When considering diseases of the exocrine pancreas in dogs, pancreatitis occurs much more commonly than pancreatic adenocarcinoma, or exocrine pancreatic insufficiency. Pancreatitis is an inflammatory condition of the pancreas.

**Classification**

There have been many different classification methods employed for pancreatitis, which can be confusing if reading material from different authors. In contrast in human medicine the classification has been significantly simplified over recent years, with the main classification being as either acute or chronic disease. The main difference between the two is the potential ‘reversibility’ of the pancreatic changes. With acute pancreatitis, once the inciting cause has been removed, the inflammation and disease is completely reversible. In the case of chronic pancreatitis there is longer standing inflammation with consequent irreversible changes on histopathology, typically fibrosis and atrophy. It is important to realise based upon this classification the determination of whether pancreatitis is acute or chronic can only be made definitively based upon a biopsy and histopathological examination. The differentiation cannot be made upon clinical signs alone. Whilst acute pancreatitis can tend to be more severe, in some cases it is mild, and the clinical signs with chronic disease can sometimes be severe.

**Aetiology and Pathophysiology**

In most cases of pancreatitis in dogs the aetiology remains undetermined. There are a number of potential risk factors that have been identified however.

Obesity has been suggested as a risk factor for the disease, and the disease has been reported as less severe when experimentally induced in lean dogs. Hyperlipidaemia, often grossly recognised in patients with acute pancreatitis, may be the consequence of abdominal fat necrosis, or may potentially induce the disease. In the case of Miniature Schnauzers, there is a possible link between the familial hyperlipidaemia recognised in the breed and the apparent increased incidence of pancreatitis. In humans hereditary pancreatitis occurs, related to mutations that result in conformational changes in trypsin rendering it more resistant to autodigestion. Such changes have not been detected as yet in dogs. Concurrent endocrinopathies (diabetes mellitus, hyperadrenocorticism, hypothyroidism), and epilepsy have been considered risk factors.

There are a number of drugs that have been suggested as inducing agents of pancreatitis, however definitive evidence to prove a causal link is often lacking. Glucocorticoids were long implicated, but evidence to support this is lacking, other than perhaps the very high dose regimes sometimes used for patients with spinal cord injury. Other drugs that have been suggested as risk factors include chemotherapeutic drugs (L-Asparaginase, vinca alkaloids), cytotoxic drugs (azathioprine), diuretics (frusemide, thiazides), anticonvulsants
(potassium bromide), antimicrobials (sulphonamides, tetracyclines), and non steroidal anti-inflammatories such as salicylates.

Some toxins have been associated with the disease, including cholinesterase inhibitors or cholinergics. The theory is that they stimulate hypersecretion. Other toxins include zinc and scorpion venom.

Hypercalcaemia has also been recognised as a cause of pancreatitis in dogs. This may be spontaneous (malignancy, hyperparathyroidism, renal failure, hypoadrenocorticism, granulomatous disease, destructive bone disease), or may be iatrogenic (vitamin D toxicity).

Reflux of duodenal juice into the pancreatic duct can cause pancreatitis, but rarely occurs in a normal patient because of the anatomy of the duodenal papilla, which has a muscular sphincter and is also covered by a special piece of mucosa. It may be more likely to occur after surgical intervention in the area, such as the formation of a closed duodenal loop.

Obstruction of the pancreatic ducts typically results in pancreatic atrophy and fibrosis. However if pancreatic secretion is stimulated inflammation may occur. Clinical causes of pancreatic duct obstruction can include surgical manipulation of the area, neoplasia, oedema of the duct or duodenal wall, a strategically located duodenal foreign body, trauma, parasites, spasm of the sphincter, or biliary calculi.

Pancreatic trauma may induce pancreatitis. This may be the result of blunt abdominal trauma, but may be iatrogenic with surgery. Whilst many people are nervous about pancreatic biopsies, they rarely induce pancreatitis, and the same also holds true for removal of pancreatic masses.

