Proceeding of the SEVC
Southern European Veterinary Conference

Oct. 2-4, 2009, Barcelona, Spain

http://www.sevc.info

Next conference:

October 1-3, 2010 - Barcelona, Spain

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FELINE INFLAMMATORY LIVER DISEASE

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Feline liver disease typically involves components of the biliary system, with involvement of the surrounding hepatocytes being uncommon (and usually secondary to the primary cholangitis). Therefore, a recent review of the nomenclature has suggested that the term Cholangitis Complex is applied to Feline Liver disease, with the subgroups, lymphocytic cholangitis and neutrophilic cholangitis (which may be either suppurative or chronic).

Suppurative Cholangitis

Suppurative cholangitis does not appear to be a precursor to the nonsuppurative form, but is a separate disease process. Typically suppurative cholangitis occurs secondary to bile stasis and therefore cats with extrahepatic bile duct obstruction, cholelithiasis, acute severe IBD or pancreatitis are predisposed to the disease. Young, male cats may be predisposed to the development of disease. Typically cats present with acute clinical signs which include fever, lethargy, inappetence, painful abdomen, acute vomiting/diarrhoea, and may be jaundiced. The liver is usually normal sized. Cholelithiasis is occasionally seen in cases of suppurative cholangitis, and the majority of cases of cholelithiasis are related to suppurative cholangitis. Choleliths are typically (but not exclusively) radiodense, and may lead to obstruction of the bile duct, in which instance they require surgical removal.

Diagnosis

Serum biochemistry may reveal mild to moderate increases in ALP, GGT and bilirubin initially. However, as the inflammation extends throughout the hepatic parenchyma there will be subsequent increases in ALT, AST and bile acids. In addition cats with concurrent diseases may have biochemical changes associated with the underlying disease. Haematology may reveal a mild to moderate leukocytosis, although with chronicity there may be anaemia, lymphopenia or lymphocytosis and/or thrombocytopenia. In addition, clotting times may be prolonged due deficiency of the Vitamin K dependant clotting factors.

Typically radiography is not helpful, whilst ultrasonographic examination may reveal one or more predisposing factors, and may reveal changes in the appearance of the hepatic echogenicity, dilation of the bile ducts and even sediment within the gallbladder, diagnosis of suppurative cholangitis requires aspiration and culture of the bile (taken through the right medial liver lobe to minimise the risk of bile peritonitis) and biopsy of the liver. Bile aspirates should be sent for both aerobic and anaerobic culture. Bile culture is positive in 18-25% of submission, and typically reveals growth of a single organism (90%), most often these are gram negative aerobes (E.coli, Enterococcus, Streptococcus), but anaerobes such as Bacteroides and Clostridium spp have also been cultured. However, bacteria can be found in any disease which leads to cholestasis and therefore histology of the liver, demonstrating neutrophilic infiltration of the walls and lumen of the intrahepatic ducts, bile duct epithelial degeneration and necrosis, is needed to confirm the diagnosis.

Treatment options

If a diagnosis of suppurative cholangitis is made elimination of cholestatic factors and systemic infection is imperative. Whenever possible, underlying diseases should be treated. In addition, four-six weeks of an appropriate antibiotic therapy (based on culture and sensitivity) should be implemented. In addition, hydrocholeresis with ursodeoxycholate and antioxidants are beneficial. In addition, supplementation of B vitamins, Vitamin E, Vitamin K has been advocated (see treatment of non-suppurative cholangitis). Dietary support is imperative, as these cats are at risk of developing hepatic lipidosis.

Non-suppurative Cholangitis

The clinical signs are typically chronic and insidious in nature and may include cyclic lethargy, weight loss, anorexia or occasionally polyphagia, vomiting, diarrhea, and polydipsia. The cyclical nature of the disease may due to co-existing pancreatic or GI inflammation, as the association between the feline common bile duct and pancreatic duct provides a conduit for sharing infectious agent, inflammatory mediators, and obstructing debris. Co-existing diseases lead to a predominance of the signs of either GI or pancreatic diseases. However, in some cases jaundice may be present; this can be an intermittent feature. Occasionally in severe disease hepatic encephalopathy may be evident.

Physical examination may reveal a normal-enlarged liver, and there may be mild generalised lymphadenopathy. However, typically, unless severe, abnormalities found on physical examination are non-specific.
**Diagnosis of non-suppurative cholangitis**

Serum biochemistry often reveals mild to moderately (occasionally severely) increased liver enzymes, increased bile acids, hyperbilirubinaemia, hyperglobulinaemia, and hypoalbuminaemia. However, such changes may be cyclical and may not be evident when clinical signs are not present. Biochemical changes associated with concurrent GI or pancreatic disease may be evident.

