A Case-based Approach to the Feline Patient with vomiting and Increased Liver Enzymes (Part 1: Hepatic Lipidosis)

Joseph Taboada, DVM, Dipl. ACVIM (Internal Medicine)
School of Veterinary Medicine, Louisiana State University
Baton Rouge, Louisiana

Most of the noninvasive techniques used in evaluating the feline patient with suspected hepatobiliary disease, such as hepatic enzymology, liver function tests, and hepatobiliary imaging are useful in localizing disease to the liver or biliary system, however, they can rarely be used to establish a definitive diagnosis or an accurate prognosis. Invasive techniques are usually required for this purpose. Invasive (laparotomy, laparoscopic, ultrasound guided percutaneous, or blind percutaneous) techniques are necessary to obtain liver tissue for cytologic or histopathologic evaluation. Techniques for biopsy of the liver may require anesthesia, special equipment, and carry the risk of complications. Fine needle aspiration (FNA) can be utilized to obtain liver tissue for cytology. FNA of the liver is a relatively safe procedure that is simple to perform while requiring no special equipment and minimal patient sedation. Together with the rest of the diagnostic evaluation, FNA can be a useful tool in establishing a diagnosis and prognosis in selected patients with hepatobiliary disease. Additionally, it is a non-invasive technique that can be useful in deciding which subset of patients may require biopsy.

Hepatic Ultrasonography and Ultrasound Guided Biopsy

Ultrasonography is becoming more and more routine in the evaluation of the patient with hepatobiliary disease, especially in the referral setting. Indeed, the availability of ultrasound is often used by the primary care practitioner when making the decision whether or not to refer a patient. Hepatobiliary ultrasonography is readily available and often considered the non-invasive procedure of choice for trying to differentiate between primary hepatic and post-hepatic causes of cholestasis, for identifying portosystemic vascular anomalies, and for identifying focal or multifocal hepatobiliary abnormalities. Recent work has tried to correlate hepatic ultrasonographic images with histopathologic findings. Hepatic lipidosis in cats and hepatocutaneous syndrome (superficial necrolytic dermatitis, necrolytic migratory erythema) in dogs are examples of diseases where findings on hepatic ultrasonography are helpful in making a diagnosis. Care must be taken not to over-interpret results, however, because unfortunately,
there can be tremendous variability in the echogenic pattern produced by a given disease. It is usually difficult, if not impossible, to predict the histopathologic infiltrate from the echogenic pattern observed.

One of the advantages of ultrasonographic evaluation of the liver is that ultrasound may be used to guide placement of needles for biopsy or FNA. This technique is especially useful when investigating focal or multifocal disease that might be missed by blind techniques. Biopsy guides are available for most transducers to facilitate ultrasound-guided biopsy. Visualization of the needle and biopsy site during the procedure may improve accuracy of biopsy and detection of complications. Ultrasound guided biopsy is widely considered safer than other biopsy techniques but studies supporting or refuting this contention are lacking. The small gauge needle used for biopsy in many of the percutaneous ultrasound guided techniques can be a limiting factor when trying to interpret hepatic biopsies obtained.

Numerous liver biopsy techniques have been described. Blind percutaneous techniques are the simplest and most cost effective in many situations. There is a perception, however, that they are less accurate than other techniques and carry a higher risk of complication. Few studies have looked at the relative risk and diagnostic accuracy of percutaneous biopsy in the dog and cat. A 0% to 8.4% risk of complication has been reported in the few small studies reported. There was positive correlation between biopsy and necropsy findings in 80% of the cases in one study. In man, larger studies (189,085 people biopsied) have identified a complication rate of 0.28% and a mortality rate of 0.03%. Anemia and cancer would appear to be factors positively correlating with an increased risk of complication. Type of needle used, operator experience, biopsy technique (transabdominal vs. transthoracic), and platelet count are not.

