G – Gastroenterology

UPDATE ON PANCREATITIS IN DOGS

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From a clinical perspective pancreatitis can be broadly categorized as acute, recurrent acute or chronic. It can be further classified according to its effect on the patient as mild or severe, non-fatal or fatal, and also by the presence of sequela such as abscess formation. Histologically, acute pancreatitis is characterized by findings that range from pancreatic edema to necrosis, variable infiltrates of mononuclear and polymorphonuclear cells, and local changes such as peri-pancreatic fat necrosis and thrombosis. Acute pancreatitis may resolve or persist and can be complicated by secondary infection and pseudocyst or abscess formation. It is tempting to equate mild acute pancreatitis with pancreatic edema, and severe or fatal pancreatitis with pancreatic necrosis, but this relationship has not been critically examined in patients with naturally occurring pancreatitis. Chronic pancreatitis is characterized by fibrosis and low grade mononuclear inflammation and may be a sequela of recurrent acute pancreatitis or a subclinical disease process that may present as diabetes mellitus or exocrine pancreatic insufficiency (EPI).

Etiology and Pathogenenesis

The etiology and pathogenesis of spontaneous pancreatitis is poorly understood. The major factors which have been implicated (by association) as causes of acute pancreatitis in the dog and the experimental evidence to support their involvement are summarized as follows:

Potential aetiology	Clinical	Experimental
Hyperlipidemia	Lipemia Abnormal lipid profiles Lipodystrophy	High fat diet IV Free Fatty Acids
Diet	Diet indiscretion Obesity	Fat >>protein diet Ethionine supplementation
Bile reflux	Concomitant biliary disease (?cats)	Bile infusion
Hypercalcemia	Ca infusion ? Hyperparathyroidism	Ca infusion
Corticosteroids	? Hyperadrenocorticism ? + Disc surgery?	Increased CCK sensitivity Pancreatic duct hyperplasia
Drug/toxin related	Organophosphates L-asparaginase Azathioprine, sulphonamides Potassium bromide and Phenobarbital Zinc	Organophosphates
Ischemia/reperfusion	Post-GDV	Ex-vivo pancreas
Hereditary predisposition	? Miniature Schnauzer, Min. poodle, Terriers, non-sporting dogs	
Endocrinopathies	? Hypothyroidism, diabetes mellitus	

Irrespective of the initiating cause pancreatitis is generally believed to occur when digestive enzymes are activated prematurely within the pancreas. In the normal pancreas safeguards are present to ensure that harmful pancreatic enzymes are not activated until they reach the intestinal lumen. Enzymes are stored in zymogen granules within the acinar cell in the presence of pancreatic secretory trypsin inhibitor (PSTI) and are released at the apical surface directly into the duct system. They are only activated in the intestine, by trypsin, following the cleavage of trypsin activation peptide (TAP) from trypsinogen by enterokinase. Potential sites for the intrapancreatic activation of pancreatic enzymes can therefore logically be divided into interstitial (within the duct system and interstitium) and intracellular (within the acinar cell). Experimental studies suggest that bile and enteric reflux, and intravenous free fatty acid (FFA) infusion initiate pancreatitis by an interstitial mechanism whereas hyperstimulation with caerulein or organophosphates, pancreatic duct obstruction and choline deficient ethionine supplemented diet (CDE diet) result in intracellular activation. Experimental pancreatic hyperstimulation with cholecystokinin (CCK: or its analogue cerulein), dietary supplementation with ethionine, and obstruction of the pancreatic duct lead to the formation of large intracellular vacuoles in acinar cells. Vacuole formation is thought to be a consequence of the uncoupling of exocytosis of zymogens and abnormal intracellular trafficking of digestive and lysosomal enzymes. These subcellular alterations are considered to precipitate the intracellular activation of digestive enzymes. Pancreatic hyperstimulation may be of direct relevance to naturally occurring pancreatitis in dogs. CCK is normally released by cells in the duodenum in response to intraluminal fat and amino acids and coordinates and stimulates pancreatic secretion and gallbladder contraction during digestion. It is possible that high fat diets exert their effects via the excessive release of cholecystokinin and that hypercalcemia, organophosphates and high levels of circulating glucocorticoids also facilitate (potentially by changing pancreatic sensitivity to hyperstimulation), or cause pancreatic hyperstimulation; however, this is not proven. Edematous pancreatitis induced by CCK hyperstimulation in dogs is characterized by a rapid but self-limiting, burst of trypsinogen activation suggesting that the pancreas has a feedback mechanism to limiting trypsinogen synthesis and activation (see nutritional management). This concept of pancreatic down regulation is important when considering nutritional intervention in acute pancreatitis.

