Management of Acute Pancreatitis

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Introduction

Acute pancreatitis is a potentially life-threatening disease characterized by inflammation of the pancreas, uncontrolled activation of pancreatic enzymes, cellular damage, and with systemic dissemination of pancreatic enzymes and mediators of tissue inflammation. Pancreatitis is associated with the development of sepsis and multiple organ dysfunction syndromes, in both humans and animals. Pancreatitis is a known predisposing condition in the development of acute renal failure, acute respiratory distress syndrome, disseminated intravascular coagulopathy, cardiac dysfunction, and intestinal dysfunction.

The diagnosis and management of pancreatitis in small animal patients presents the clinician with several challenges including how to control pancreatic inflammation, and support the patient during therapy. The aim of this presentation is to present a brief overview of current thoughts and treatments, and to relate this to the practicality of managing the patient with acute pancreatitis.

Structure and Innervation of the Pancreas

The structure of the exocrine pancreas resembles that of the salivary glands. The pancreas contains microscopic, blind-ending tubules surrounded by polygonal acinar cells, and are organized into lobules (acini). The primary function of these lobules is to secrete the enzyme component of pancreatic juice. Granules containing the digestive enzyme component of pancreatic juice (zymogen granules) are formed within the cells and are discharged by exocytosis from the apexes of the cells into the lumens of the pancreatic ducts. The small duct radicles coalesce into a single duct that usually joins the common bile duct to form the ampulla of the bile duct. The ampulla opens through the duodenal papilla, and its orifice is encircled by the sphincter of Oddi. In some individuals, there is an accessory pancreatic duct.
The aqueous component of pancreatic juice is produced principally by the columnar epithelial cells that line the pancreatic ducts.
The pancreas is supplied by branches of the celiac and mesenteric arteries. The portal vein drains the pancreas. The pancreas is innervated by branches of the vagus nerve. Vagal fibers form synapses with cholinergic neurons that lie within the pancreas; these neurons innervate both acinar and islet cells. Postganglionic sympathetic nerves from the celiac and superior mesenteric plexuses innervate pancreatic blood vessels. Secretion of pancreatic juice is stimulated by parasympathetic activity, and inhibited by sympathetic activity.

Physiology of the Normal Pancreas

- Secretion of pancreatic juice is controlled partly by reflex, and partly by the gastrointestinal hormones secretin and cholesystokinin-pancreozymin (CCK-PZ), which are released from the duodenal mucosa. The average human secretes about 1500 mL of pancreatic juice per day.

- Pancreatic juice is alkaline, and has a high bicarbonate concentration, with concentrations ranging from 70-130 mEq/L.
- The pancreas secretes 19 enzymes which are secreted as inactive pro-enzymes contained in granules called zymogen granules, which are surrounded by lipoprotein membrane.
- Pancreatic enzymes are activated by the action of the intestinal enzyme enterokinase, which is secreted by the duodenal mucosa. Enterokinase secretion is stimulated by CCK-PZ; enterokinase converts trypsinogen to the active trypsin enzyme. Trypsin converts pro-enzymes into active enzymes. The pancreas contains a trypsin inhibitor to decrease pancreatic damage in the event of trypsin leaking into the pancreas.
- A protease inhibitor circulates in plasma in case of hematogenous spread of enzymes, called alpha$_1$ antitrypsin (α_1 antitrypsin). Alpha$_1$ antitrypsin binds hematogenous pancreatic enzymes, and transports them to circulating alpha-macroglobulins from where they are delivered to tissue macrophages.
- Vagal stimulation, and CCK-PZ cause release of an enzyme rich secretion; secretin release stimulates a low enzyme – high bicarbonate concentration secretion from the pancreas. Secretin also augments the sensitivity of pancreatic acinar cells to CCK-PZ.
- CCK-PZ and Acetylcholine effects are mediated by calcium release from intracellular binding sites.