**Hepatic Fine Needle Aspirate (FNA)**

Fine needle aspirate of the liver is simple and requires no special equipment. It can be performed with a 6- or 12-cc syringe and a 22-gauge, 1.5- to 3.5-inch disposable hypodermic or spinal needle. The 22-gauge spinal needle is useful in larger animals because of the longer sizes available but is rarely necessary when being used in cats. The needle is inserted into the liver via a percutaneous transabdominal (in cats and most dogs) or transthoracic approach (in large deep chested dogs) and gentle suction (3-5 ml) is applied. While maintaining suction, the needle is gently but quickly thrust into the liver parenchyma and then brought back to the original position without exiting the liver. The suction is then released and the needle is
withdrawn. If the technique is properly performed, blood will rarely be noted in the syringe or needle hub as the entire specimen should remain in the needle. To transfer the specimen to a clean glass slide detach the needle, draw a few milliliters of air into the syringe, reattach the needle, and gently expel the liver sample onto the slide. Do not forcibly "blow" the specimen onto the slide as this may damage the cells and result in preparation artifacts. Squash prep smears or blood film techniques may be used to smear hepatic samples.

The transabdominal technique can be performed either in dorsal or right lateral recumbency with the pelvis of the animal positioned slightly lower than the head. I prefer lateral recumbency because patient restraint is generally easier. With the animal in lateral recumbency the needle is inserted at the point where the left costal arch begins its dorsal ascent. It is angled at about 45° and slightly caudal to the point where the needle is to be inserted. Once the peritoneal cavity has been entered the needle is brought parallel to the body wall and slowly advanced while gently feeling down for the liver with the tip of the needle. Once the liver is felt the needle is again angled at 45° and the aspirate is performed.

FNA is most useful in evaluating patients with hepatomegaly but it often gives valuable information in patients with normal sized livers as well. Diffuse infiltrative, inflammatory, and neoplastic diseases lend themselves best to an FNA diagnosis. FNA is less applicable to focal or multifocal diseases or diseases in which cells do not exfoliate easily, such as fibrosis or sarcoma. Kristensen, et al. recently described a classification scheme for interpretation of hepatic cytology: their categories include normal, hyperplastic, inflammatory, degenerative, necrotic, cholestatic, neoplastic, mixed reactions, other reactions, and non-diagnostic.

**Hepatic Cytology**

The predominant cell type in a normal hepatic FNA is the hepatocyte, often found in cohesive clusters or regular sheets. Hepatocytes are large polyhedral to rounded cells with abundant gray to basophilic cytoplasm. They have a single (occasionally two) eccentric nucleus with uniformly course chromatin and a small, distinct nucleolus. The cytoplasm is usually granular with a small amount of green bile pigment occasionally present. Small columnar epithelial cells of biliary origin may also be observed. Low numbers of macrophages (Kupffer's cells) with or without intracellular hemosiderin are sometimes seen. Because of the highly
vascular nature of the hepatic sinusoidal milieu a background of erythrocytes and blood-borne leukocytes is invariably present.

Degenerative diseases are characterized by cytoplasmic vacuolar changes. The differential diagnosis for hepatic vacuoles includes fat, glycogen, hydropic degeneration, and storage diseases. Feline hepatic lipidosis is the characteristic example of diseases of this type. In the dog, glycogen deposition associated with steroid hepatopathy or hydropic degeneration associated with an ischemic or toxic insult is more likely. Extracellular deposition of amorphous material is seen in hepatic amyloidosis. It is not uncommon to see mild hepatocellular vacuolization in cats with a large variety of chronic diseases so care must be taken in interpreting the finding vacuolar hepatopathy in this species. Inflammatory specimens are characterized by increased numbers of inflammatory cells interspersed between normal and/or reactive hepatocytes. The predominant inflammatory cell type characterizes the inflammation present. A definitive diagnosis can be made in some protozoal or systemic fungal diseases based on the presence of identifiable organisms. Histoplasmosis is the systemic fungal disease most likely to be diagnosed via hepatic FNA. One of the most useful applications of hepatic FNA is the diagnosis of hepatic neoplasia. Lymphosarcoma, biliary carcinoma, or metastatic neoplasias are the most likely hepatic tumors to be diagnosed.