Other potential causes of pancreatitis include ischaemia (associated with shock, hypotension, or venous occlusion), infectious agents (uncommon, but viral, parasitic and mycoplasmal causes have been suggested, as has Babesia), or potentially immune mediated disease.

The basic mechanism of the disease is autodigestion of the pancreas. There are several mechanisms in place in the pancreas to try and avoid this process. The first is that the digestive enzymes (both proteolytic and phospholipolytic) are produced and then stored in an inactive form, referred to as catalytically inactive zymogens. The process of activation is achieved by the enzymatic cleavage of a small activation peptide from the amino terminal of the polypeptide chain. The activation typically occurs in the small intestine after secretion of the zymogens. The duodenal enterocytes secrete an enzyme called enteropeptidase that is very effective at cleaving the activation peptide from trypsinogen. The activated enzyme, trypsin, then cleaves the activation peptide from the other zymogens. It is important to remember though that enteropeptidase and trypsin are not the only enzymes that have the capability to activate the zymogens. There are lysosomal proteases that have this capability. A second mechanism to try and avoid pancreatitis is the strict separation of the digestive enzymes during synthesis, storage and secretion from other cellular enzymes, including the lysosomal enzymes. The digestive enzymes are stored in zymogen granules, separate from lysosomes. Calcium also plays a role in enzyme activation, and it can have both an inhibitory and activating role. At low concentrations (as in acinar cells), calcium binding protects trypsinogen activating peptide from exposure. Whereas at higher calcium concentrations (as
found in the pancreatic duct and intestine), calcium increases the sensitivity of trypsinogen to activation by trypsin. Higher pH levels in the pancreas and ducts also minimise enzyme activation.

In the situation where some intra-pancreatic activation of trypsinogen occurs, there are other mechanisms to help prevent activation of the zymogens. Firstly, trypsin effectively hydrolyses itself, so a small amount of activation is rarely problematic. The second protective mechanism is a specific trypsin inhibitor referred to as pancreatic secretory trypsin inhibitor (PSTI). PSTI is synthesised, stored and secreted with the digestive zymogens. It is thought that PSTI will inhibit trypsin activity if there is significant trypsin activation within the acinar cell or duct system. The effectiveness of PSTI is limited at a low pH found within fusion vacuoles.

If adequate activation of the trypsin takes place within the pancreatic cells and ducts, the other zymogens (including proelastase and prophospholipase) will be activated, further increasing pancreatic damage. As further enzyme is activated within the pancreas, a mild oedematous pancreatitis may progress to more severe haemorrhagic or necrotic disease, and then more systemic signs of disease will manifest.

If activated digestive enzymes gain access to the vascular space, there are plasma protease inhibitors that are very important in minimising their adverse effects, which may be fatal. The protease inhibitors include alpha macroglobulins and alpha 1 protease inhibitor. The most important of these are the alpha macroglobulins. Once bound to alpha macroglobulin the proteases undergo a conformational change, and are then cleared by the monocyte macrophage system. If they are not bound the free proteases will induce disseminated intravascular coagulation by activating the coagulation, fibrinolytic, kinin and complement systems. The effect of alpha 1 protease inhibitor is limited by the fact that the enzyme binding is reversible. It therefore is a more transient inhibitor until the alpha macroglobulins can have their effects.

In addition to the activation of the coagulation and fibrinolytic systems, the activated enzymes stimulate the activity of numerous inflammatory mediators. These include, but are not limited to tumour necrosis factor, interleukins, interferon, nitric oxide, and platelet activating factor. It is these mediators, along with systemic inflammation, that result in the systemic signs seen in some patients with pancreatitis.

**Clinical Presentation**

Whilst any dog can be affected, middle aged and older and overweight dogs are more commonly affected. Other risk factors were discussed in an earlier section of the notes. The clinical signs will vary with the severity of the disease process. In more severe cases common clinical signs may include anorexia, vomiting, weakness, abdominal pain, diarrhoea, and obtundation. In some severe cases there may be more systemic clinical signs including fever, tachypnoea or dyspnoea, or signs of shock. Abdominal pain has not been reported as frequently in canine patients as in human patients. The abdominal pain may be manifest by the assumption of an unusual posture (prayer position), or a pain response upon physical examination.
Other physical examination findings may include the presence of a palpable cranial abdominal mass, or evidence of a peritoneal effusion. Some patients may have respiratory distress, icterus, dehydration, or signs of a bleeding disorder. Cardiac arrhythmias may also be apparent. Some severely affected patients may be hypothermic.

