

Diagnosis and management of canine and feline pancreatitis – a disease that remains difficult

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Introduction

The incidence of exocrine pancreatic disorders is quite large in both dogs and cats. The most common pancreatic disease is pancreatitis in both dogs and cats, and while it has traditionally been assumed that acute pancreatitis is more common in dogs and chronic pancreatitis more common in cats, recent data would suggest that in both species chronic pancreatitis is about two times more common than acute pancreatitis. Also, it has recently been suggested that the true prevalence of pancreatitis in dogs and cats is by far greater than previously believed. In one study of 208 dogs undergoing necropsy at the Animal Medical Center in New York City for a variety of reasons more than 21% had macroscopic lesions suggesting pancreatitis. Pancreata from all dogs were sectioned every 2 cm and a total of 64% had histological lesions of acute and/or chronic pancreatitis. These data suggest that pancreatitis is far more common in dogs than previously suspected. However, the data also suggest that infiltration of the pancreas with inflammatory cells is not necessarily clinically significant and more research is needed to better characterize clinically significant disease. Similar data have also been reported for cats. In a study of 115 cats submitted for necropsy at the University of California in Davis, 75.7% showed lesions suggestive of acute and/or chronic pancreatitis. This would suggest that, similarly to dogs, feline pancreatitis is far more common than previously expected, but also that more work is needed to clearly characterize clinically significant disease.

According to the current classification system of human pancreatitis acute pancreatitis is an inflammatory condition of the pancreas that is completely reversible after removal of the inciting cause. Chronic pancreatitis is characterized by irreversible histopathologic changes of the exocrine pancreatic tissue, such as atrophy or fibrosis. Both forms can be mild or severe. Mild forms of pancreatitis are associated with no or little pancreatic necrosis and systemic effects and often allow recuperation of the patient. In contrast, severe forms of pancreatitis are associated with extensive pancreatic necrosis, multiple organ involvement, and often a poor prognosis.

Clinical picture

Clinical signs in dogs with pancreatitis depend on the severity of the disease. Mild cases may remain subclinical. More severe cases may present with anorexia (91%; data from a study of 70 dogs with fatal pancreatitis), vomiting (90%), weakness (79%), abdominal pain (58%), dehydration (46%), and diarrhea (33%). Severe cases can present with systemic clinical signs such as fever or even cardiovascular shock. Cats, even with severe pancreatitis, present with even less specific clinical signs than do dogs. In one study of 40 cats with severe pancreatitis the following clinical signs were reported: lethargy (100%), anorexia (97%), dehydration (92%), hypothermia (68%), vomiting (35%), abdominal pain (25%), a palpable abdominal mass (23%), dyspnea (20%), ataxia (15%), and diarrhea (15%). Especially remarkable is the low incidence of vomiting and abdominal pain, both of which are common clinical signs in human and canine

pancreatitis patients. Clinical signs in patients with pancreatitis are due to pancreatic inflammation or systemic effects of the pancreatic inflammation.

Imaging

Radiographic changes seen in some cases include a decreased contrast in the cranial abdomen and displacement of abdominal organs. However, these changes are rather subjective and abdominal radiography is non-specific for canine or feline pancreatitis.

Abdominal ultrasound is useful in the diagnosis of pancreatitis in dogs and cats. The sensitivity of abdominal ultrasonography is dependent on operator experience and has been reported to be up to 68% in dogs and up to 35% in cats. Changes identified include pancreatic swelling, changes in echogenicity of the pancreas (hypoechoogenicity of the pancreatic parenchyma in cases of pancreatic necrosis and rarely hyperechoogenicity of the pancreatic parenchyma in cases of pancreatic fibrosis) and of peripancreatic fat (hyperechoogenicity in cases of peripancreatic fat necrosis), fluid accumulation around the pancreas, and less frequently a mass effect in the area of the pancreas. Other findings that have been described are a dilated pancreatic duct or an enlarged duodenal papilla.

Abdominal computed tomography is a routine procedure in humans suspected of having pancreatitis, but appears to be very insensitive for the diagnosis of pancreatitis in the cat and has never been systematically evaluated in the dog.