Because FNA is usually a blind tissue sampling technique it is most applicable when the clinical evaluation suggests diffuse parenchymal disease. Focal diseases are less likely to be diagnosed by blind aspirate techniques. The accuracy of hepatic FNA can be improved by obtaining multiple aspirates so at least 3 aspirates taken from slightly different angles should be routinely obtained.

Complications of hepatic FNA are extremely rare. Bleeding is rarely a clinically significant problem even in animals with coagulation abnormalities. Using a blind technique to aspirate cells from the liver will occasionally result in inadvertent gall bladder aspiration. Aspiration of the gall bladder rarely causes serious problems for the patient. In fact, with ultrasound guidance the technique is routinely used to sample bile in cases of suspected cholangitis or liver fluke infestation. It should be noted that while FNA is a quick and easy technique, the sample does not always accurately reflect the underlying histopathologic diagnosis. Few studies have looked at correlation between FNA cytology and histopathology in the dog and cat. There was a 66% correlation in one study. The fact that correlation is not 100% stresses the point that care should be taken when interpreting results that do not seem to fit the presenting clinical picture. Liver biopsy is still often needed for definitive diagnosis.
Feline Hepatic Lipidosis

Feline hepatic lipidosis is the most common feline liver disease in many studies. It is characterized by massive hepatocellular accumulation of triglycerides accompanying a disruption in hepatic lipid metabolism that often results in severe liver dysfunction. Most cases are idiopathic but diabetes mellitus, prolonged starvation, over-nutrition, hyperthyroidism, and hyperparathyroidism are possible initiating causes. Female cats are affected almost twice as frequently as males. Chronic vomiting is the most common presenting sign. Anorexia, weight loss, icterus, and hypersalivation are also seen. Many affected cats are (or were) obese yet show significant muscle wasting at the time of diagnosis. Not all cats with hepatic lipidosis are obese. Total bilirubin, SAP, SALT, SAST, and GGT are usually increased (>2-5 times normal about 75% of the time). About half of affected cats will be hyperglycemic (glucose > 200 mg/dl). Abdominal radiographs may reveal mild hepatomegaly and ultrasound may reveal increased hepatic echogenicity. Diagnosis is dependent on demonstration of heavily vacuolated hepatocytes on fine needle aspirate or liver biopsy. Aggressive treatment is important. If an underlying disease process is evident it should be treated. General therapy should include treating dehydration, hypoglycemia (if present), hypokalemia, hypophosphatemia, and hepatoencephalopathy (lactulose 1-3 ml/cat adjust to maintain soft stool and metronidazole 7-10 mg/kg PO bid-tid). Vitamin K1 (0.5 to 1.5 mg/kg SQ) can be administered if cholestasis has resulted in a bleeding tendency. PIVKA will be increased if vitamin K1 is needed. Nutritional support is the most important aspect of therapy. Total caloric intake should be 80-100 Kcal/kg/day. Protein supplementation is important. Diets based solely on carbohydrates may worsen the disease so moderate or even high protein diets such as Hills Prescription Diet® p/d™ or a/d™, Eukanuba Veterinary Diets® Nutritional Recovery Formula™/Canine & Feline, or Abbott Animal Health™ Clinicare® Canine/Feline Liquid Diet or Clinicare® RF should be used. Switch to a lower protein diet if signs of hepatoencephalopathy ensue. Dietary supplements that have been recommended but not critically evaluated in cats with hepatic lipidosis include l-carnitine (250-500 mg/day), taurine (250-500 mg/day), B-complex, zinc (7-10 mg/kg elemental Zn/day), and vitamin E (20-100 mg/day). Force feeding or enteral feeding is invariably necessary to maintain appropriate caloric intake. Appetite stimulants may assist the owner who wishes to force feed their cat but will rarely result in enough of an increase in appetite to meet the nutritional needs appropriate to treatment goals. Cyproheptadine [Periactin®] 2 mg/cat, mirtazapine [Remeron®] 1/8 to ¼ of a 15 mg tablet per cat, and oxazepam [Serax®] 1 mg/kg
sid-bid may be used. Diazepam (0.1 ml IV) and Midazolam (2-5 mcg/kg IV) can also result in appetite stimulation. The effect of diazepam is usually short lived and causes significant sedation. Midazolam may cause a more lasting stimulation and less sedation. Care must be taken if benzodiazepines such as oxazepam or diazepam are used because they may worsen hepatoencephalopathy. Oral diazepam has been noted to occasionally be hepatotoxic. Enteral feeding will probably be needed in most cats with hepatic lipidosis. Esophagostomy, gastrostomy, or naso-esophageal feeding may all be used successfully. Gastrostomy and esophagostomy feeding is tolerated well by most cats. The tubes can be placed surgically or percutaneously via endoscopy or blind techniques. Enteral feeding may need to be continued for months in some cases. With aggressive nutritional support 75-95% of cats have a good prognosis while without aggressive nutritional support less than 10% of cats will do well. Pancreatitis as a concurrent disease process should be considered in cats not responding to therapy. Refeeding induced hypophosphatemia is a rare complication that can cause hemolysis or neurologic signs that may mimic hepatoencephalopathy.

