UPDATE ON CANINE PANCREATITIS: DIAGNOSIS AND MANAGEMENT

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The incidence of pancreatitis characterized by significant histologic changes identified at necropsy is 1.3% in cats and 1.5% in dogs. This is where the similarities between the two species diverge. Most dogs have acute pancreatitis while most cats have chronic pancreatitis.

PATHOPHYSIOLOGY

The pancreas secretes high quantities of enzymes required for digestion of a meal. If these enzymes become activated within the pancreas, serious damage (autodigestion) to the organ will take place. Under normal conditions this does not occur because a number of protective mechanisms exist. Enzymes produced by the pancreas are secreted as inactive zymogens and these zymogens or proenzymes must become activated prior to being functional. Normal enzyme activation takes place only in the intestine. It is generally believed that pancreatitis develops when there is activation of digestive enzymes within the gland and subsequent autodigestion. The location of the initiation of enzyme activation is thought to begin at the intercellular level, but the exact mechanism is unclear at this time. Experimental studies have shown that excessive acinar stimulation with cholecystokinin (CCK) or with high-fat diets results in zymogen redistribution with vacuolization and activation by lysosomal enzymes in the presence of calcium. Lysosome enzymes then activate trypsinogen, which begins the autodigestive process.

Other observations suggest that the depletion of acinar glutathione in the pancreas may stimulate oxidative stress and that contributes to tissue injury. Disturbances in glutathione, a tissue antioxidant, may alter zymogen protein processing, impair zymogen transport, and assist in activation of pancreatic enzymes. Oxidative stress from ischemia and hypoxia may therefore result in pancreatic acinar damage. In animals, superoxide dismutase and catalase therapy reduced experimental pancreatitis, suggesting that antioxidant therapy started early in the course of pancreatitis may be of benefit. Certain drugs are also associated with development of pancreatitis.

Once there is activation of trypsinogen all zymogens become activated. Damage is amplified by elastase and phospholipase. The proteases will activate the kinin, coagulation, fibrinolytic, and complement cascades. Local complement activation induced by certain toxins or from local ischemia to the pancreatic microcirculation may play a role in initiating the cascade of events. Simply put, local pancreatic damage is associated with autodigestion by enzymes and systemic effects are generally associated with inflammatory cytokines and other mediators and less likely due to the release of activated pancreatic enzymes.

Pancreatitis and subsequent autodigestion may be mild associated with an edematous pancreatitis or may become more severe associated with pancreatic acinar necrosis. It is the more severe pancreatic necrosis that tends to have the severe clinical signs and a poorer prognosis associated with systemic...
disease, such as systemic inflammatory response syndrome (SIRS) or multiple organ dysfunction (MODS).

**CLINICAL CONDITIONS**

Considerable confusion and controversy exist regarding the pathogenesis, diagnosis, and treatment of acute pancreatitis in the dog. The spectrum of clinical disease can range from mild signs resulting in rapid recovery following symptomatic therapy to those that are fulminant and frequently fatal requiring extensive critical care. The discussion of medical management in this section will cover the more complex cases of pancreatitis.

In almost all cases of pancreatitis the etiology is never determined. In many cases over nutrition is a common factor. The ingestion of high-fat diets especially in the obese patient is a well-accepted etiology. Animals getting into the trash have a higher risk of developing pancreatitis. Hyperlipoproteinemia is also common in pancreatitis. Whether this is a result of fat necrosis secondary to the pancreatitis or possibly the hyperlipidemia resulting in pancreatic ischemia is unknown. It is postulated that high concentrations of triglycerides may become activated by pancreatic lipase and produce pancreatitis. Pancreatitis is common in Schnauzers and other dogs that have a primary hyperlipidemia.

