**Feline Triaditis - Current Concepts**

*World Small Animal Veterinary Association World Congress Proceedings, 2013*

Stanley L. Marks, BVSc, PhD, DACVIM (Internal Medicine, Oncology), DACVN

School of Veterinary Medicine, University of California-Davis, Davis, CA, USA

**DEFINITION**

The term "triaditis" is a lay term and refers to the syndrome of concurrent cholangitis, pancreatitis, and inflammatory bowel disease (IBD) in cats. The association of these entities may reflect a common underlying disease mechanism. It is felt that the predominant signs of triaditis are attributable to hepatobiliary disease, with pancreatitis and IBD occurring as secondary complications. Despite the relatively high prevalence of triaditis in cats, the temporal nature of the relationship, as well as the specific cause(s) of cholangitis, pancreatitis, and feline IBD have not been well elucidated to date.

**PANCREATITIS**

Acute pancreatitis is characterized by the sudden onset of inflammation affecting the pancreatic parenchyma and peripancreatic tissues. Chronic pancreatitis is a continuing inflammatory disease characterized by irreversible morphological change, possibly leading to permanent impairment of function. Acute and chronic pancreatitis cannot be differentiated clinically or biochemically in cats, and the ultrasonographic differentiation can also be challenging. The underlying cause of feline pancreatitis is usually unknown, but a variety of risk factors have been identified including parasites (*Toxoplasma gondii*, *Amphimerus pseudofelineus*), viral causes such as Herpesvirus and FIP, blunt trauma, pancreatic ischemia, and intercurrent disease, particularly hepatobiliary disease and IBD. Obesity does not appear to be a risk factor for feline pancreatitis.

The history and clinical signs in cats are extremely variable and nonspecific. In a retrospective study of 40 cats with necropsy-confirmed acute necrotizing and acute suppurative pancreatitis, reported clinical signs were lethargy in 100% of the reported cases, anorexia in 97%, dehydration in 92%, hypothermia in 68%, vomiting in 35%, abdominal pain in 25%, palpable abdominal mass in 23%, dyspnea in 20%, ataxia, and diarrhea in 15%. In contrast, vomiting and abdominal pain are the most consistent clinical signs in dogs and in people suffering from pancreatitis. Mild, chronic pancreatitis may be subclinical and may be associated with anorexia and weight loss. Changes in the CBC and chemistry panel are often mild and nonspecific. Elevations in hepatic enzymes (ALP, ALT) are common in severe cases, and can reflect concurrent hepatic lipidosis, cholangitis, and/or extra-hepatic biliary obstruction. In addition, elevations in serum bilirubin can reflect concurrent hepatic disease (hepatic lipidosis or cholangitis) or post-hepatic biliary obstruction secondary to pancreatitis. Many cats are hyperglycemic secondary to stress, although diabetes mellitus and diabetic ketoacidosis are not uncommon in cats with pancreatitis. Hypocalcemia secondary to saponification of fat and chelation is occasionally observed, and a decreased ionized calcium fraction has been associated with a poorer prognosis in cats.
Abdominal radiography is a relatively insensitive diagnostic tool for pancreatitis, and may show evidence of increased soft-tissue opacity and/or diminished abdominal detail in the right anterior quadrant. Abdominal ultrasonography is more sensitive for pancreatitis and may detect a hypoechoic pancreatic parenchyma because of edema, and a hyperechoic surrounding mesentery associated with focal peritonitis. Additional changes include enlargement of the pancreas, an irregular pancreatic border, dilation of the cystic duct, and mild abdominal effusion. Measurements of serum amylase and lipase activity are of low diagnostic yield in cats, and increased activities of both enzymes can occur secondary to disorders of the stomach, bowel, liver, and kidney. Measurement of serum trypsinogen-like immunoreactivity (TLI) is a relatively insensitive test for the diagnosis of feline pancreatitis. Recent studies have shown the superior performance characteristics of the feline pancreatic lipase immunoreactivity (fPLI) assay for the diagnosis of feline pancreatitis; however, the assay is less sensitive for cats with mild pancreatitis. A combination of the fPLI assay with abdominal ultrasound will result in an increased sensitivity compared to either test alone. The current “gold standard” for diagnosing pancreatitis is pancreatic biopsy for histologic evaluation. Pancreatitis can have a patchy or multifocal distribution in cats, necessitating multiple biopsies of the pancreas for histologic confirmation.