Chronic pancreatitis, or milder acute pancreatitis may have less specific clinical signs, and in some patients there may be no clinical signs at all. Therefore it is more likely that the diseases may remain undiagnosed.

**Diagnostic Evaluation**

*Clinical Pathology*

Routine haematology and biochemical profile changes tend to be relatively non-specific in the diagnosis of the disease. A neutrophilia and left shift is a relatively common finding in affected patients. Neutropaenia is occasionally noted. Thrombocytopenia may be noted in over 50% of cases, and may serve as an indicator for DIC. The packed cell volume may be elevated secondary to haemoconcentration, or may be reduced.

A biochemical profile may reveal azotaemia, which could be secondary to dehydration, or could indicate renal damage and the onset of acute renal failure. Elevated liver enzymes may be the result of bile duct obstruction, ischaemia, or the drainage of toxic material from the pancreatic veins into the portal vein. Hyperbilirubinaemia may occur for similar reasons to the hepatic enzymes. Hyperglycaemia can be the result of elevated levels of cortisol, catecholamines and glucagon, or damage to the endocrine pancreatic tissue. Some patients may become diabetic. Hypoalbuminaemia may be the result of loss because of vasculitis or effusion. Hypocalcaemia may be secondary to the hypoalbuminaemia, or the formation of calcium salts with fatty acids associated with fat necrosis. Hypercholesterolaemia and hypertriglyceridaemia are commonly recognised. Electrolyte and acid base abnormalities are frequently recognised, secondary to vomiting and hypovolaemia.

Urinalysis is important in affected animals to aid in the interpretation of the biochemical profile. The urine specific gravity may be elevated because of dehydration. The presence of azotaemia and an inappropriately low specific gravity raises questions about renal function. In the presence of acute renal failure there may be active urine sediment present, with casts noted.

If DIC is suspected, coagulation parameters should be measured (prothrombin time, activated partial thromboplastin time, D-dimers or fibrinogen degradation products).

Many non invasive tests clinical pathologic tests for the diagnosis of pancreatitis have been evaluated and many have found to be of limited diagnostic value.

Serum amylase and lipase have long been used to try and confirm the diagnosis of canine pancreatitis. However both have limited sensitivity and specificity. Whilst the pancreas synthesises lipase, so do other tissues and the catalytic assay utilised does not differentiate the source of lipase. This is evidenced by the fact that patients with exocrine pancreatic insufficiency may have a normal lipase. Lipase elevations may occur with renal failure, glomerulonephritis, hepatic disease, intestinal disease, the administration of glucocorticoids (especially dexamethasone), or heat stress. The information for serum amylase is very similar,
with many non pancreatic sources. It is important to note that about 50% of patients with an elevated serum amylase, lipase, or both do not have pancreatitis.

Trypsinogen activation peptide (TAP) will be released into the vascular space in pancreatitis. The diagnostic value of serum TAP levels, or a urinary TAP to creatinine ratio have been evaluated. There was reasonable to high sensitivity for the tests, but low specificity. The tests are also not readily available, and the cost is high, further limiting their value. An assay was developed for trypsin-alpha-1-protease inhibitor complexes, but it was found that the levels were not significantly increased in dogs with pancreatitis.

The serum trypsinogen-like immunoreactivity test (TLI) detects trypsinogen and some trypsin in the circulation, and is a species specific test. The test has proven to be very specific for the diagnosis of EPI in dogs and cats. It was found that dogs with experimentally pancreatitis had elevated TLI levels. Some dogs with spontaneous pancreatitis will have an elevated TLI level, but this may be less than 40% of patients. Sensitivity and specificity have been reported as 65% and 33% respectively, limiting the diagnostic value.