A number of drugs are also shown to cause pancreatitis including thiazides, furosemide, tetracycline, L-asparaginase, and azathioprine. The role of corticosteroids as a cause of pancreatitis has been suggested but as yet is unproved and is still controversial. In a study of 70 dogs with confirmed pancreatitis certain risk factors were identified (note that the animals included in this study were all necropsy cases and thus likely had severe disease). It was concluded that the breed, overweight body condition, small breed size, prior gastrointestinal diseases, diabetes mellitus, hyperadrenocorticism, and hypothyroidism were risk factors for developing acute pancreatitis. It is thought that around one fourth of the dogs presented with acute diabetes mellitus also have concurrent pancreatitis. No concurrent medications, glucocorticoid therapy, anesthesia, or trauma were associated with increased risk. Dogs with surgery in the 2 weeks prior had more pancreatitis than the control population in this study. The breeds at most risk were Yorkshire terriers, toy poodles, and miniature Schnauzers.

Acute pancreatitis is one of the most difficult diseases to diagnose and there is no one diagnostic test with a very high sensitivity for pancreatitis. One must have a degree of suspicion based on the risk factors listed above and the clinical findings; however, the signs can be quite variable. Acute or chronic vomiting is a major clinical sign associated with pancreatitis. The clinical spectrum can vary dramatically from case to case. In the above study of 70 dogs with severe pancreatitis, vomiting (90%), weakness (79%), abdominal pain (58%), dehydration (46%), and diarrhea (33%) were reported. In experimental pancreatitis, colitis signs (often a bloody mucoid stool) were common presumably due to the extension of inflammation from the inflamed pancreas to the transverse colon that lies in close proximity to the pancreas. Severe cases also have systemic clinical signs such as fever or even cardiovascular shock.
DIAGNOSIS

Laboratory findings are quite variable and to some extent parallel the severity of the clinical disease. Leukocytosis is usually present and represents the inflammatory nature of the disease. The biochemistry profile will show variable changes. Azotemia may occur secondary to dehydration; however, acute renal failure from acute tubular necrosis can also be present. Elevated liver enzymes are also expected in pancreatitis. Increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) are most often observed. In experimental pancreatitis in dogs, histologic evidence of secondary hepatopathies occurred in all cases. Occasionally partial or complete blockage of the common bile duct from periductal inflammation can result in icterus with increases in total bilirubin concentrations. Hyperglycemia and hypokalemia may also be present. Acid–base changes are quite variable. Severe cases may have a marked acidosis; however, severe vomiting can also result in a metabolic alkalosis. When disseminated intravascular coagulopathy (DIC) and coagulopathies occur, it generally reflects a poor prognosis.

Amylase and lipase have been used for years to diagnose pancreatitis in the dog. Unfortunately they are not consistently reliable. The specificity of both of these parameters only approximates 50%. Factors such as azotemia will increase serum amylase and lipase due to decreased renal removal and dexamethasone will increase serum lipase levels. Furthermore, both amylase and lipase are found in a number of other organs that will contribute to total lipase and/or amylase measurement. Decreased concentration of trypsin-like immunoreactivity (cTLI) is specific for the diagnosis of exocrine pancreatic insufficiency in the dog; however, elevated cTLI concentrations can occur in early in pancreatitis. The cTLI often quickly falls to low concentration with acute pancreatitis making it a poor test for the diagnosis.