Causes of Acute Pancreatitis

- High fat/protein diets stimulate release of CCK-PZ, gastrin, and secretin and result in increased synthesis of pancreatic enzymes.
- Diets with a high fat content (60% or greater) reduce resistance of acinar cell membranes to the lytic effects of trypsin.
- Abdominal trauma and thoracolumbar disease may decrease blood supply to the pancreas and alter nerve supply by decreasing parasympathetic tone, producing intestinal ileus and gastroparesis. Direct trauma to the pancreas or pancreatic ducts may also result in pancreatitis.
- Hypercalcemia may induce vasculitis within pancreatic microcirculation, causing plugging of pancreatic ducts due to cellular edema and vascular thrombus formation.
- Hyperlipidemia causes sludging of blood in the pancreatic microcirculation producing ischemia and cell damage.
- Drugs – high dose corticosteroids (under question), alcohol, azathiaprine, estrogens, tetracycline, furosemide, thiazide diuretics.
- Corticosteroids may inhibit clearance of alpha macroglobulin complexes by macrophages, and may sensitize pancreas to CCK-PZ stimulation, resulting in increased synthesis and release of enzyme-rich pancreatic secretions.
- Ischemia, and hypovolemia or shock syndromes may result in pancreatic hypoxia and pancreatic acinar damage.
- Infection – FIP, Toxoplasmosis, ascending bacterial infection from the gastrointestinal tract.
- Renal failure/uremia result in decreased gastrin clearance. Hyper-gastrinemia stimulates secretion of hydrochloric acid in the stomach, which is a stimulus for pancreatic secretion.

- Pancreatic duct obstruction by biliary calculi, neoplasia, or surgical manipulation.
- In chronic pancreatitis, there is evidence of immune-mediated antibody production to pancreatic tissue.

Risk Factors in Acute Pancreatitis

- Increasing age.
- Obesity.
- Neutering.

Pathogenesis of Acute Pancreatitis

The first step in the development of acute pancreatitis involves pancreatic acinar damage; the second involves activation of digestive enzymes within the gland, with resultant pancreatic auto-digestion.

Damage to acinar cells may be predisposed to by any of the factors mentioned above, including trauma, shock, and high fat diets, although much of the evidence supporting these causes remains speculative at present. Activation of complement by endotoxin, elevated plasmin found in ischaemic tissues, activated enzymes from pancreatic duct reflux, and infections all result in damage to pancreatic tissue.

In ischaemic disease, the enzyme xanthine dehydrogenase converts to xanthine oxidase under the influence of trypsin. During ischaemia, ATP breakdown produces hypoxanthine, which is converted to xanthine by xanthine oxidase, producing oxygen free radicals. Oxygen free radicals cause further acinar damage, and damage to zymogen granules, and activate compliment, which results in cell swelling, dissolution of zymogen granules, and the release of trypsinogen. Trypsinogen is converted to trypsin by lysosomal enzymes released from damaged lysosomes. Excessive trypsin levels rapidly saturate trypsin inhibitors in the pancreas and plasma. Pancreatic enzymes are probably not essential early in the pathogenesis, however, once enzyme activation has occurred, the normal defense mechanisms of the pancreas such as storage of pro-enzymes in zymogen granules, presence of antitrypsin etc. are overwhelmed.

Enzyme activation within the pancreas causes progressive damage to the gland, probably through the following mechanisms:

- Trypsin – causes proteolysis, and further activation of pro-enzymes. Trypsin may also activate complement cascade, leading to an influx of inflammatory cells, and production of multiple cytokines and further production of oxygen free radicals. Trypsin activity leads to activation of the coagulation and fibrinolytic pathways, resulting in microvascular thromboses and disseminated intravascular coagulopathy (DIC).
- Kallikrein – catalyses conversion of plasma kininogens to kinins, which cause regional and systemic vasodilatation.
- Elastase – damages the elastic lamina of blood vessels causing hemorrhage and necrosis
- Phospholipase A_2, and lipase oxidize cell membranes, and contribute to pancreatic hemorrhage and necrosis; and degrade lung surfactant, contributing to acute respiratory distress syndrome and low pressure pulmonary edema.
- Lysosomal enzyme release.
- Amylase – not important in the pathophysiology of pancreatitis.

Grossly, the pancreas appears swollen, edematous, and soft. Fibrinous adhesions are common. Occasionally, fluid collections around the pancreas will contain fat droplets. The pancreas may be liquified in severely affected areas, may be abscessed, or contain pseudocysts.