The management of feline pancreatitis is largely supportive and includes maintenance of fluid and electrolyte balance, colloids when warranted, and analgesics. Antibiotic administration is controversial and is typically avoided, but is indicated if the patient is febrile or exhibits toxic changes on the hemogram, or exhibits evidence of breakdown of the intestinal mucosal barrier (melena, hematochezia). Antiemetic therapy is indicated if the vomiting is persistent or severe. Potent antiemetics such as ondansetron (Zofran) or maropitant (Cerenia) work well, although prokinetic drugs such as metoclopramide as a continuous rate infusion (1–2 mg/kg/24 h) may also be helpful. It is important to emphasize that metoclopramide is a relatively ineffective, centrally acting antiemetic in cats, and its benefit is derived from its prokinetic activity and inhibitory effects at the 5-HT3 receptor. Respiratory distress, neurological problems, cardiac abnormalities, bleeding disorders, and acute renal failure are all poor prognostic signs, but attempts should be made to manage these complications by appropriate supportive measures. Gastric mucosal protection with an H2 blocker (famotidine or ranitidine) is recommended in patients with acute pancreatitis where gastric mucosal viability is compromised. Severe pancreatitis is also associated with a marked consumption of plasma protease inhibitors, as activated pancreatic proteases are cleared from the circulation. Saturation of available α2-macroglobulins is rapidly followed by acute DIC, shock, and death. Although controversial, transfusion of fresh frozen plasma (20 ml/kg IV) or whole blood to replace a α2-macroglobulin may be lifesaving under these circumstances. Colloid support to enhance pancreatic perfusion can be supplied with hydroxyl starch or high molecular weight dextran (10–20 ml/kg/day IV). Corticosteroids (prednisolone), particularly at anti-inflammatory doses, have been anecdotally felt to be effective in cats with pancreatitis, and may improve outcome. The use of dopamine by constant rate infusion at 5 µg/kg/min has been shown to be beneficial in preventing exacerbation to severe hemorrhagic pancreatitis in a feline model of pancreatitis. This effect is probably mediated by ameliorating increases in microvascular permeability that could promote pancreatic edema. Unfortunately, this effect was only shown when dopamine was administered within 12 hours of initiating pancreatitis in these cats. Clinical trials evaluating dopamine in cats with spontaneous
pancreatitis are warranted before this drug can be uniformly endorsed. Pancreatic enzyme supplements may decrease abdominal pain, probably by feedback inhibition of endogenous pancreatic enzyme secretion. Similarly, somatostatin and its analogues inhibit pancreatic secretions, although clinical studies have failed to show any ameliorating effects in spontaneous pancreatitis in human beings.

Cats that are not vomiting intractably should be offered a fat-restricted or maintenance diets orally if tolerated. In anorectic cats, enteral feeding via nasoesophageal, esophageal, gastrostomy or percutaneous jejunostomy tube is a reasonable and effective means of alimentation. The prognosis for cats with pancreatitis is extremely variable, and is related to the severity of disease, concurrent disorders (IBD and cholangitis), and tolerance to oral alimentation.

**FELINE CHOLANGITIS**

Inflammation centered on the biliary tree is a common form of hepatic disease, and appears to be the second most common form of liver disease after hepatic lipidosis. A new simplified classification scheme proposed by the WSAVA Liver Diseases and Pathology Standardization Research Group recognizes 3 distinct forms of cholangitis in cats. The new proposed classification scheme also prefers the term *cholangitis* to cholangiohepatitis, as inflammatory disruption of the limiting plate to involve hepatic parenchyma is not always a feature, and when present, is an extension of a primary cholangitis.

**Neutrophilic (Bacterial) Cholangitis**

Neutrophilic (bacterial) cholangitis is characterized by infiltration of large numbers of neutrophils into portal areas of the liver and into bile ducts, and is usually referable to ascending bacterial infection, but also rarely reported in protozoal infections. Organisms include *E. coli*, *Bacteroides*, *Actinomyces*, Clostridia, and alpha hemolytic *Streptococcus*. Inspissation of bile, which may cause partial or complete obstruction of the common bile duct, gall bladder, or intrahepatic bile ducts frequently accompany cholangitis and may require treatment before the cholangitis can be controlled or resolved. Neutrophilic cholangitis can be divided into 2 categories, namely acute and chronic. Their distinction histologically is based on the presence of increased plasma cells, lymphocytes ± macrophages with the chronic phase.

**Lymphocytic Cholangitis**

Lymphocytic cholangitis is felt to represent a later stage of neutrophilic cholangitis, or may represent a separate disease entity. It is characterized by a moderate to marked infiltration of the portal areas by small lymphocytes ± biliary hyperplasia, portal or periductal fibrosis, or bridging fibrosis. Diseases frequently associated with lymphocytic cholangitis include inflammatory bowel disease and pancreatitis. Inflammatory bowel disease may give rise to retrograde bacterial invasion of the common bile duct with resultant pancreatitis and cholangitis. Despite the high incidence of inflammatory infiltrates in the small intestine, diarrhea is not a frequent finding in cats with cholangitis.