General clinical pathology

Complete blood count and serum chemistry profile often show mild and nonspecific changes. More severe changes can be observed in patients with severe forms of pancreatitis. Thus, findings from general clinical pathology are not clinically useful for establishing a diagnosis of pancreatitis, but are extremely useful to rule out other differential diagnoses and to evaluate the patient for systemic complications of pancreatitis.

Serum amylase and lipase activities

Serum amylase activity can be measured by use of enzymatic assays, but both sensitivity and specificity are poor and the diagnostic value of measurement of serum amylase activity in dogs and cats is very limited. Serum lipase activity can be measured by three different methods all using a different substrate. Most assays utilize a 1,2-diazyglycerol as a substrate. These assays have been shown to have a limited specificity (approximately 50%) for the exocrine pancreas and a limited sensitivity (also approximately 50%) for canine pancreatitis. Over the last 20 years a synthetic substrate, resorufin (DGGR), has been used as an alternative substrate in both human and veterinary medicine. While some studies would suggest a higher specificity for the exocrine pancreas than 1,2-diazyglycerol-based assays, other studies did not confirm these findings. Overall, the clinical utility of DGGR-based assays is probably better than those that are based on 1,2-diazyglycerol, but more studies are needed to confirm these results, and this substrate is by no means specific for the exocrine pancreas in dogs or cats, which has been suggested by some recent studies. A point of care assay has been described that uses triolein as a substrate. However, so far the only studies that are available show this assay to correlate with the measurement of serum pancreatic lipase immunoreactivity when exclusively evaluated in serum samples that are neither lipemic, icteric, or hemolyzed, changes that are rather common in dogs with pancreatitis. Another study suggested a good sensitivity and specificity of this assay, but dogs were retrospectively chosen and only included dogs with very high Spec cPL

concentrations, which is not typical of the overall population of dogs with pancreatitis. Thus, overall, serum amylase and lipase activities are of limited clinical value for the diagnosis of pancreatitis in dogs or cats.

Trypsin-like immunoreactivity

Trypsin-like immunoreactivity is specific for exocrine pancreatic function. However, the sensitivity of serum TLI concentration for pancreatitis in dogs and cats is only approximately 30-60%, making it a suboptimal diagnostic test for pancreatitis in both species. However, serum TLI concentration remains the diagnostic test of choice for the diagnosis of EPI.

Pancreatic lipase immunoreactivity (PLI)

Specific assays for the measurement of pancreatic lipase immunoreactivity in dogs and cats (cPLI and fPLI, respectively) are available. Many different cell types in the body synthesize and secrete lipases. In contrast to catalytic assays for the measurement of lipase activity, use of immunoassays does allow for the specific measurement of lipase originated from the exocrine pancreas. Serum cPLI was measured in a group of dogs with exocrine pancreatic insufficiency and the median serum cPLI concentration was significantly decreased compared to clinically healthy dogs. In addition, serum cPLI concentration was non-detectable in most of the dogs and minimal serum cPLI concentrations were observed in the rest of the dogs, indicating that serum cPLI concentration originates from the exocrine pancreas and is specific for exocrine pancreatic function. In another study serum cPLI was evaluated in dogs with experimentally induced chronic renal failure. While serum cPLI was significantly higher in dogs with experimentally induced chronic renal failure than in clinically healthy dogs, most dogs had serum cPLI concentrations within the reference range and none of the dogs had serum cPLI concentrations that were above the currently recommended cut-off value for pancreatitis. These data would suggest that serum cPLI concentration can be used as a diagnostic test for pancreatitis even in dogs with renal failure. Also, long-term oral administration of prednisone did not have any effect on serum cPLI concentration.

The sensitivity of different minimally-invasive diagnostic tests was compared in dogs with proven pancreatitis. The sensitivity of serum TLI concentration was below 35% and that of serum lipase activity was less than 55%. In contrast, the sensitivity for serum cPLI concentration for pancreatitis was above 80%. More recent clinical studies show similar results, suggesting that the measurement of Spec cPL concentration is the most sensitive and specific diagnostic test currently available.