**Feline Inflammatory Liver Disease**

Cholangitis and cholangiohepatitis is a complex of related inflammatory hepatobiliary disorders. They accounted for approximately 26% of the liver diseases reported in cats in one large retrospective study (Gagne, et al. JAVMA, 1999; 214:513). This was second to hepatic lipidosis which accounted for approximately 50% of the cases. Inflammatory liver diseases are characterized by the predominant inflammatory cell infiltrate seen histopathologically. The inflammation is usually seen in the portal areas; and can be characterized as suppurative (neutrophilic), non-suppurative (lymphocytic/plasmacytic); sclerosing lymphocytic cholangitis, or biliary cirrhosis (fibrosis). There have been many terms used in the veterinary literature to describe inflammatory liver diseases prompting the World Small Animal Veterinary Association (WSAVA) Liver Standardization Group to suggest standardized criteria for diagnosis of liver diseases of dogs and cats. The standards define three main forms of cholangitis which are recognized to occur in feline patients: neutrophilic cholangitis, lymphocytic cholangitis, and chronic cholangitis associated with liver fluke infestation. Cholangitis is often associated with periportal necrosis. Neutrophilic cholangitis can be further subdivided into acute (also termed suppurative by some authors) in which neutrophils are seen and chronic in which a mixture of neutrophils and lymphocytes/plasma cells are seen. Lymphocytic cholangitis (formerly lymphocytic portal hepatitis) is the term that has become accepted to describe the histologic
classification in which lymphocytes and/or plasma cells are noted to infiltrate the portal areas. This replaces the older term, “lymphocytic/plasmacytic cholangiohepatitis.” Lymphocytic cholangitis was more common than neutrophilic cholangitis; being seen in 61% of the cats with inflammatory liver disease in the study by Gagne, et al. Although other studies have noted that chronic neutrophilic cholangitis may be more common. Whether these classifications represent different stages in the progression of one disease or are separate etiologic entities is not known. Nor is the underlying etiology of inflammatory liver disease in cats. Bacterial, allergic, and immune mechanisms have all been speculated to be involved. Bacterial cholangitis may either initiate the inflammatory process or perpetuate it early in the disease course. Immune mechanisms probably also play a role especially in chronic neutrophilic cholangitis and lymphocytic cholangitis. Cats with inflammatory hepatobiliary disease, especially those with suppurative disease, may also have pancreatitis and inflammatory bowel disease. The relationship between these three inflammatory conditions is not well worked out but it has been speculated that the underlying initiator of the inflammatory process may affect the liver, the pancreas, and the small intestine concurrently. The term, “triaditis” has been coined to describe those situations in which inflammation of the liver, pancreas, and small intestine are seen to occur concurrently. While not a very accurate description, the term seems to have stuck.