Clinical Signs of Acute Pancreatitis

The clinical signs of pancreatitis are variable, with some symptoms ranging in severity from mild to marked, and include the following:

- Vomiting (most common) – due to gastroparesis, ileus, pain and abdominal distension.
- Anorexia – due to gastroparesis, ileus, pain and abdominal distension.
- Diarrhoea.
- Depression.
- Cranial abdominal pain (not always).
- Abdominal distension.
- Dehydration.
- Prayer stance.
- Fever may be present due to the systemic release of mediators of inflammation.
- Jaundice may occur with concurrent obstruction of common bile duct, neoplasia, and swelling or obstruction of the sphincter of Oddi.
- Respiratory distress – occurs due to pain, and the disruption of the capillary/alveolar membrane by circulating phospholipase-A_2, resulting in neutrophil migration and oxygen free radical release. This results in a high protein edema and ARDS.
- Cardiac arrhythmias.
- Coagulopathy – release of proteases causes activation of the clotting cascades, resulting in thrombosis and DIC.
- Sepsis, shock.
- Presence of pleural fluid.
- Neurologic symptoms result from demyelination and a syndrome of pancreatic encephalopathy.

Diagnosis of Acute Pancreatitis

No single test can reliably indicate pancreatitis. To definitively diagnose pancreatitis requires visualization +/- biopsy of the affected organ.

Amylase and lipase elevations – both of these enzymes may originate from the intestinal mucosa, and liver, and therefore serum levels of these enzymes will increase with other causes of gastroenteritis. Both enzymes have very short half-life in serum (4-6 hrs) and so levels may be normal when tested. In addition, both enzymes excreted by kidneys, and levels may be elevated with renal disease, pre-renal conditions, and post renal obstruction.

Lipase has a specificity of 72%; therefore, 28% of cases with elevations in lipase have no pancreatic disease (such as with malignancy, renal, or hepatic disease).
Alanine transferase, aspartate transferase enzymes may be elevated.
Glucose – Hyperglycemia is common and is due to excessive glucagon release from the damaged pancreas, and decreased insulin secretion from islet cell destruction. Stress may also produce mild elevations in glucose.
Serum triglycerides – Hyperlipidemia may be present.
Calcium – may be elevated, normal or decreased.
Hypoproteinemia may be present due to third space losses.
Alkaline Phosphatase is frequently elevated. If alkaline phosphatase levels are normal, consideration should be given to other diagnoses.
Hematology may show an elevated hematocrit due to hemoconcentration and dehydration, and splenic contraction. A leukocytosis with left shift is common.
Radiography may be normal in up to 50% of cases. Typically, the right cranial quadrant shows a loss of detail, and a so-called "ground glass" appearance. There may be displacement of the duodenum to the right, and the pyloric antrum to the left. There may be a static duodenal or colonic gas pattern consistent with intestinal ileus.
Diagnostic Peritoneal Lavage may reveal a serosanguinous fluid, elevated leukocyte count, and degenerate neutrophils. The amylase concentration of abdominal effusion is always more elevated than serum levels.

Treatment of Acute Pancreatitis

1. **Correction of fluid, electrolyte and acid/base imbalances** – Fluid loss into third spaces can be significant in the patient with acute pancreatitis. Hypovolemia should be corrected within the first hour of presentation. Dehydration should be corrected in the following 4-6 hours. Patients may have ongoing fluid requirements of between 2 and 7 times maintenance. The use of synthetic colloids such as dextran 70 or natural colloids such as plasma will reduce fluid losses into third spaces, and improve pancreatic microcirculatory blood flow. Fresh frozen plasma also contains alpha$_2$ antitrypsin, albumin, and clotting factors important in managing the complications of acute pancreatitis. Withholding oral intake reduces the stimulus for pancreatic secretions, as does nasogastric suctioning of gastric fluid.

2. **Nutrition** – Nil per os (NPO) has traditionally been considered an important therapy in acute pancreatitis. It has been reported to improve patient comfort, and reduces the stimulus for pancreatic secretion. However, recent research and retrospective analysis of patients with pancreatitis has shown that fasting may have a negative effect on outcome in pancreatitis. In acute pancreatitis, the following may occur:
   (a) Oral nutrition may be prohibited by many factors, including abdominal pain, nausea, vomiting, gastric atony, and partial duodenal obstruction caused by pancreatic swelling and enlargement.
   (b) Decreases in luminal pancreatic enzymes may cause maldigestion and malabsorption of ingested nutrients.
   (c) Inflammation of the pancreas and abdominal cavity may produce excessive protein loss.
   (d) Energy expenditure is increased in as many as 50% of patients (the remainder have normal energy expenditure (40%), or are hypometabolic (10%)).