Often pancreatic inflammation is a self-limiting process, but in some animals reduced pancreatic blood flow and leukocyte and platelet migration into the inflamed pancreas may cause progression to pancreatic necrosis. Secondary infection may arise by bacterial translocation from the intestine. Release of active pancreatic enzymes and inflammatory mediators from the inflamed pancreas, such as Tumor Necrosis Factor-α (TNF-α) interleukin-1 (IL-1) and phospholipid platelet activating factor (PAF), amplifies the severity of pancreatic inflammation, and adversely affects the function of many organs (systemic inflammatory response), and cause derangement in fluid, electrolyte and acid-base balance. It is the development of multisystemic abnormalities that separates mild from severe, potentially fatal pancreatitis.

Diagnosis and Treatment

There is currently no single specific test for pancreatitis in dogs and diagnosis is based on a combination of compatible clinical, clinicopathological and imaging findings. Surgical biopsy may be required to confirm a diagnosis, and to distinguish inflammation from neoplasia.

Clinical findings

Signalment and History: Midlle aged to old dogs (>5yrs years old) who are overweight appear at higher risk. Miniature Schnauzers, Yorkshire and Silky Terriers, non-sporting breeds and perhaps miniature poodles may be at increased risk of developing pancreatitis. There is no clear sex predisposition. Endocrinopathies such as hypothyroidism, diabetes mellitus and hyperadrenocorticism may also be risk factors. Thirteen percent of 221 dogs with diabetes mellitus had histological evidence of acute pancreatitis. Hyperlipidemia is another potential risk factor.

The history may reveal a recent episode of dietary indiscretion, toxin ingestion or drug administration. Common clinical signs include lethargy, anorexia, hunched stance, vomiting (± blood), diarrhea (± blood), increased respiratory rate and enlarged abdomen. Some dogs have a history of icterus preceded by vomiting. Polyuria and polydipsia may be present in dogs with diabetes mellitus and pancreatitis.

Physical Examination: hysical findings in dogs with acute pancreatitis are variable and range from depression, to mild dehydration with signs of abdominal pain, to acute abdominal crisis with shock (tachycardia, prolonged capillary refill time, tacky mucous membranes, hypothermia), petechiation, icterus and ascites. An abdominal mass is palpated in some dogs.

Diagnostic approach and differential diagnosis

The differential diagnosis of acute pancreatitis in dogs is usually centered round the problems of vomiting and abdominal pain.

In vomiting dogs the initial approach is to distinguish self-limiting from more severe causes of vomiting on the basis of physical findings and a minimum database (e.g. Packed cell volume, total protein, azostick, urinalysis, plasma concentrations of sodium and potassium). Where vomiting is associated with systemic signs of illness, or is persistent, the clinician has to differentiate metabolic, polysystemic infectious, toxic and neurologic causes from intra-abdominal causes. This is usually achieved on the basis of combined historical and clinical findings coupled with a minimum database and the evaluation of hematology and serum chemistry profile, urinalysis and abdominal radiography. Measurement of serum amylase or lipase is often reported on routine serum chemistry profile. Additional procedures such as ultrasonography, abdominal paracentesis or assay of trypsin-like immunoreactivity, TAP or immunoreactive canine pancreatic lipase are usually performed on the basis of these initial test results and help to distinguish pancreatitis from other intra-abdominal causes of vomiting.

Where abdominal pain is the major finding localizing abnormalities such as abdominal distension are rapidly pursued with radiography, ultrasonography and paracentesis while providing supportive treatment on the basis of physical findings and a minimum data base and awaiting the results of hematology, serum chemistry profile and urinalysis. Abdominal pain can arise from any intra-abdominal structure. Musculoskeletal disorders such as discospondylitis and prolapsed discs can be hard to distinguish from abdominal causes of pain.