Haematology may reveal mild anaemia, lymphopenia or lymphocytosis, monocytosis, and/or thrombocytopenia. Blood clotting times are frequently prolonged.

Ascitic fluid, if present, is typically high in protein.

Ultrasound examination may show blotchy hepatic hyperechogenicity, biliary tree distention and irregularity, ‘sludging’ of bile, a thickened gall bladder wall (which is most typically associated with the presence of a secondary infection), and/or evidence of common bile duct obstruction. Associated findings may include enlarged mesenteric lymph nodes, pancreatic irregularity, and/or thickening of the duodenal walls.

Diagnosis of non-suppurative cholangitis requires a liver biopsy, this may be obtained surgically or percutaneously, under ultrasound guidance. However, prior to undertaking a biopsy the clotting times and platelet function should be assessed. Histopathology of non-suppurative cholangitis allows it to be classified as either chronic neutrophilic cholangitis: characterised by mild to severe infiltration of the portal areas by plasma cells, lymphocytes and neutrophils, with biliary epithelial degeneration and necrosis. There may be lymphoid aggregates in the portal areas. Inflammation is usually centred within the walls and lumen of the intrahepatic ducts and may extend through the limiting plate to involve the periportal hepatic parenchyma. Biliary hyperplasia, periductal (sclerosing) fibrosis and bridging fibrosis may also be present or lymphocytic cholangitis: which demonstrates moderate to marked infiltration of small lymphocytes restricted to the portal areas, often associated with variable portal fibrosis and biliary proliferation. Lymphoid aggregates may be present, as may obliteration of the bile ducts, biliary hyperplasia and fibrosis, or bridging portal fibrosis. There may be a few portal plasma cells and/or eosinophils. Chronic cases may develop biliary cirrhosis. It can be difficult to differentiate between lymphocytic cholangitis and well-differentiated lymphocytic lymphoma.

**Treatment**

**If an underlying condition can be identified this should be treated.**

- Analgesia should be provided in cats which have undergone surgical liver biopsy or in which a potentially painful underlying condition may be present (ie Pancreatitis), Buprenorphine (20 μg/kg IV, SQ, PO q8h) is the authors drug of choice in such cases.
- IV fluids and nutritional support with a balanced diet should be implemented (see earlier notes).
- Antiemetics maybe required if there is concurrent GI or pancreatic disease or severe jaundice.
- Some authors advise the empirical use of antibiotics, as it is know that bacteria can translocate from the gut to the liver in as little as 8 hours. Ampicillin (10-40 mg/kg q 8 hours PO), amoxicillin/clavulinate (11-22 mg/kg q 8-12 hours PO), or cephalexin (10-35 mg/kg q 8-12 hours PO), enrofloxacin (5 mg/kg PO q24h) - all are well concentrated in bile. Metronidazole may be used for its effect against anaerobes and its immunomodulating effects (7.5-10 mg/kg every 12 hours PO). Do not use higher doses, as these can be hepatotoxic.
- Immunosuppressive agents (with chronic neutrophilic cholangitis and lymphocytic cholangitis): Immunosuppressive doses of corticosteroids (prednisolone 1-4 mg/kg q12-24 hours PO, then taper over 6-12 weeks to 1.0 mg/kg PO q48h) and maintain on every other day doses if needed. However, there is some evidence that use of Prednisolone alone may decrease long-term survival and that it should always be used in combination with an anti-oxidant such as SAMe (see below). It has been shown that steroids to impart oxidative stress by pre-empting membrane release of arachidonic acid that initiates inflammatory eicosanoid production, crucial to membrane oxidation. Therefore, some authors advocate a move away from the traditional corticosteroid therapies and advise alternative immunomodulatory medications such as mexitrexate (0.13 mg/cat every 12 hours x 3 doses PO or a total of 0.4 mg PO - into 3 over 24h; given q7-10d), chlorambucil (2-5 mg/m^2 PO up to once every 48h), or Cyclosporin A (measure serum levels, start at 2 mg/kg PO q12h). Do not give azathioprin. Care – these drugs are all potentially hepatotoxic