**Chronic Cholangitis**

Chronic cholangitis associated with infection by liver flukes (*Amphimerus pseudofelineus*, *Platynosomum concinnum*, etc.) represents the 3rd distinct form of cholangitis. Chronic cholangitis secondary to fluke
infestation is characterized by severe ectasia of the bile ducts, mild to severe hyperplasia of the biliary epithelium, severe concentric periductal fibrosis, and the occasional presence of adult flukes and/or operculate eggs within bile duct lumina.

Clinical signs associated with inflammatory liver diseases are variable and nonspecific, and are frequently similar to those associated with hepatic lipidosis. Partial or complete anorexia is the most common, and sometimes the only clinical sign. Other less frequently observed clinical signs include weight loss, lethargy, vomiting, diarrhea, and fever. Cats with acute cholangitis tend to be younger (mean age 3.3 years) than cats with chronic cholangitis (mean age 9.0 years) or hepatic lipidosis (mean age 6.2 years). Male cats are more frequently affected with acute neutrophilic cholangitis. Cats with acute cholangitis are more acutely and severely ill than cats with most other types of liver disease. Laboratory changes typically seen with cholangitis include moderate to marked increases in serum bilirubin, serum alkaline phosphatase (SAP), and alanine aminotransferase (ALT). Most cats with acute or chronic cholangitis have no detectable alterations in the echogenicity of the hepatic parenchyma. Conversely, most cats with hepatic lipidosis have a diffusely hyperechoic hepatic parenchyma. Bile duct abnormalities may be observed in cholangitis. These abnormalities include gall bladder and/or common bile duct distention, cholelithiasis, cholecystitis, and bile sludging. The common bile duct can usually be seen as an anechoic, tortuous, tubular structure, 2 to 4 mm in diameter with an echogenic wall. Distention of the gall bladder and common bile duct (i.e., greater than 5 mm in diameter) occurs as a result of cholecystitis, or biliary obstruction. The gall bladder wall may become thickened as a result of inflammation or edema. Definitive diagnosis requires histologic evaluation of liver biopsy specimens following coagulation testing. Bile and/or liver parenchyma bacterial cultures should be performed when feasible.

Specific treatment is dictated by the results of liver biopsy. Neutrophilic cholangitis is managed with antimicrobial therapy. Antimicrobials chosen for treatment of cholangitis should be excreted in the bile in active form, and should be active against aerobic and anaerobic intestinal coliforms. Tetracycline, ampicillin, amoxicillin, erythromycin, chloramphenicol, and metronidazole are excreted in the bile in active form; however, several of these have significant adverse side effects. Erythromycin is not effective against gram-negative bacteria, tetracycline is hepatotoxic, and chloramphenicol may cause anorexia. As a result, ampicillin or amoxicillin combined with clavulanic acid is frequently used. These drugs may be combined with enrofloxacin to extend the spectrum. Treatment with antibiotics for 2 months or longer is recommended. Cats with lymphocytic cholangitis are typically managed with immunomodulatory therapy, including a combination of prednisolone and chlorambucil. The choleretic drug, ursodeoxycholic acid (Actigall), is recommended for cats with all types of inflammatory liver disease. It has anti-inflammatory, immunomodulatory, and antifibrotic properties, as well as increasing fluidity of biliary secretions. Ursodeoxycholic acid has safely been administered to cats at a dose of 10–15 mg/kg q24h PO. Denamarin can be used as an antioxidant to reduce hepatocellular injury. Treatment with injectable vitamin K_1 (5 mg/cat q 1–2 days SQ) can be given if bleeding diatheses develop. Nutritional support is of paramount importance in cats with cholangitis, and many cats undergo esophagostomy tube placement to facilitate enteral nutritional support. Surgical intervention is
recommended if discrete choleliths or complete biliary obstruction is identified. When complete extrahepatic bile duct obstruction is identified, surgical decompression and biliary-to-intestinal diversion (i.e., cholecystoduodenostomy or cholecystojejunostomy) is performed. The prognosis for cats with neutrophilic cholangitis is less favorable than that for the lymphocytic form. Cats with the lymphocytic form can survive for months to years.

**Feline Inflammatory Bowel Disease**

The inflammatory bowel diseases (IBD) are the most common causes of chronic vomiting and diarrhea in dogs and cats, and refer to a group of poorly understood enteropathies characterized by the infiltration of the gastrointestinal mucosa by inflammatory cells. The cellular infiltrate is composed of variable populations of lymphocytes, plasma cells, eosinophils, macrophages, neutrophils, or combinations of these cells. Changes in the mucosal architecture characterized by villous atrophy, fusion, fibrosis, and lacteal dilation frequently accompany the cellular infiltrates. Although the etiology of feline IBD is poorly understood, there is provocative evidence from clinical observations and animal models to incriminate normal luminal bacteria or bacterial products in the initiation and perpetuation of IBD. Evidence of the role of enteric microflora in the pathogenesis of IBD in people is supported by clinical responses to fecal stream diversion treatment in patients with Crohn's disease (CD) and antimicrobial therapy in CD and ulcerative colitis (UC) patients. Additionally, there are increases in circulating and intraluminal humoral and T-cell responses to the enteric microflora in human IBD patients. Furthermore, genetic mutations in NOD2/CARD15 and TLR-4 (Toll-like-receptor-4) in IBD patients make them less able to detect bacterial components, resulting in defective responses to enteric microflora. Dietary factors also appear to play a role in the etiopathogenesis of IBD in dogs and cats based on the clinical response to elimination or "hypoallergenic" diets in many of these animals.