Diarrhea, which was bloody in some cases, is reported as a more frequent sign than vomiting in dogs with experimental acute pancreatitis. Acute pancreatitis and its complications (infection, pseudocyst or abscess formation) should also be considered in the differential diagnosis of icterus and pyrexia. Some dogs with pancreatitis exhibit few localizing clinical signs. Diagnosis in these animals requires a high index of suspicion and use of versatile diagnostic tests such as ultrasonography.

Clinicopathological findings

Hematology: Extremely variable, ranging from mild neutrophilia and slightly increased haematocrit, through marked leukocytosis with or without a left shift, to thrombocytopenia, anemia and neutropenia with a degenerative left shift. Thrombocytopenia in dogs with pancreatitis is often associated with DIC and additional tests of hemostasis (OSPT, APTT, FDP or D-dimer, fibrinogen, antithrombin III) are performed to determine if DIC or other coagulopathies are present.

Serum biochemistry: Serum biochemical abnormalities include azotemia (pre-renal and renal), increased liver enzymes (ALT, AST, AP), hyperbilirubinemia, lipemia, hyperglycemia, hypoproteinemia, hypocalcemia, metabolic acidosis and variable abnormalities (usually decreased) in sodium, potassium and chloride.

Urinalysis: Enables azotemia to be characterized as renal or pre-renal. Proteinuria occurs in some dogs with acute pancreatitis and is usually transient. The presence of glucose or ketonuria should prompt consideration of diabetes mellitus.

Pancreas specific enzymes: Classically, elevations in serum amylase and lipase activity have been used as indicators of pancreatic inflammation in dogs. However these enzymes can be increased in non-pancreatic disease, and dogs with confirmed pancreatitis may also have normal amylase and lipase activity. For example, in dogs with histologically confirmed pancreatitis, lipase is normal in 28 to 61% of dogs, and amylase is normal in 31 to 47% of dogs. These limitations have led to the development of assays for enzymes or markers considered pancreatic in origin such as trypsin-like immunoreactivity (TLI), trypsinogen activation peptide (TAP), and pancreatic lipase immunoreactivity (PLI). Experimental studies have documented high concentrations of TLI, TAP and PLI in dogs with experimental acute pancreatitis. The utility of TLI, TAP and PLI for the diagnosis spontaneous pancreatitis in dogs has not been thoroughly evaluated. Normal, subnormal and increased concentrations of TLI have been observed in dogs with confirmed pancreatitis. Elevations of TAP have been observed in the serum and urine (TAP: creatinine) of dogs with severe pancreatitis, and TAP may be a better prognostic than a diagnostic indicator of pancreatic inflammation. Experience with PLI is even more limited, though it appears more promising than TLI, as serum elevations of PLI seem more substantial and prolonged than TLI. Diseases such as renal disease can increase TLI, TAP and PLI.

Radiography: Radiographic findings in dogs with acute pancreatitis are generally non-specific and include loss of serosal detail, increased opacity in the right cranial quadrant of the abdomen, displacement of the duodenum ventrally and/or to the right, dilated hypomotile duodenum

and caudal displacement of the transverse large intestine. Punctate calcification may occasionally be identified in dogs with long-standing pancreatitis; it indicates saponification of mesenteric fat around the pancreas.

Thoracic radiographs may enable the detection of pleural fluid, edema or pneumonia which has been associated with pancreatitis in dogs and cats.

Ultrasonography: Ultrasonographic findings include enlarged, hypoechoic pancreas, cavitary lesions such as abscess or pseudocyst, dilated pancreatic duct, swollen hypomotile duodenum, biliary dilatation and peritoneal fluid. One study of dogs with fatal acute pancreatitis indicated that ultrasound supported a diagnosis of pancreatitis in 23/34 dogs. Disorders other than pancreatitis e.g. pancreatic neoplasia, pancreatic edema (associated with hypoproteinemia or portal hypertension) and enlarged peri-pancreatic structures, can have identical ultrasonographic appearance to pancreatitis. Fine needle aspirates of cavitary lesions may be useful to distinguish abscess from pseudocyst.

Abdominal paracentesis: Examination of peritoneal fluid may aid the detection of various causes of acute abdominal signs such as pancreatitis, gastrointestinal perforation or ruptured bile duct.