Recently a new test has become available for the diagnosis of pancreatitis in the dog, pancreatic specific lipase immunoreactivity (PLI; called cPLI at Texas AM University GI Lab or Spec cPL, IDEXX Labs). An advantage of this test is that a number of organs synthesize and secrete lipases but PLI measures lipase that only originates from the exocrine pancreas. The sensitivity of cPLI for the diagnosis of pancreatitis in the dog is approximately 90%. Data would suggest that serum cPLI can be used as a diagnostic test for pancreatitis even in dogs with renal failure and prednisone does not have any effect on cPLI values. In a recent abstract presented at the American College of Veterinary Internal Medicine (ACVIM) Forum in June 2009 a prospective study of cases with clinical evidence of pancreatitis found the test had a 93% sensitivity and a 78% specificity using the IDEXX cutoff value of <200 µg/L as normal. The conclusion was if the Spec cPL was < 200 µg/L (normal) that it was likely that the patient did not have pancreatitis. If the value was above the normal reference range pancreatitis should be included in the differential diagnosis. Elevations in the Spec cPL without evidence of acute pancreatitis may be due to occult pancreatitis or more likely the result of secondary pancreatic damage from a primary non-pancreatic disease (i.e., the innocent bystander theory). The Spec
cPL also was also reported to decline during recovery in a second abstract presented at the ACVIM Forum suggesting it would be useful to monitor the patient’s PLI concentrations during recovery. The SNAP cPL correlates well with the Spec cPL values with regard to cutoff values of normal and abnormal.

Abdominal radiographs may reveal increased density, diminished contrast and granularity in the right cranial abdomen with displacement of the stomach to the left, and widening of the angle between the stomach and the duodenum. A non-homogenous mass and loss of echodensity in the area of the pancreas is often noted on ultrasonographic examination. Occasionally dogs having pancreatitis may also have thoracic effusion as well, probably due to extension of inflammation through the diaphragm. One study found the sensitivity of ultrasound to be 68% but this varies based on operator skill.

We will frequently perform a fine needle aspiration of suspected areas of pancreatitis; cytology showing suppurative inflammation also supports the diagnosis. We consider cytology to be safe as a diagnostic tool. Abdominocentesis and cytology is also very helpful if effusion is present. Suppurative nonseptic inflammation is the typical finding and is rarely septic. Some have combined abdominal fluid analysis with measurement of abdominal fluid lipase concentrations compared with serum lipase concentrations (or more recently suggested Spec cPL. An abdominal lipase concentration markedly higher than serum lipase was considered to suggest the diagnosis of pancreatitis in one study.

Finally, biopsy provides the definitive diagnosis. Surgery and laparoscopy are two options to consider for biopsy. Although acute pancreatitis is not considered to be a surgical condition, indications for surgery would include septic peritonitis, pancreatic abscess, or to place a jejunostomy feeding tube. Surgery for pancreatitis is often associated with a poor survival rate especially in cases having a pancreatic abscess.

**TREATMENT**

Treatment of pancreatitis is supportive and should be tailored for the individual case. Basic therapy involves correction of fluid and electrolyte imbalance, nutritional considerations, pain management and the control of secondary complications such as vomiting. The material in the following section deals with management considerations for the severe and often life-impending acute pancreatitis case. Mild cases of pancreatitis may require minimal treatment or only a portion of the recommendations included below.

**Fluid and electrolyte** therapy is given in virtually every case of pancreatitis for improving pancreatic perfusion and correcting the effects of fluid loss into the peritoneal cavity, and vomiting losses coupled with the vasoactive factors released from the pancreas producing a hypovolemic or possibly endotoxic shock. Fluid losses through vomiting may also result in a hypochloremic metabolic alkalosis. Most cases, however, usually have a metabolic acidosis with depletion of total potassium stores. A balanced crystalloid electrolyte solution often supplemented with additional potassium is indicated in almost all cases. Careful monitoring of electrolyte concentrations and patient hydration and renal output is essential in the severe pancreatitis case. Colloids
such as Hetastarch (10–20 mL/kg/day) may also be beneficial in improving pancreatic blood flow.

When protein levels decline plasma therapy has been suggested for improving oncotic pressure, pancreatic perfusion, and replacing protease inhibitors. More recently there have been questions on the benefit of fresh frozen plasma for protease replacement and one study failed to demonstrate the benefit in patients given plasma compared with those only given crystalloids. Probably the most important use of plasma is for factor replacement associated with coagulopathies or DIC.