The clinical findings seen in cats with inflammatory liver disease are similar to those seen with hepatic lipidosis and other liver diseases. Vomiting, anorexia, lethargy, and weight loss are typical. Fever is occasionally seen. Diarrhea while not usual is more common than in cats with hepatic lipidosis and may represent the subset of cats with concurrent inflammatory bowel disease. Affected cats are rarely obese. Cats with neutrophilic cholangitis tend to be younger and are more likely to be severely systemically ill when compared to those cats with lymphocytic cholangitis. Any age cat can be affected. Males predominate in populations of cats with neutrophilic cholangitis as compared to those with lymphocytic cholangitis. Suppurative disease often has an acute course while disease characterized by lymphocytic/plasmacytic inflammation may be more chronic. In evaluating liver enzymes, alkaline phosphatase tends not to be as elevated as in cats with hepatic lipidosis and transaminase activities tend to be higher. It is important to note that liver enzymes can be normal, even in cats with significant hepatobiliary inflammation. Neutrophil counts, transaminase activities, and total bilirubin concentrations tend to be higher in cats with neutrophilic cholangitis when compared to cats with lymphocytic cholangitis. All liver enzymes may be normal early in the course of disease, however. Diagnosis is usually dependent on biopsy as FNA is often normal or reveals non-
specific changes. Biopsy for both histopathology and culture should be performed if inflammatory liver disease is suspected. The advent of readily available ultrasonography has resulted in Tru-cut needle biopsy becoming the most popular method of obtaining tissue for histopathology. The diagnostic accuracy of Tru-cut obtained biopsies has been questioned (Cole, et al. JAVMA, 2002; 220:1483-90). In the study by Cole, et al. liver biopsies obtained from dogs and cats by tru-cut techniques were compared to wedge biopsies. Paired 18 g Tru-cut needle biopsies commonly yielded a different diagnosis than wedge biopsy. If it is assumed that the wedge biopsy is the “gold standard” then the 18 g Tru-cut biopsies were highly inaccurate. Larger samples obtained with a 14 g needle may be more accurate. Laparoscopically obtained samples should be considered when feasible. Prior to biopsy, coagulation parameters should be evaluated. PIVKA may be the most sensitive indicator of potential bleeding tendencies. Vitamin K1 (0.5-1.5 mg/kg SQ given within 24 hours of biopsy may decrease the risk of bleeding.