**Supportive therapies (all forms of cholangitis):**

- Ursodeoxycholic acid (10-15 mg/kg PO q24h) (UDCA, Destolith): Synthetic hydrophilic bile acids that aids bile flow. It protects against membranocytic bile acids and has anti-inflammatory, immuno-modulatory, and anti-fibrotic activities, and is cytoprotective to hepatocytes. Where complete biliary obstruction is present it should be removed before starting treatment
- Antioxidants
- S-Adenosylmethionine (SAMe) (18-40 mg/kg PO q24h): Nucleotide synthesized by all cells (from methionine + ATP). It is essential for major hepatic biochemical pathways; especially transmethylation (for gene expression and for maintaining stable cell membranes), aminopropilation (for cell replication and liver regeneration and repair), and transshulphuration (for the generation of the major hepatic anti-oxidant glutathione [GSH] and [in dogs] for taurine production). GSH (+ taurine) = hepatic anti-oxidants + essential
for detoxification. GSH is significantly reduced in liver disease; in >50% of dogs and >75% of cats. Giving oral SAMe repletes GSH in the liver and the red blood cells (The latter is very important in cats as cat red cells are extremely sensitive to oxidative damage)

• N-Acetylcysteine (NAC) (140mg/kg iv with NaCl or 5% dextrose administer over 20mins and follow up with 70mg/kg iv 2-4 times daily as indicated): Used IV for crisis intervention: Like SAMe, NAC is a thiol donor and aids the production of GSH. Anaphylactic reactions have been reported.

• Vitamin E - an anti-oxidant and free radical scavenger with significant hepatoprotective properties (20-100 mg/cat PO, IM q24h)

• Colchicine – an anti-fibrotic which may be used where significant fibrosis is occurring (0.01-0.03 mg/kg PO q24h)

• B12 (125-250 μg/cat SQ q7-28 days), B1 (100 mg/cat SQ, PO q12-24h), B-Complex (1-2 ml/l of fluids – keep out of light): B vitamin depletion is common in anorexic cats, and can lead to GSH deficiency, neurological signs, lethargy, weakness and inappetence. Therefore B vitamin supplementation can be useful in chronic liver diseases.

• L-carnitine (250-500 mg/cat PO q24h) supplementation is recommended in cats with hepatic lipidosis as hepatic carnitine synthesis is limited in catabolic cats and it is thought that cats require carnitine for adequate fatty acid oxidation and dispersal. It has been demonstrated that supplementing cats with Hepatic lipidosis with L-carnitine leads to an increased survival rate.

• Taurine (250-500 mg/cat PO q24h) : Taurine conjugates the membranocytolytic bile acids, mitigating their toxic effects on cells.

• Zinc (7-10 mg/kg elemental Zn PO q24h): Zinc deficiency increases the susceptibility to GSH deficiency. In addition, Zn antagonises redox-active transition metals: Fe & Cu. Plasma levels should be monitored if supplementation is provided.

• Milk thistle (Silybinin-PPC 2-5mg/kg/day)). Use has been proven beneficial in recovery from certain toxins and in the treatment of Hepatitis C in people. Its benefit in colangitis is debated. It is though to have some anti-inflammatory, anti-fibrotic and anti-fibrotic effects. It promotes protein synthesis, interferes with some cytochrome P450 enzymes and reduces uptake/activation of some toxins.

• Abnormal clotting times are seen in >80% of cats and >90% of dogs with various forms of liver disease. This results from reduced synthesis and increased consumption of clotting factors. Vit K is required for the normal function of factors II, VII, IX + X. It comes from the diet and is made by small intestinal microflora. However, because it is fat soluble it needs bile salts for absorption. Vit K levels are low in 50% of cats with liver disease. This is due to inappetence (causing reduced intake), concurrent small intestinal disease (causing reduced production) and cholestasis (resulting in reduced absorption)

• Acute treatment: Vit K1 (0.5-1.5 mg/kg SQ, IM, q12h for 1-2 days before biopsy or surgery) N.B. Vit K cannot help in very severe liver disease when ~ all clotting factors may be lost; fresh whole blood or plasma (6-10 ml/kg IV, as needed)

• Chronic treatment: Vit K1 (0.5-1.5 mg/kg PO, SQ, q7-21days (Care, excess can cause Heinz body anaemia) Surgery is required where complete biliary obstruction occurs (cholecystotomy or cholecystoduodenostomy).

Prognosis
For all forms of cholangitis the prognosis is very variable and often unpredictable. Some cases respond well and only need temporary treatment, others require continued therapy to maintain remission, while others progress relatively rapidly and require euthanasia. Once severe fibrosis, cirrhosis or ascites has developed the prognosis is usually guarded.