**Analgesics** should be considered in all patients with pancreatitis, even if there is no outward evidence of abdominal pain. For mild pain meperidine hydrochloride (5–10 mg/kg intravenously [IV], intramuscularly [IM] as needed), morphine (0.1–0.5 mg/kg IV, subcutaneously [SC], or IM as needed) or butorphanol tartrate (0.1–1.0 mg/kg SC every 1 to 6 hours) are suggested. With moderate to severe pain fentanyl is given as a continuous rate infusion (CRI, 2–5 µg/kg/hour) or 4–10 µg/kg SC, IM not to exceed 500 µg/dog. With severe pain we increase the dose of fentanyl (5–10 µg/kg/hour) and may add either ketamine (0.2–0.4 mg/kg/hour CRI) or lidocaine (5–30 µg/kg/min CRI). The animals should be monitored for side effects, particularly respiratory depression. In some cases there is severe wind-up pain and alternative measures may be required to block the pain before traditional analgesics are effective. Spinal blocks and local analgesia should be considered in this case. We have treated some patients having severe abdominal pain with some success using intrathoracic or intra-abdominal placement of local anesthesia. Either lidocaine (1.5 mg/kg) or bupivacaine (Marcaine, 1.5 mg/kg) can be used. Bupivacaine has a longer duration of action and is my preference. We generally use a butterfly catheter or over-the-needle-catheter placed in the 8th mid-intercostal space or peritoneal cavity near the pancreas. Following injections the dog is rolled around and placed on its back so the anesthesia will drain into the area of the vagal nerves.

**Antiemetics** usually are given routinely if the patient has nausea and vomiting to help prevent fluid loss and make the patient more comfortable and possibly enhance return to early nutrition. The ideal antiemetic for pancreatitis should work both centrally and peripherally. Metoclopramide is given for antiemetic effects and to improve gastrointestinal tone (0.2–0.4 mg/kg four times daily [QID] PO or SC, or 0.01–0.02 mg/kg/hr CRI). In my opinion, metoclopramide has only poor prokinetic effects and is limited as an antiemetic in that it only works centrally. Anticholinergic agents are not indicated because of the profound effects on decreasing GI motility and little if any effects in changing pancreatic secretion. Dopamine antagonists may also decrease pancreatic perfusion. My antiemetic of choice is maropitant (Cerenia, 1 mg/kg every 24 hours given SC or IV slowly or 2 mg/kg every 24 hours given PO). It is a broad-spectrum antiemetic that works both centrally and peripherally. Recent evidence by us have shown that it also blocks visceral pain – at least in a visceral pain model given at the dose 1 mg/kg. Maropitant is a neurokinin-1 antagonist that blocks receptors found in the emetic center, CRTZ, and in peripheral afferent nerves.
Antibiotics should be considered for prophylactic therapy in the severe case or whenever there is evidence of sepsis or pancreatic infection. Infectious etiology of pancreatitis is rare in dogs but an experimental pancreatitis study in dogs suggests antibiotic therapy improves survival. Broad-spectrum antibiotics effective against aerobes and anaerobes should be given. I generally place my severe pancreatitis cases on a second-generation cephalosporin or a combination of amoxicillin and enterofloxacin for this purpose.

Nutritional supplementation in severe pancreatitis is very important. Enteral nutrition is favored over parenteral nutrition. Pancreatic rest in the form of fasting is the traditional recommendation for any patient with pancreatitis by giving nothing per os (NPO) for several days. The belief is that feeding results in the release of pancreatic secretagogues that will stimulate pancreatic secretions and exacerbate the pancreatitis. Studies have now shown, however, that adequate nutrition improves survival in experimental and human pancreatitis pancreatitis. We now believe that severe vomiting and/or pain associated with eating would be the only reasons to fast patients. If the patient is not predicted to be eating on its own within about 3 days nutritional support is definitely indicated. Nutrition not only improves patient survival but improved gut integrity. Parenteral nutrition is expensive and fraught with complications. It appears that enteral feeding does not significantly increase pancreatic secretions and actually improves gut integrity, with clinical improvement in the patients being fed. Free choice feeding or tube feeding (nasoesophageal, esophageal, gastrostomy or jejunostomy tube feeding) should be considered in moderate to severe cases. We generally begin feeding CliniCare Canine/Feline Liquid Diet (Abbott Animal Health) through a small-diameter feeding tube. During recovery I generally feed a low-fat diet given in small frequent meals.