As discussed previously, one of the limitations of the catalytic assay for lipase is that it does not differentiate the many sources of lipase in the body. The different lipases do have different molecular structures. The gastrointestinal laboratory at Texas A and M University purified classical pancreatic lipase (cPL) from dog pancreas, and developed antisera against this in rabbits. Further testing demonstrated that the only cell type staining positively for cPL was the pancreatic acinar cell, and a reference range was developed using 74 clinically healthy dogs. A radiommunoassay and ELISA were developed and validated, with the ELISA commercially available. The cPLI levels were demonstrated to be reduced in dogs with EPI. The cPLI was evaluated in dogs with chronic renal failure, and it was found that the levels were within reference ranges, and promising results were obtained in patients with gastritis. The levels are not affected by the administration of prednisolone. Another study compared the results of various diagnostic tests in cases of biopsy proven pancreatitis. The sensitivity was shown to be over 80%. Further evaluation may be necessary in patients with mild or chronic disease.

Imaging
Abdominal radiography has the advantage of being freely available to almost all practitioners. In patients with pancreatitis there may be a number of possible abnormal findings. These may include an increased density, or a loss of detail in the abdomen, or a granularity or ground glass appearance, especially in the right cranial quadrant. The stomach may be displaced to the left, increasing the angle between the pylorus and duodenum, and the descending duodenum may be displaced to the right. Gas accumulation may be noted in the descending duodenum, with a suggestion of a thickened duodenal wall, or there may be gas accumulation in the transverse colon with caudal displacement. There may be gas accumulation in the stomach, and if barium is administered there may be delayed transit through the stomach and duodenum, with an irregularity of the duodenal wall. However none of the aforementioned findings are definitive. Pleural effusion may be noted in a small number of dogs with severe disease.

Abdominal ultrasonography is a frequently used technique for diagnosis of acute pancreatitis, but is not without limitations. There are well defined criteria for the diagnosis,
and if applied, the sensitivity is good (~70%). Pancreatic enlargement alone is not diagnostic, because there can be other causes of pancreatic oedema, including portal hypertension. Local effusion alone is also not diagnostic. Altered pancreatic echogenicity is important. Decreased echogenicity may suggest oedema or necrosis, and the gland may appear mottled. The pancreatic dimensions are variable. The surrounding tissue may be hyperechoic, typically the inflamed mesentery with fat necrosis. Generalised or regional effusion may be noted. The liver and biliary system should also be evaluated, especially if the patient has elevated hepatic enzymes or icterus. Chronic pancreatitis may be associated with increased echogenicity in the pancreas associated with fibrosis.

Advanced imaging options are available. Contrast enhanced CT is frequently used in humans as a diagnostic tool. MRI may also have potential value. However both are expensive and require general anaesthesia.

**Pancreatic Biopsy**

Pancreatic biopsy and histopathological examination is typically considered the gold standard test for diagnosis. It is important to note that even this technique has its limitations. Studies have shown that pancreatic inflammation typically occurs in discrete areas within the gland, rather than diffusely. There is also random distribution within the gland of the inflammation. It may be possible that a single biopsy or even multiple small biopsies may not identify inflammation. The presence of inflammation or necrosis is certainly diagnostic, but their absence does not rule out the diagnosis. Biopsies can be obtained at laparotomy, or laparoscopically. Biopsy is the only way to definitively classify pancreatitis as acute or chronic.

**Treatment**

It is important to remember that there is no single therapy that has been shown to be totally effective in pancreatitis.

The traditional therapy for pancreatitis was focused on resting the pancreas with a nil by mouth approach, and the correction of fluid, electrolyte and acid base balance with intravenous fluid therapy. However the prolonged withdrawal of food can result in immunosuppression, adverse effects in the gastrointestinal tract, increased bacterial translocation, sepsis, and reduced survival. NPO is necessary in patients with intractable vomiting, but ideally should be employed for the shortest time possible.