Clinical studies in cats have shown similar results. In a group of cats with experimentally induced pancreatitis both serum fTLI and fPLI concentrations did increase initially but serum fPLI stayed elevated much longer than did serum fTLI concentration suggesting that, as in the dog, serum PLI concentration is much more sensitive for pancreatitis than serum TLI concentration. In another study of cats with spontaneous pancreatitis serum fPLI concentration was more sensitive and more specific than serum fTLI concentration or abdominal ultrasonography. Thus, in both dogs and cats serum PLI concentration is the most sensitive and specific diagnostic test for pancreatitis currently available. Commercial assays for the measurement of cPLI and fPLI, Spec cPLTM and Spec fPLTM, respectively are now available. Also, patient-side tests for the semi quantitative assessment of pancreatic lipase are now available. These SNAP assays are useful to rule out pancreatitis in dogs or cats with suggestive clinical signs when the test is negative. Also, a positive test result suggests the presence of

pancreatitis. However, a serum sample should also be sent to the laboratory for measurement of Spec cPL/Spec fPL to confirm the diagnosis and to get a baseline value that can then be used to monitor the progression of the disease.

Cytology and histopathology

Cytologic evaluation of a fine-needle aspirate of the pancreas is a great diagnostic modality to confirm a diagnosis of pancreatitis. Various studies have shown that if care is taken there is little risk of a fine needle aspiration of the pancreas. The presence of pancreatic acinar cells confirms the successful aspiration of the pancreas and presence of inflammatory cells in the same aspirate confirms the presence of pancreatic inflammation. However, in patients with severe pancreatic necrosis only cellular debris may be aspirated and the cytological evaluation may be inconclusive. Also, lack of inflammatory cells in the infiltrate does not rule out pancreatitis as the inflammatory lesions may be highly localized.

Traditionally, a pancreatic biopsy has been viewed as the most definitive diagnostic tool for pancreatitis. Pancreatic biopsies can be collected during abdominal exploratory or by laparoscopy. The presence of pancreatitis can easily be diagnosed by gross appearance of the pancreas in many cases. However, the absence of pancreatitis can be difficult to prove and even if multiple biopsies are being collected, pancreatic inflammation, especially in cases of chronic pancreatitis, may easily be missed. It should also be noted that while a pancreatic biopsy in itself is not associated with many complications, many patients with pancreatitis have a higher anesthetic risk than a healthy patient.

Treatment of Inciting Cause

Whenever possible the inciting cause of the disease should be removed or treated. However, this may be difficult to accomplish as most cases of canine and feline pancreatitis are considered idiopathic.

Several diseases and risk factors have been associated with pancreatitis. Dietary indiscretion is considered to be an important risk factor for pancreatitis in dogs. Also, severe hypertriglyceridemia (statistically significant increase in risk for serum triglyceride concentrations > 850 mg/dL) is considered a risk factor for pancreatitis. Pancreatitis is especially common in the Miniature Schnauzer and recently 3 different mutations have been identified in the SPINK-1 gene of affected dogs. This gene has also been associated with hereditary pancreatitis in humans. Traumatic pancreatitis (due to road traffic accidents in both dogs and cats or falling from heights in cats) has been reported. Surgical trauma can cause pancreatitis, but many human patients that undergo surgery of organs distant from the pancreas have also been shown to be at an increased risk for pancreatitis suggesting that hypoperfusion of the exocrine pancreas during anesthesia may be of bigger concern than surgical handling of the organ itself. Infectious agents have been shown to cause feline pancreatitis, with the strongest causal relationship for *Toxoplasma gondii*, and rare cases of *Amphimerus pseudofelineus* infestation in cats. *Babesia canis* has been reported to be associated with pancreatitis in dogs. Weaker evidence has been presented for feline panleukopenia virus infections in kittens and infections with feline herpesvirus I and feline infectious peritonitis virus. Two cases of feline pancreatitis after topical use of fenthion, an organophosphate cholinesterase inhibitor, have been reported. Many other pharmaceutical compounds have been implicated in causing pancreatitis in humans and dogs, but no cases have been reported in the cat. Hypercalcemia or calcium infusions can also be

associated with pancreatitis. Chronic hepatitis in dogs and cholangitis in cats may coexist in patients with pancreatitis, but there is no evidence that they play a causative role.