Surgery for pancreatitis is controversial and indications would include septic peritonitis, to lavage the abdomen, treatment of pancreatic abscesses, feeding tube placement, or possibly for treatment of a biliary obstruction. Surgery for pancreatitis or obstructive biliary tract disease has a guarded prognosis. We do have a small series of cases that underwent laparoscopic exploration, lavage and jejunostomy tube placement that did well. Most obstructive biliary complications will resolve as the pancreatic inflammation obstructing the common bile duct resolves.

Other therapy should be considered only after careful evaluation of the individual case. Because oxidative damage is thought to be the result of cellular membrane death antioxidants may be of benefit in the acute management of cases. Studies show that perfusion of the pancreas with free radical scavengers ameliorates the severity of pancreatitis in experimental canine models. Vitamin E is a potent membrane antioxidant and S-adenosyl L-methionine (SAMe) replaces glutathione stores that may have some benefit in pancreatitis. Pancreatic enzyme supplementation has been reported to decrease the pain that accompanies chronic pancreatitis in humans by the feedback inhibition by endogenous pancreatic enzyme secretion. It is not known if enzymes are helpful in acute cases.
PROGNOSIS

Acute pancreatitis can vary in severity of signs and often results in multi-system involvement. In one report a clinical severity index was developed looking at the prognosis for survival. The premise of this paper was that the greater systemic organ involvement (such as liver disease, renal disease, DIC, peritonitis, etc.), the poorer the prognosis.

DRUGS COMMONLY USED IN PANCREATITIS THERAPY

(These are only suggested doses and medications should be adjusted for individual patient)

<table>
<thead>
<tr>
<th>Action</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesic</td>
<td>Fentanyl</td>
<td>2-10 µg/kg/h</td>
<td>IV</td>
<td>CRI</td>
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<td>Analgesic</td>
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<td>IV, IM</td>
<td>Prn</td>
</tr>
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<td>0.1-1 mg/kg</td>
<td>SQ</td>
<td>q6h</td>
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<td>Analgesic</td>
<td>Hydromorphone</td>
<td>0.1-0.2 mg/kg</td>
<td>IV, IM, SQ</td>
<td>q6-8h</td>
</tr>
<tr>
<td>Analgesic</td>
<td>Methadone</td>
<td>0.1-0.5 mg/kg</td>
<td>IV, IM, SQ</td>
<td>q6-8h</td>
</tr>
<tr>
<td>Analgesic</td>
<td>Ketamine*</td>
<td>10-20 µg/kg/min</td>
<td>IV</td>
<td>CRI</td>
</tr>
<tr>
<td>Analgesic</td>
<td>Lidocaine*</td>
<td>30-50 µg/kg/min</td>
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<td>CRI</td>
</tr>
<tr>
<td>Antiemetic</td>
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<td>IV, IM, SQ</td>
<td>q8h</td>
</tr>
<tr>
<td>Antiemetic</td>
<td>Metoclopramide</td>
<td>1-2 mg/kg</td>
<td>IV</td>
<td>CRI q24h</td>
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<tr>
<td>Antiemetic</td>
<td>Metoclopramide</td>
<td>0.1-0.4 mg/kg</td>
<td>IM, SQ</td>
<td>q8h</td>
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<tr>
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<td>IV</td>
<td>q8-12h</td>
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<td>Antiemetic</td>
<td>Maropitant</td>
<td>1 mg/kg</td>
<td>SQ, IV</td>
<td>q24h</td>
</tr>
</tbody>
</table>

* usually given in conjunction with Fentanyl both as a CRI

SUGGESTED READING