In addition to the supportive and nutritional support used to manage cats with hepatic lipidosis, antibiotics should be used when treating cats with inflammatory liver disease. For patients with suspected loss of hepatic function, it is ideal to select drugs that rely on the kidneys for elimination rather than hepatic biotransformation. In the case of antibiotic therapy, the β-lactam antibiotics (penicillin, ampicillin, cephalosporins) are the best choice. (Hepatic reactions observed in people caused by amoxicillin-clavulanate were associated with a specific leukocyte antigen and have not been reported in animals.) The fluoroquinolones (enrofloxacin, marbofloxacin, orbifloxacin, difloxacin) have had a good safety record and increased risk of toxicity in animals with hepatic disease has not been documented. Although some of these drugs are metabolized, the clearance is low and probably not affected unless there is substantial loss of hepatic function. These drugs are also cleared by the kidneys. Fluoroquinolones have been known to cause central nervous system (CNS) problems in susceptible individuals. This is most likely caused by penetration across the blood-brain-barrier (BBB) and inhibition of the action of the GABA neurotransmitter. Problems observed have been seizures, excitement, and disorientation. Animals with seizure disorders caused by hepatic encephalopathy may be more prone to CNS problems caused by fluoroquinolones. If a complication is observed after prescribing a fluoroquinolone drug, a switch to a safer drug is appropriate. Macrolides (erythromycin, azithromycin, and similar drugs) are sometimes used for infections in animals with hepatic disease. There are no specific problems identified in patients with hepatic disease, but these antibiotics are often associated with gastrointestinal problems in
animals (diarrhea and vomiting). Therefore, when prescribing these drugs, veterinarians should be careful not to mistake a drug-related problem for an underlying disease, or complicate an already-existing problem. Metronidazole and related drugs (tinidazole, ronidazole) are sometimes used in patients with hepatic disease because of the anaerobic spectrum. They have been safe drugs when prescribed according to standard dose recommendations, but when doses have been exceeded, problems may arise. The most serious problem caused by metronidazole has been attributed to CNS toxicity and include seizures, ataxia, nystagmus, tremors, and rigidity. These signs have been attributed to interfering with the inhibitory neurotransmitter GABA. Because animals with hepatic disease also may be prone to CNS disorders that also share these clinical signs, veterinarians should understand the risks of metronidazole, and become familiar with the signs associated with toxicity. When using other antimicrobials, veterinarians should be aware of the common adverse effects that may occur if a drug accumulates because of a deficiency in metabolism. Drugs to avoid, if possible, include: trimethoprim-sulfonamides, tetracyclines, rifampin, nitrofurantoin, and chloramphenicol.

Immunosuppressive agents should be added to the treatment regime in cats with lymphocytic disease and in cats with neutrophilic disease that fail to respond to antibiotics alone or antibiotics and nutraceuticals. Prednisolone (2-4 mg/kg/day initially then slowly tapered to 1 mg/kg QOD) is used most commonly. Other immunosuppressives that may be used in cats responding poorly to glucocorticoids include chlorambucil (1.5 to 4 mg/M² twice a week to every other day; approximately 1 mg < 7 lb cat, 2 mg > 7 lb cat) [probably a safer alternative to azathioprine in the cat], azathioprine (0.3 mg/kg q24-72 hrs) [Note that cats are much more sensitive to the myelosuppressive effects of azathioprine than dogs], methotrexate (0.4 mg divided into 3 doses and given over 24 hours and repeated every 7-10 days has been advocated as a pulse therapy but has not been extensively studied). Ursodeoxycholic acid (Actigall®) 10-15 mg/kg PO SID is a safe treatment alternative that can be used in cats with either suppurative or non-suppurative disease. The drug appears to have multiple actions including shifting the bile acid pool to a less toxic hydrophilic population, a choleretic effect, reducing expression of Class 2 major histocompatibility complex, and an antiinflammatory effect. Vitamin E (aqueous alpha tocopherol, 10-100 IU/kg/day) has been advocated for its antioxidant effects. SAMe (90-180 mg PO SID; Denosyl® NutraMax) is a precursor of glutathione. Glutathione is an important antioxidant that has been shown to be reduced in dogs and cats with liver disease. The nutriceutical SAMe may help replace glutathione. It also may have hepatoprotective effects in preventing programmed cell death (apoptosis) that occurs during
inflammatory liver disease. Milk thistle (silymarin) is a nutriceutical that is widely used for its hepatoprotective effects. It may be of benefit as an antioxidant, as an antifibrotic agent, or as an aid in hepatic regeneration. Many studies have evaluated its use in people and show mixed results. Studies in dogs and cats are lacking. Anecdotal evidence would suggest it may be useful at a dose of 50-200 mg/kg PO SID. NutraMax markets a product for cats, Marin®, that is a combination of silybin and vitamin E. Silybin is one of the active ingredients in milk thistle. In Marin® it is complexed with phosphatidylcholine to increase the bioavailability. The amount of vitamin E in the tablets is lower than is generally recommended in treating liver disease. A combination of silybin and SAMe is available as the nutriceutical Denamarin®.