A serum chemistry profile should be performed to rule out hypertriglyceridemia or hypercalcemia. Exposure to unnecessary drugs, especially those implicated in causing pancreatitis in dogs, cats, or other species, should be avoided. Thus, a careful, drug history should be taken and the clinician should carefully determine whether treatment is still needed. For example, a patient that is treated with an anticonvulsant medication may need to be maintained on some anticonvulsant therapy, but, if being treated with potassium bromide and/or phenobarbital, the patient should be switched to another anticonvulsant medication.

Supportive Care

Aggressive fluid therapy is the mainstay of supportive therapy for dogs and cats with severe forms of pancreatitis. Fluid, electrolyte, and acid-base imbalances need to be assessed, and corrected as early as possible. This is especially important since systemic complications are associated with a worse outcome and many of the systemic complications, once established, are difficult to treat. Recent studies in humans have shown that minimal differences in blood urea nitrogen concentrations at time of admission to the hospital and also minimal changes of BUN during the first 24 to 48 hours after admission to the hospital can have a dramatic impact on the outcome in humans with acute pancreatitis.

Traditionally, dogs and cats with pancreatitis have been held off food, but over the last 10 years this practice has been questioned based on experiences in human patients with pancreatitis. There is good evidence in humans with severe forms of pancreatitis that alimentation is crucial to counterbalance the catabolic effects of pancreatitis. Also, it has been shown in several studies that enteral nutrition is superior for the nutritional management of human pancreatitis patients. A recent study has made similar observations in dogs. While there was no difference in mortality between dogs fed by esophagostomy tube or total parenteral nutrition, dogs fed by esophagostomy tube improved significantly faster than dogs fed parenterally. Also, studies in humans have shown that alimentation that enters the digestive tract before the duodenal papilla is not associated with a worse outcome when compared to patients fed by a jejunostomy tube. In fact, feeding patients through nasogastric tubes has been shown to be quite effective in humans with pancreatitis. Thus, in general dogs and cats with pancreatitis should be fed whenever possible. An ultra low-fat diet should be chosen in dogs and a moderately fat-restricted diet in cats. If patients are not interested in food feeding by gastrostomy, esophagostomy, or nasogastric tube should be attempted. If the patient vomits relentlessly a jejunostomy tube should be placed or the patient should be fed by partial or total parenteral nutrition.

Analgesia

Abdominal pain is the key clinical sign in human patients with pancreatitis and is recognized in excess of 90% of all pancreatitis patients. Abdominal pain is much more commonly recognized in dogs than in cats with pancreatitis, but even in dogs the reported rate of abdominal pain is only approximately 58% and is even lower in cats. It is unlikely that abdominal pain occurs less frequently in dogs and cats than in humans and it is much more likely that abdominal pain remains unidentified in veterinary species. Thus, the presence of abdominal pain should be assumed and analgesic drugs are indicated in all small animal patients with pancreatitis. Meperidine, butorphanol tartrate, morphine, fentanyl, or combinations of multiple analgesic drugs can be used in hospitalized patients. Outpatients can be treated with oral butorphanol, tramadol, or a fentanyl patch.

Antiemetics

Until recently, the choices for antiemetic agents for use in dogs and cats with pancreatitis was limited. Metoclopramide, a dopamine inhibitor, was most widely used. However, its effect on splanchnic perfusion remains in question and the author does not like to use metoclopramide in dogs or cats with pancreatitis. Fortunately, several other antiemetic agents have become available over the last few years.

Most recently, a new drug, maropitant, an NK₁ antagonist has become widely available for use in dogs and cats. Maropitant is a highly efficacious antiemetic agent through both peripherally and centrally-mediated mechanisms and can be used both parenterally in patients that are actively vomiting and orally in patients that appear mostly nauseous.

Dolasetron and ondansetron are 5HT₃ antagonists and are also very effective antiemetic agents in both dogs and cats. The injectable formulation of dolasetron can be used for intravenous, subcutaneous, or oral administration and is being used at 0.3-0.6 mg/kg q 12-24 hr in both dogs and cats. Since maropitant and 5HT₃ antagonists work through different mechanisms both drugs can be combined.