When providing nutrition, there is the choice of enteral versus parenteral nutrition. Parenteral nutrition can be total (TPN), or partial (PPN). Total parenteral nutrition is the provision of all essential nutrients via an intravenous route. There can be a high rate of complications, which may be metabolic (e.g. hyperglycaemia), mechanical (e.g. occluded lines), or septic. TPN must be provided via a central venous line. PPN supplies part of the nutritional requirements of the patient, and can be administered via a central or peripheral intravenous line. PPN solutions typically contain glucose, amino acids, and lipid. There should be a devoted line for the PPN solution. The lines should not be disconnected, aseptic technique should be maintained, solutions should be changed each day, and they require protection from light. Electrolytes, glucose and lipid levels must be monitored regularly.
Enteral nutrition is considered to be preferable to parenteral nutrition. It is considered to help maintain enterocyte nutrition, and thereby improve the gut barrier and improve intestinal motility. There is also an improvement in immune function. There are a number of alternatives for route of feeding. Naso-oesophageal or nasogastric tubes can be placed with the use of topical anaesthesia. They are useful for the provision of microenteral nutrition, and nasogastric tubes can also be used for suction purposes. Oesophagostomy tubes or gastrostomy tubes can also be used, but require the use of general anaesthesia. Care must be taken to ensure that oesophagostomy tubes are not ‘vomited up’, but the risk is less if a larger diameter tube is used. Gastrostomy tubes can be placed percutaneously, endoscopically or surgically. They can also be used for gastric suctioning. Feeding via these routes may require concurrent use of antiemetics. Jejunostomy tubes have the advantage of minimal stimulation of pancreatic secretion, and the material will not be vomited. They can be placed surgically, laparoscopically, or endoscopically. Disadvantages include anaesthesia time, and the fact that continuous rather than bolus feeding is necessary, limiting their ‘at home’ usefulness. Some studies suggest it is the diet formulation rather than the route of feeding that minimises pancreatic secretion, with elemental diets (free amino acids and low fat) are best.

Pain control is an important part of the therapy for pancreatitis. Untreated pain can reduce immune function and may reduce survival. Opioids are the mainstay of therapy in this situation, with alternatives including fentanyl (continuous rate infusion or transdermal), methadone, buprenorphine, or morphine. The latter may cause contraction of the sphincter of Oddi, increasing bile duct pressure, but this is not proven. Potential disadvantages include constipation, vomiting, and potential ileus. Other alternatives may include the use of local anaesthetic drugs. Lignocaine or bupivacaine can be administered intraperitoneally, or lignocaine can be used intravenously as a continuous rate infusion (20-30 ug/kg/minute). Ketamine can be used as an infusion to decrease central wind up and overall pain (2-5 ug/kg/min), but ideally blood pressure should be monitored. Epidural analgesia has the limit of duration of action unless an epidural catheter is placed.

Fluid therapy is an essential part of the management of patients with pancreatitis. Typically balanced electrolyte solutions are used. The volume required can be calculated based upon the fluid deficit, maintenance requirements, and ongoing losses, such as those experienced due to continued vomiting. The deficits can be replaced over 12-24 hours, but if the patient is seriously hypovolaemic, shock rates can be administered. Patients will typically have a potassium deficit, so levels should be monitored and fluids should be appropriately supplemented with potassium. Potassium should not be added to fluids if administering shock rates. If hypokalaemia is refractory to therapy, the patient may be hypomagnesaemic, and levels should be checked and supplemented if necessary. Any acid base abnormalities should be assessed based on a biochemical profile for metabolic abnormalities, or a blood gas for metabolic and respiratory abnormalities, and corrected.

Metabolic abnormalities may occur. Electrolytes, blood glucose and renal parameters should be monitored. Hyperglycaemia will usually resolve as the pancreatitis does, but occasionally diabetes mellitus will develop. The patient should also be monitored for signs of a systemic inflammatory response syndrome, or other organ dysfunction.
Some patients may have ongoing vomiting and gastrointestinal ileus. Metoclopramide is often a first line antiemetic, and it can act as a prokinetic. Continuous rate intravenous infusions appear to be most effective (1-2 mg/kg/day), and can be set up as a separate infusion. If metoclopramide alone does not control the vomiting, other drugs may become necessary, such as prochlorperazine, or ondansetron. Maropitant is also an effective broad-spectrum antiemetic that may be useful in patients with vomiting. Gastrointestinal ulceration may be a contributing factor, so the use of an H2 antagonist such as ranitidine or famotidine, or proton pump inhibitors such as omeprazole may be indicated. Ranitidine also has some prokinetic action.