The diagnosis of IBD is based on the exclusion of known causes of diarrhea, vomiting, and weight loss, followed by histological confirmation of infiltration of the gastrointestinal mucosa by inflammatory cells and changes in mucosal architecture. The standard work-up for a cat suspected of IBD should include a detailed and accurate history, including a dietary history, and comprehensive physical examination, followed by a minimum database consisting of a centrifugation fecal flotation and direct wet preparation, CBC, chemistry panel, and urinalysis. Abdominal ultrasound is a valuable diagnostic tool for evaluating the gastric and intestinal wall for alterations in thickness, alterations in the layering pattern (particularly the mucosa and muscularis layers), assessing changes in mesenteric lymph node size and echo texture, and assessing the ultrasonographic appearance of the liver, pancreas, and kidneys. Measurement of serum B12 (cobalamin) and folate is commonly performed by veterinarians to evaluate the absorptive capacity of the ileum and jejunum, respectively. Additional diagnostic tests that should be performed on a case-based nature include the measurement of serum thyroxin concentration; FeLV and FIV serology; fecal culture or PCR for *Trichomonas foetus*; fecal DFA or ELISA for *Giardia* and/or *Cryptosporidium* spp., and a fecal enteric panel for enteropathogenic bacteria. Regardless of the method used to procure intestinal biopsies (endoscopy, laparotomy, laparoscopy), the interobserver variation among histopathologic evaluations of intestinal tissues from dogs and cats is unacceptably high. Endoscopically obtained biopsies should be obtained perpendicular
to the intestinal mucosa, and biopsies must be carefully placed in a biopsy cassette to facilitate proper sectioning by the pathologists. With the support of the WSAVA, the Gastrointestinal Standardization Group has proposed a standardized histologic evaluation system that will be applied to dogs and cats with IBD.

Management of feline IBD includes the use of elimination or hypoallergenic diets, administration of antimicrobials and/or immunomodulatory drugs, and supplementation with cyanocobalamin. Treatment failures are usually due to an incorrect diagnosis, suboptimal medical or dietary therapy, poor client compliance, and/or the presence of concurrent disease such as pancreatitis or hepatobiliary disease.

**Feline Triaditis - Fact or Fiction?**

There is a dearth of published prospective studies supporting the simultaneous association between feline cholangitis, pancreatitis, and IBD. Ascending passage of bacteria or bacterial products from the intestine is a plausible factor in the development of pancreatitis, and it is highly likely that the retrograde ejection of bile up the pancreatic and common bile ducts during vomiting increases the risk for pancreatic inflammation and cholangitis. Interestingly, a recent study by Warren et al. comparing histopathologic features, immunophenotyping, clonality, and fluorescence in situ hybridization (FISH) in 51 cats with lymphocytic cholangitis failed to document strong evidence implicating in situ bacterial colonization as an etiopathogenesis of lymphocytic cholangitis. A similar study, critically evaluating the role of bacterial colonization in cats with neutrophilic cholangitis, is warranted. Weiss et al. reported an association between inflammatory liver disease and IBD, pancreatitis, and interstitial nephritis in 78 cats at necropsy. Although the temporal relationship between disease entities could not be established, all cats with cholangitis should be evaluated for concurrent IBD and pancreatitis. It is plausible that altered mucosal integrity secondary to IBD could precipitate inflammatory mediators, endotoxins, and microbial components access to the portal circulation with consequent deposition of immune complexes in the liver, activation of the complement system, and hepatocellular necrosis. Measurement of serum cobalamin concentrations is warranted in all anorexic cats, particularly those with IBD, pancreatitis, or hepatobiliary disease, given the high incidence of subnormal cobalamin concentrations in these cats. Cobalamin should be supplemented parenterally (SQ) at a dose of 250 µg per cat (0.25 mL) given once weekly for 6 consecutive weeks. Cobalamin concentrations should be periodically reevaluated thereafter and continued on an as-needed basis.

**References**


**Stanley L. Marks, BVSc, PhD, DACVIM (Internal Medicine, Oncology), DACVN**
School of Veterinary Medicine
University of California-Davis
Davis, CA, USA