(e) Impaired beta-cell production of insulin, and stress results in an increase in the glucagon: insulin ratio, and increased gluconeogenesis.

(f) Fat metabolism is altered in favor of increasing lipolysis and lipid oxidation, resulting in hyperlipidemia.

(g) Protein catabolism and protein loss is accelerated.

(h) Micronutrient losses occur commonly, particularly with calcium, magnesium, zinc, thiamine, and folate.

(i) Negative energy balance occurs due to reduce nutrient intake, and is associated with increasing mortality.

As mentioned above, nutritional management of pancreatitis has included pancreatic rest – the withholding of enteral nutrition in an effort to reduce pancreatic secretions, and the stimulus for ongoing release of pancreatic enzymes into the abdominal cavity. Traditional recommendations for nutrition of patients with pancreatitis have centered about providing parenteral nutrition. However, parenteral nutrition in patients with pancreatitis produces longer hospital stays, and higher rates of infections, and has been compared to giving no nutrition at all. The provision of parenteral nutrition in patients with pancreatitis has no benefit.

Provision of early enteral nutrition in patients with pancreatitis shortens hospital stay, results in lower incidence of sepsis and infection, and a more rapid resolution of elevated markers of inflammation. The optimal route for nutritional support in patients with pancreatitis is via the jejunum, followed by the duodenum, and the stomach. Nutritional support should begin within 12-24 hrs of presentation to the ICU. The ideal diet for patients with pancreatitis is a diet providing most calories in the form of carbohydrates.

3. **Ancillary measures that may** be beneficial in the management of the patient with acute pancreatitis include the following:

(a) **Antibiotics** – the use of antibiotics in patients with pancreatitis is controversial. However, the use of antibiotics may be beneficial, especially if the patient has clinical signs of sepsis, disseminated intravascular coagulopathy, or infection. Trimethoprim-sulpha, enrofloxacin, or beta-lactam antibiotics are preferred.

(b) **Analgesia** should be provided with an opiate analgesia. Fentanyl, butorphanol or buprenorphine are preferred. Morphine may result in contraction of the sphincter of Oddi, and is less preferred over fentanyl in patients with severe abdominal pain.

(c) **Disseminated intravascular coagulopathy** is managed by ensuring the patient has adequate circulating blood volume, hematocrit, blood pressure, tissue oxygenation, and the administration of blood clotting factors, e.g., fresh frozen plasma. Note that some studies have found macroglobulin concentrations to be low in stored blood products, and question their use for supplying macroglobulins to patients. Current recommendations are to administer fresh frozen plasma to patients with pancreatitis at 10-20 ml/kg q 12-24 hrs in order to supply clotting factors, naturally occurring anticoagulants such as anti-thrombin III, albumin (provides colloid oncotic pressure, and binds detergents and free fatty acids), and anti-trypsin factors such as macro-globulins. Administration of heparin with plasma is recommended.

(d) **Selenium** dosed at 0.1 mg/kg slow IV q 24 hrs has shown promising results in improving mortality in one canine study, and warrants further investigation.

Currently however, there is little evidence to support the current use of selenium in the management of pancreatitis until further research is performed.

(e) **Anti-inflammatory drugs** are not currently recommended in the management of pancreatitis. There is no evidence that they improve the clinical outcome of patients with acute pancreatitis. Corticosteroids may impair the removal of macroglobulin-bound proteases from the plasma by the monocyte-macrophage system.

(f) **Anti-emetic and H_2 receptor antagonists** may improve patient comfort, but do not alter the clinical course of the disease.

(g) **Anti-inflammatory cytokine treatment** – administration of anti-inflammatory cytokines, and hormones such as somatostatin, and enzyme inhibitors have not shown benefit in large-scale human trials. More research is ongoing into the potential benefit of these molecular-based treatments. Administration of atropine, glucagon, and calcitonin have not shown to be of benefit.