Some patients may continue to deteriorate despite therapy. Blood product transfusion has some theoretical benefits in such situations. In severe cases there is typically consumption of plasma protease inhibitors, and when exhausted there is increased risk of DIC, shock and death. Plasma or whole blood may replace alpha 2 macroglobulins already consumed. There is no objective evidence to support this, but many clinicians (myself included) feel anecdotally that it is of benefit. Plasma also provides oncotic support, may help in the treatment of systemic inflammatory response syndrome, provides clotting factors and antithrombin III, and may help reduce pancreatic oedema. Synthetic colloids can provide oncotic support, but do not have the other potential therapeutic benefits of plasma, and there is the potential to exacerbate bleeding tendencies.

Other therapies may be indicated on a case by case basis. Pancreatitis is typically sterile in dogs. However if there is a concern of bacterial translocation in the GI tract, or there is evidence based upon cytology or histopathology of bacteria in the pancreas, antimicrobials may be indicated. The antimicrobial choice should address at least anaerobic organisms and gram negatives. In patients at risk of DIC, or there is evidence of DIC developing, heparin therapy may be indicated along with plasma transfusion. Vitamin B supplementation should be considered in patients with prolonged fasting. The use of glucocorticoids has been advocated in some circles to stabilise lysosomal membranes, reduce inflammation, and alleviate shock, but there is no evidence to support their benefit. Blood pressure should be monitored, and if there is hypotension refractory to fluid therapy, further intervention may be required, such as inotrope infusions. In cases with pancreatic abscessation, or severe peritonitis, surgery may be indicated to debride the pancreas, or for peritoneal lavage.

Attempts to rest the pancreas have been made by the administration of inhibitors of secretion such as atropine, acetazolamide, glucagon, calcitonin or somatostatin. There is no evidence that such strategies have been effective. Anticytokine drugs to try and avoid more systemic disease may be a future strategy.

If any potential causes for pancreatitis can be identified, they should be addressed. This may include for example the correction of hypercalcaemia, or the cessation of drugs that may cause pancreatitis.

Once the patient is not vomiting, first water and then small volumes of a fat restricted diet can be gradually reintroduced. A low fat maintenance diet should be used in the long term. There has been suggestion that oral pancreatic enzyme supplements may reduce the abdominal pain associated with chronic pancreatitis in humans. This is unknown in dogs, but
a therapeutic trial could be attempted in canine patients with the disease that manifest abdominal pain or inappetence.

**Complications**
Potential complications of pancreatitis include DIC, systemic inflammatory response syndrome, chronic disease, recurrence or death. Pancreatic abscession may develop, with similar clinical signs to pancreatitis. Ultrasonography, plus or minus aspiration, with cytology and microbiology can be supportive of the diagnosis. Typically the abscesses are sterile. Surgical drainage is an option, but some may be managed more conservatively. Antimicrobials are indicated based upon a positive culture. Bile duct obstruction may occur in some patients with pancreatitis, which can manifest as icterus. This may spontaneously resolve as the pancreatitis does, but in some cases it may not. The total bilirubin concentration should be monitored. If it continues to rise, and the patient becomes unwell, and there is ongoing evidence of an extrahepatic bile duct obstruction, a biliary diversion procedure may become necessary. Alternatives include a cholecystoduodenostomy, or a cholecystojjunostomy.

**Prognosis**
The prognosis is variable with the severity of the disease, and can be difficult to predict. Patients with fulminating acute disease may still die despite aggressive therapy, whereas others may survive. Even patients with chronic, recurrent pancreatitis may ultimately be euthanased because of the recurrent nature of the disease.

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