 3 times a week), prednisolone and supplementation of B₁₂.

**Pancreatitis.** Acute pancreatitis is less common than chronic pancreatitis but acute can often progress to chronic pancreatitis or even exocrine pancreatic insufficiency. Acute (suppurative) pancreatitis carries a particularly poor prognosis. Complicating factors that can modify the situation are bacterial translocation and biliary obstruction. Fluid therapy, analgesics, antiemetics and assisted alimentation are the basis of therapy. Antimicrobial therapy is warranted in moderate to severe cases and is supported by the finding of positive FISH staining in over 1/3 of the cases investigated. *E. coli, Streptococcus* spp and *Enterococcus* spp are the most common organisms identified. Amoxicillin-clavulanic acid, cephalosporins, fluoroquinolones or metronidazole are reasonable considerations. In cats with suspected disease exploratory laparotomy with biopsy of the pancreas, liver and intestine with appropriate cultures of pancreas and liver is frequently required to optimize therapy. Persistent biliary obstruction from pancreatitis is another indication for surgery and may be amenable to stenting or cholecystojejunosotomy. It should be noted that corticosteroids are not typically employed in the treatment of feline acute pancreatitis.

**Chronic pancreatitis** is more common than acute pancreatitis in the cat. Lymphocytic or lymphocytic plasmacytic pancreatitis with fibrosis is the characteristic finding. In some cases the pancreatic damage can be so severe resulting in exocrine pancreatic insufficiency requiring pancreatic enzyme supplementation. Bacteria can also be a component of chronic pancreatitis so I generally begin with antibiotic (same listed above) and antioxidant therapy (i.e. SAMe, milk thistle, vitamin E). If there is a failure to respond to antibiotics or with evidence of IBD and or lymphocytic cholangitis then corticosteroid therapy would be indicated. Many cats will also require vitamin B₁₂ supplementation.

**Cholangitis.** The management of cholangitis is based in part on culture results and
histopathology. The acute neutrophilic (suppurative) cholangitis or chronic neutrophilic (lymphocytic plasmacytic neutrophilic) cholangitis are often associated with bacteria. The specific antibiotic therapy to use is best determined based on culture and sensitivity of the liver biopsy or bile aspirate. Short of a positive culture antibiotic therapy should be directed at enteric coliforms as suggested in the pancreatitis section. Other adjunct therapy may include ursodiol (ursodeoxycholic acid 10-15 mg/kg q 24h or divided bid), SAMe, milk thistle products or other antioxidants. The acute form usually responds quickly while the chronic form is less predictable. Generally a 4-week course of antibiotic therapy is indicated. If the patient fails to improve after several weeks of antibiotics I will begin prednisolone therapy. The lymphocytic cholangitis is thought to be likely immune mediated and rarely has a bacterial component. But because pancreatitis is common with cholangitis and bacteria could play a role in both I will usually also institute a course of antibiotic therapy. Cats having lymphocytic cholangitis will however generally require prednisolone therapy and sometimes even immunosuppressive therapy such as chlorambucil or others. A recent study found ursodiol was inferior to steroids based on follow up biopsies after a course of therapy. I use ursodiol as an additional adjunct therapy in these cases. General supportive therapy, antioxidants and vitamin B₁₂ are generally used in these cases.

Suggested References