4. **Surgical drainage and debridement** of the patient with acute pancreatitis may be a useful adjunct to standard medical therapy. Lavage of the abdomen helps to lessen the severity of disease because it removes significant amounts of active pancreatic enzymes, and reduces the burden on the plasma protease inhibitor system. Indications for surgery include:

(a) Intractable or progressive clinical signs.

(b) Suspicion of pancreatic neoplasia.

(c) Sepsis or septic peritonitis.

(d) Pancreatic abscess.

(e) Biliary tract obstruction.

(f) Intestinal perforation or obstruction.

(g) To facilitate enteral feeding tube placement.

(h) DPL indicating at least 2 of the following:

- WBC lavage fluid of > 20,000/ul
- Differential WBC count lavage fluid > 90% segmented neutrophils
- Cytology of lavage – intracellular bacteria, vacuolated WBC
- Amylase of lavage fluid > 200 IU, and increasing
- Lipase of lavage fluid > serum lipase, and increasing

The goals of surgery in acute pancreatitis include:

(a) To explore entire abdomen.

(b) To take pancreatic biopsies.

(c) To debride and remove all necrotic and suppurative tissue.

(d) To provide copious abdominal irrigation with warm saline.

(e) Gastrojejunostomy.

(f) Placement of J-tube in the distal 2/3 of the jejunum; (can get reverse peristalsis in proximal 1/3).

(g) To manage peritonitis with a closed or open abdomen as appropriate.

5. **Recovery phase** – therapy includes dietary considerations, and careful observation for symptoms of relapse, diabetes mellitus, and exocrine pancreatic insufficiency.

Sepsis in Acute Pancreatitis

Sepsis is a common sequel to acute pancreatitis, and should be anticipated. Attention to tissue oxygen delivery and the use of a standard protocol for diagnosing and managing patients in sepsis is crucial to improving survival of these patients. Patients should be assessed every 6-12 hours using a standard checklist to ensure they are receiving the most appropriate treatment for their condition. An example of a checklist is given below:

Checklist of Monitoring in Patients with Pancreatitis

Parameter	Target Range	Suggested Treatment
Blood pressure (systolic)	100-130 mm Hg	Fluid therapy, colloids, transfusion
Urine output	1.5-4.0 ml/kg/hr	Fluid therapy, colloids, transfusion, prostaglandin E, diuretic therapy
Heart rate	80-120 beats per minute	Fluid therapy, analgesia, colloid therapy, transfusion, oxygen supplementation
Pulse oximetry	90-100%	Oxygen supplementation
Gut motility	Presence of gut sounds	Fluid therapy, micro-enteral nutrition, anti-emetic therapy, analgesia, colloid therapy, nutritional support
Neurological status	Normal mentation	Fluid therapy, oxygen delivery, glucose administration
PCV/TP	Within normal limits	Fluid therapy, colloid therapy, plasma transfusion, red cell transfusion, nutrition
Clotting profile (ACT)	70-120 seconds	Fluid therapy, oxygen supplementation, colloid therapy, analgesia, plasma transfusion
Nutrition	Prevention of malnutrition	Enteral nutrition, gastrointestinal pro-kinetics, analgesia, fluid therapy, colloids, plasma transfusion

Summary

Management of the patient with acute pancreatitis requires removal of the inciting cause, and the provision of intensive medical treatment aimed at treating shock, restoring normal tissue hydration and perfusion, and vigilance in monitoring and addressing potential complications of the disease. In many patients, exploratory laparotomy can provide benefit in aiding removal of inflammatory cells and debris, resection of diseased tissue, and establishing a route for nutritional support.

References

Westfall, D.S., "Acute Pancreatitis in the Dog" In the Veterinary ICU Book, Raffe/Wingfield (Ed); Teton New Media 2002, P 771-783.

Williams, D.A., et.al, "Treatment of Canine and Feline Pancreatitis", ACVIM 2002.

Frick, T., "Drug-associated pancreatitis: Facts and fiction. Pancreas, 1997; 15:215.

Williams, D.A., "The Pancreas", In Small Animal Gastroenterology, Strombeck/Guilford (Ed); Saunders Publishing Co, 1996; 381-410.