Fresh Frozen Plasma

Studies in dogs suggest that when α_2 -macroglobulin, one of the scavenger proteins for activated proteases in serum, is depleted death ensues rapidly. Fresh frozen plasma and fresh whole blood not only contain α_2 -macroglobulin, but also albumin, which has many beneficial effects in patients with severe pancreatitis. Plasma also contains both anticoagulant and coagulation factors. In clinical trials in human patients with acute pancreatitis there was no benefit of plasma administration. Also, in dogs the benefit of plasma has not been demonstrated. However, anecdotally, fresh frozen plasma is believed to be useful in dogs with severe forms of pancreatitis.

Antibiotics

In contrast to humans, infectious complications of pancreatitis are rare in dogs and cats with pancreatitis. Also, even though such complications occur frequently in human pancreatitis patients and are estimated to be responsible for approximately 25-50% of all deaths associated with acute pancreatitis, a clear advantage of antibiotic use has not been demonstrated to date. Therefore, the use of antibiotic agents should be limited to those cases when an infectious complication can be identified or is strongly suspected.

Antiinflammatory Agents

Glucocorticoids have not shown any benefit in human patients with acute pancreatitis that do not have autoimmune pancreatitis and their use should be limited to canine and feline patients with cardiovascular shock. Nonsteroidal antiinflammatory agents all have been implicated in potentially causing pancreatitis and also did not show any benefit in human studies.

Other Therapeutic Strategies

Many other therapeutic strategies, such as the administration of trypsin-inhibitors (e.g. trasylol), platelet activating factor inhibitors (PAFANTs), dopamine, antacids, antisecretory agents (i.e., anticholinergics, calcitonin, glucagon, somatostatin), or selenium, and peritoneal lavage all have been evaluated in human patients with pancreatitis. With the exception of PAFANTs and selenium, none of these have shown any beneficial effect at this point. The efficacy of selenium, which has also been shown to decrease mortality in dogs in a single uncontrolled study, needs to be further evaluated before its use can be recommended. Also, dopamine has been shown to be useful in preventing progression of pancreatitis when administered within 12 hours of initiating pancreatitis in cats. While this time-limit would preclude dopamine to be effective in routine therapy of pancreatitis, patients with pancreatitis that have to undergo anesthesia may benefit from treatment with dopamine during the procedure.

Mild Chronic Pancreatitis

It should be noted that many small animal patients, both canine and feline, have mild forms of chronic pancreatitis. Often times these patients have concurrent conditions, most notably IBD. Very little is known about appropriate therapy for these patients and management is often limited to evaluation and treatment of the concurrent condition, and careful monitoring of the pancreatitis.

Serum calcium and triglyceride concentrations should always be evaluated in these patients in order to identify any risk factors that can potentially be addressed therapeutically.

Also, the use of low fat diets is recommended in these patients. This is especially important in dogs where an ultra-low-fat diet should be chosen.

Over the last two decades a new form of pancreatitis, autoimmune pancreatitis has been described in humans. Autoimmune pancreatitis is now more commonly recognized in humans and is characterized by a lymphocytic-plasmacytic infiltration of the pancreas. Human patients with autoimmune pancreatitis respond favorably to the administration of corticosteroids. Recently, several clinicians have started to cautiously treat canine and feline patients with chronic pancreatitis with corticosteroids and have found this treatment strategy to be beneficial in a portion of cases. Also, successful treatment of a canine patient with chronic pancreatitis with cyclosporine has been reported in the literature. However, further studies are needed before these treatment strategies can be recommended for more routine use in dogs and cats.

Regardless of the management, progress of the disease should always be monitored. Just as in human patients with chronic pancreatitis, canine and feline patients with chronic pancreatitis are at risk for developing episodes of severe pancreatitis at any time or exocrine pancreatic insufficiency and Diabetes mellitus later in life.

Prognosis

The prognosis for dogs and cats with pancreatitis is directly related to disease severity, extent of pancreatic necrosis, occurrence of systemic and pancreatic complications, duration of the condition, and the presence of concurrent disease. Several prognostic systems have been developed to predict the outcome of pancreatitis in human patients early after admission to the hospital. All of these systems are aimed to identify high-risk patients early on and to be able to aggressively treat these patients. Several of these systems have been adapted for use in small animals and evaluated in dogs or cats. Unfortunately, none of these prognostic systems have been proven useful in a clinical setting in small animals. However, some of them may be useful for use in clinical studies.