Prognostic indicators

Stratifying the severity of pancreatitis is useful when deciding how aggressive to be with medical and nutritional support, and in offering a prognosis. Severe pancreatitis requires aggressive support and carries a guarded prognosis, whereas mild pancreatitis often responds to short term symptomatic therapy and has agood prognosis. Clinical and clinicopathological criteria can be used to predict the severity of acute pancreatitis. The presence of shock or abnormalities such as oliguria, azotaemia, icterus, markedly elevated transaminases, hypocalcaemia, hypoglycaemia, hypoproteinaemia, acidosis, leukocytosis, falling haematocrit, thrombocytopaenia and DIC should be considered likely indicators of severe pancreatitis in the dog and cat.

The measurement of components of the systemic inflammatory response such as TNF-α and C-reactive protein, and IL-6 may also yield information about the severity of pancreatitis that in the future might lead to the administration of specific antagonists of this response.

Potentially useful prognostic indicators that are pancreas specific include assay of trypsinogen activation peptide (TAP), trypsin complexed with inhibitors, and phospholipase A_2. Trypsinogen activation peptide has been shown to accurately predict severity in humans with pancreatitis. This peptide is released when trypsinogen, a pancreas-specific enzyme, is converted to its active form and rapidly accumulates in the urine and plasma of dogs with experimental acute pancreatitis. In spontaneous pancreatitis. Plasma and urinary TAP concentrations, as well as urinary TAP to creatinine ratio, were all increased in dogs that died with necrotising pancreatitis. Values were not increased in mild, interstitial pancreatitis. Increased plasma TAP concentrations were also present in dogs with severe renal disease. Phospholipase A_2 is elevated in dogs with severe pancreatitis.

Morphologic assesment of severity is accomplished in humans by use of contrast enhanced computed tomography (CE-CT). Where lack of pancreatic perfusion is encountered i.e. necrosis, fine needle aspiration is used to distinguish infected from sterile necrosis. Substantially reduced mortality has been achieved by the detection and surgical treatment of people with infected necrosis. CE-CT has recently been reported in 2 dogs with pancreatitis. Contrast-enhanced computed tomography (CT) findings in both dogs were compatible with pancreatic necrosis. In one dog managed medically for 11 days the follow-up CT scan disclosed decreased pancreatic size and increased contrast enhancement compatible with partial resolution of pancreatitis.

Treatment

Medical treatment is based on maintaining or restoring adequate tissue perfusion, limiting bacterial translocation and inhibiting inflammatory mediators and pancreatic enzymes; surgical treatment consists principally of restoring biliary outflow, removing infected necrotic pancreatic tissue, or coping with sequela such as pseudocysts. No studies have critically evaluated treatment modalities in dogs or cats with naturally occurring pancreatitis.

Initial management: The initial medical management of dogs with acute pancreatitis is based on the presenting clinical findings and the results of an initial database. Dehydration or hypovolemia are supported with intravenous fluid therapy e.g. LRS or 0.9% NaCl. Potassium and glucose should be supplemented where necessary. The type of fluid is tailored on the basis of electrolyte and pH measurements to restore normal electrolytes and acid-base balance. E.g. vomiting and mild dehydration are usually given crystalloids such as lactated Ringer's solution at a rate that will provide maintenance and replace both deficits and ongoing losses over a 24h period. Dogs with signs of shock require more aggressive support. The volume deficit can be replaced with crystalloids at an initial rate

of of 60-90ml/kg/h, then tailored to maintain tissue perfusion and hydration. Plasma (20ml/kg i.v.) or colloids (eg. Hetastarch, Dextran 70: 10-20 ml/kg/day i.v.). may be indicated in the presence of hypoproteinemia or shock. Colloids such as dextran 70 and hetastarch may also have antithrombotic effects that help maintain the microcirculation.

Insulin therapy is initiated in diabetic patients.

Where vomiting is a problem, antiemetics (metoclopramide or chlorpromazine) and antacids (e.g. famotidine) can be prescribed.

Prophylactic broad-spectrum antibiotics (e.g. amoxicillin ± enrofloxacin depending on severity) may be warranted in patients with shock, fever, diabetes mellitus or evidence of breakdowm of the GI barrier.

Analgesia can be provided using buprenorphine (0.005-0.01mg/kg SC q6-12hrs) or oxymorphone (0.1-0.2 mg/kg dogs IM, SC Q 1-3hrs). It may be necessary to administer low dose sedation with acepromazine (0.01mg/kg IM) to patients who become dysphoric after opioids. Buprenorphine is a partial agonist and may antagonise the administarion of more potent analgesics in animals with severe pain. A transdermal fentanyl patch (Duragesic, Janssen) applied to a clipped clean area of skin provides a longer duration of analgesia in dogs (10-20kg, 50µg/hr patch q 72hrs). Adequate fentanyl levels are not attained for between 6-48 hrs after application, so another analgesic should be administered in the short term. The author avoids using non-steroidal analgesics in patients with acute pancreatitis due to concerns for GI ulceration, renal failure and potentially hepatotoxicity.

Specific therapy: Many dogs with acute pancreatitis respond to fluid therapy and nothing by mouth for 48h. Hence, specific therapy is usually reserved for dogs that do not respond to fluid therapy or those with signs of multiorgan system involvement or DIC.

The specific treatment of pancreatitis has evolved along two paths, 1. Stopping further pancreatitis from occurring, and 2. Limiting the local and systemic consequences of pancreatitis.

Therapies aimed at inhibiting pancreatic secretion (e.g. glucagon, somatostatin) or the intracellular activation of proteases (e.g. gabexate mesilate) which have been of benefit in ameliorating the severity of experimental pancreatitis have shown little benefit in the treatment of patients with spontaneous pancreatitis, unless they are given before pancreatitis is induced (e.g. before ERCP). The lack of success with inhibiting the progression of spontaneous pancreatitis has led to increased emphasis on damage limitation; ameliorating the effects of inflammatory mediators or pancreatic enzymes on the patient and maintaining pancreatic perfusion.

Where a coagulopathy e.g. DIC, or hypoproteinemia are present, or the patient with pancreatitis is deteriorating, fresh frozen plasma (10-20ml/kg) may be beneficial in alleviating the coagulopathy, hypoproteinemia and restoring a more normal protease-antiprotease balance. Heparin (75-150IU/kg TID) may be potentially useful in ameliorating DIC, promoting adequate microcirculation in the pancreas and clearing lipemic serum. In experimental pancreatitis isovolemic rehydration with dextran has also been shown to promote pancreatic microcirculation in dogs. Therapy to abrogate the systemic inflammatory response with antagonists of PAF (e.g lexipafant), IL-1 and TNF-α holds promise for the future.

Oral pancreatic enzyme extracts have been reported to reduce pain in humans with chronic pancreatitis, though this is controversial. They are less likely to be effective in dogs as they do not appear to have a protease mediated negative feedback system.

Nutritional support

The intial aim is to identify and prevent, or treat, nutritional factors associated with pancreatitis:

Where obesity, hyperlipidemia and dietary indiscretion are reported it would seem prudent to address their underlying cause in an attempt to prevent future bouts of pancreatitis.

Precise recommendations for the dietary management of acute pancreatitis in dogs are hampered by the absence of controlled studies, and are often based on empirical wisdom and a best guess least harm approach.

The dilemma between feeding and stimulating the pancreas: Pancreatic secretion in healthy dogs occurs in response to ingested nutrients, particularly fats and amino acids delivered into the duodenum. Pancreatic secretion in response to food is mediated by hormones such as CCK and secretin, parasympathetic stimulation, and duodenopancreatic nerves. Restricting oral intake, or providing nutrients intravenously, does not stimulate pancreatic secretion. Thus it has been largely accepted that to provide "pancreatic rest" oral intake should be withheld until clinical signs resolve, or when signs persist for 72-96hrs that parenteral nutrition is introduced. This dogma is still prevalent in veterinary and human medicine.

However, there is growing evidence in people, and animals, that enteral nutrition is superior to parenteral nutrition in the treatment of acute pancreatitis. Jejunal feeding (distal to the site of pancreatic stimulation) does not exacerbate acute pancreatitis in people or experimental animals. People with acute pancreatitis fed via jejunostomy tubes (these can be oral transpyloric tubes), have

lower morbidity, shorter hospital stays and less cost than those treated with TPN. As it is now feasible to place jejunostomy tubes non-surgically in dogs, through the nose, esophagus or stomach, clinical application of this feeding strategy is not restricted by a surgical procedure. However, it remains open whether dogs with acute pancreatitis really require jejunal delivery of nutrients. There is evidence that the pancreas of dogs with acute experimental pancreatitis, and people with naturally occurring severe pancreatitis, is not as amenable to stimulation as the normal pancreas. Dogs recovering from naturally occurring pancreatitis have also been shown to have subnormal circulating TLI concentrations suggesting that pancreatic enzyme synthesis is downregulated. In addition, it appears that the major benefits of enteral support in acute pancreatitis in people and experimental dogs are due to reductions in the systemic inflammatory response and the translocation of enteric bacteria rather than a reduction in pancreatic stimulation.

Intestinal permeability and morbidity in dogs with parvovirus are positively impacted by feeding a liquid diet (41%protein, 18% fat, 3%CF) through a nasoesophageal tube supporting the concept that enteral feeding in general, rather than jejunal delivery, is the reason for the beneficial effects of EN, though this needs to be critically evaluated.

Resistance to enteral feeding of dogs with pancreatitis is anticipated, despite evidence of a beneficial effect. One common argument used to promote PN in dogs with pancreatitis is that they vomit too frequently to be fed enterally. However, recent studies in dogs with parvovirus should also help to allay this fear as these dogs tolerated nosesophageal feeding despite severe vomiting and diarrhea, with enterally fed dogs showing faster recovery rates, greater body weight gains and lower intestinal permeability than dogs that were held NPO.

This is not meant to imply that parenteral nutrition should be discarded, but it's use be restricted to patients that really need it, for instance those in whom caloric intake is severely and persistently impaired by persistent vomiting. When parenteral nutrition is indicated a choice has to be made between total and partial parenteral nutrition. Partial parenteral nutrition (PPN) is a more practical and manageable procedure than TPN in most settings and has been shown to be a safe and effective way of providing nutrition to dogs with pancreatitis and gastrointestinal disease. Interestingly dogs that received a combination of enteral and PPN survived more often than those receiving PPN exclusively.

What diet should be fed to dogs recovering from pancreatitis?

Free choice feeding is usually resumed when the appetite returns and vomiting and abdominal pain have subsided. Fat is frequently regarded as the major stimulus for CCK release and pancreatic secretion. However amino acids are also potent stimulators of pancreatic enzyme secretion and they are not restricted. Perhaps a more rational basis for fat restriction (?<15%DM) is the presence of hyperlipidemia. Avoidance of other dietary factors associated with pancreatitis, such as high fat diets, and high fat protein restricted diets designed for struvite dissolution, that have a nutrient profile similar to diest known to induce pancreatitis in dogs, is also reasonable. Obesity, a risk factor for pancreatitis, should be controlled with a balanced nutritional approach. Elemental diets cause a similar degree of pancreatic stimulation as normal diets.

Patient Monitoring

Minimal monitoring for stable patients includes regular assessment of vital signs and fluid and electrolyte balance. In those with systemic abnormalities, monitoring should be more aggressive and may include vital signs, weight, haematocrit, total protein, fluid intake and output, blood pressure (central venous and arterial), electrolytes and glucose, acid-base status, platelets and coagulation status. Monitoring pancreas specific markers and clinical signs on a sequential basis should help to support resolution or progression of pancreatic inflammation.

Ultrasound-guided fine needle aspiration of the pancreas may enable infected pancreatic necrosis to be detected. Ultrasonography may also enable detection of delayed consequences of acute pancreatitis such as pancreatic abscessation, pseudocyst formation and biliary obstruction.

Surgical intervention

Surgery is potentially indicated to remove devititalized tissue in patients with infected pancreatic necrosis and to investigate and relieve persistent biliary obstruction. The removal or drainage of abscesses is another indication for surgery. Resection or surgical drainage of pancreatic pseudocysts is not always necessary as these can resolve spontaneously or following percutaneous drainage. Pancreatitis that is recurrent or is unresponsive to treatment may also require surgery to confirm a diagnosis and to exclude pancreatic cancer.

Prognosis

The prognosis for dogs with mild acute pancreatitis is good. Severe or recurrent pancreatitis is associated with a guarded prognosis.

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