



## Canine and feline pancreatitis

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Pancreatitis is caused by inflammation of the pancreas, which may be acute or chronic in nature.

A common differential diagnosis for many patients presenting with gastrointestinal signs, pancreatitis may cause a variety of non-specific clinical signs.

There is a wide spectrum of disease severity, ranging from very mild to severe. The pathophysiology of pancreatitis is not fully understood, although there are a number of well-documented predisposing factors to clinical pancreatitis. Pancreatic histopathology is considered the gold standard for diagnosing pancreatitis in dogs;<sup>1</sup> however, it is rarely performed and the distribution of inflammation in the organ may be patchy,<sup>2,3</sup> leading to false negative results.

Over the past two decades, a number of non-invasive diagnostic assays have been developed to aid in the diagnosis of pancreatitis, each having its own advantages and disadvantages.

Supportive care is the treatment of choice for pancreatitis. Life-threatening complications, such as disseminated intravascular coagulation (DIC) may develop in severe cases.

### EXOCRINE PANCREAS PHYSIOLOGY

Pancreatic acinar cells secrete proteolytic digestive enzymes in an inactive form called zymogens. Under normal conditions, these zymogens are secreted into the pancreatic duct into the duodenum via hormonal stimulation and are only activated within the intestinal lumen. Activation is initiated by the enzyme enterokinase, which is released from the duodenal mucosa.

Enterokinase activates trypsinogen to trypsin, and trypsin can then activate further zymogens as well as more trypsinogen.<sup>4</sup> The activated proteolytic enzymes then break down ingesta to allow for subsequent absorption of nutrients. As the zymogens are not activated until they reach the duodenum, the normal pancreas is protected from the damage that may be caused by the proteolytic enzymes. Enzyme inhibitors, or anti-proteases, also prevent or limit enzyme-induced tissue injury to the pancreas.<sup>5</sup>

### PATHOPHYSIOLOGY

Pancreatitis develops when trypsinogen is inappropriately

activated within the pancreas and overwhelms the protective mechanisms of the acinar cell and anti-proteases within the circulation.<sup>6</sup> The initial activation of trypsinogen has been documented in oxidative stress and hypotension.<sup>7</sup> A number of other factors can exacerbate this, including a low pH<sup>8</sup> and a high-calcium<sup>9</sup> concentration.

The co-localisation theory helps explain how zymogens can be prematurely activated within the pancreas. An apical block in the acinar cells prevents the release of zymogen granules into the intestinal lumen. Zymogen granules and lysosomes, are normally transported to the apex of an acinar cell separately; however, the apical block means that the lysosomes and zymogen granules can fuse prematurely. The fusion allows lysosomal proteases (eg. cathepsin B) to activate trypsinogen to trypsin. Trypsin can then activate other zymogens, which, once activated, autodigest the pancreatic acinar cells. Activated enzymes ‘escape’ not only into the pancreatic tissue, but also into the systemic circulation, causing local and/or systemic side effects. This tissue damage leads to recruitment of neutrophils and macrophages, which release inflammatory cytokines that lead to systemic effects, including dehydration, from vomiting and diarrhoea, release of vasoactive substances, release of cardio-suppressant substances, and cavitory effusions.

As shown in Figure 1, the pathophysiological events of pancreatitis can be summarised as a sequence of steps, starting with an initiating event which leads to characteristic acinar changes (colocalisation) and development of pancreatitis. The severity and outcome of pancreatitis are then determined based on a number of factors (inflammatory cytokine release, development of reactive oxygen species and oxidative damage, state and degree of apoptosis).<sup>4</sup>



**Figure 1: Pathophysiological events in pancreatitis.**

**PREDISPOSING FACTORS TO PANCREATITIS**

Dogs and cats of any age, breed, or sex may develop pancreatitis, but the exact aetiology of a patient’s pancreatitis is rarely definitively confirmed. There are a number of well-documented predisposing factors that can increase a patient’s risk of developing pancreatitis: genetic factors, breed, diet, obesity, hypertriglyceridemia, endocrine disorders, and certain drugs.

**HEREDITARY PANCREATITIS**

In humans, hereditary pancreatitis may be associated with mutations of the serine protease inhibitor Kazal-type 1

(SPINK1) gene, which encodes for pancreatic secretory trypsin inhibitor (PTSI). PTSI acts as a defense mechanism against premature activation of trypsinogen. Mutations in the SPINK1 gene are suspected to cause altered protein function, leading to autodigestion of the pancreas.<sup>10</sup> Three variants of the SPINK1 gene have been identified in Miniature Schnauzers and may be associated with the development of pancreatitis in this breed.<sup>11</sup>

**BREEDS**

Many studies have evaluated the breed prevalence of acute and chronic pancreatitis. The results of these studies are inconsistent. Breed predispositions are likely a combination of a genetic predisposition for pancreatitis or a predisposition to a predisposing factor (eg. hypertriglyceridemia).<sup>4</sup> The majority of cats with acute or suppurative pancreatitis are domestic shorthair cats, although Siamese cats are also over represented.<sup>12</sup> The most consistently reported at-risk breeds for acute pancreatitis include the Miniature Schnauzer, Yorkshire terriers, and other terrier breeds. At-risk breeds for chronic pancreatitis include Boxers, Cavalier King Charles Spaniel, English Cocker Spaniels and Collies.<sup>13</sup>

<b>Canine acute pancreatitis</b>	<ul style="list-style-type: none"> <li>• <b>Miniature Schnauzer</b></li> <li>• <b>Yorkshire terrier</b></li> <li>• <b>Other terrier breeds</b></li> </ul>
<b>Canine chronic pancreatitis</b>	<ul style="list-style-type: none"> <li>• <b>Boxers</b></li> <li>• <b>Cavalier King Charles Spaniel</b></li> <li>• <b>English Cocker Spaniel</b></li> <li>• <b>Collies</b></li> </ul>
<b>Feline pancreatitis</b>	<ul style="list-style-type: none"> <li>• <b>Domestic shorthair</b></li> <li>• <b>Siamese</b></li> </ul>

**Table 1: Breed predispositions to pancreatitis.**

**DIET AND OBESITY**

Early studies documented that high fat diets induced pancreatitis in some dogs,<sup>14</sup> and that high-fat diets increase the severity of experimentally-induced pancreatitis in dogs.<sup>15</sup> Other dietary factors that predispose to pancreatitis include ingestion of unusual food items (odds ratio 6:1), access to table scraps (odds ratio 2:2) and access to trash (odds ratio 13:2).<sup>16</sup> Obese patients are also predisposed to pancreatitis.

**HYPERTRIGLYCERIDEMIA**

Primary hypertriglyceridemia is a risk factor for pancreatitis in Miniature Schnauzers.<sup>17,18</sup> The severity of hypertriglyceridemia is important in determining the risk for pancreatitis, with patients with a serum triglyceride > 862mg/dl determined to be at an increased risk of pancreatitis in a recent study.<sup>17</sup> This link has not been proven in other breeds.

**ENDOCRINE DISEASE**

Patients with diabetes mellitus, hypothyroidism, and hyperadrenocorticism are at an increased risk of pancreatitis. It is unclear whether the increased risk is due to the disease or due to secondary hypertriglyceridemia.<sup>4</sup>

**DRUGS**

Due to the low incidence of drug-induced pancreatitis, these cases are often considered idiosyncratic drug reactions.<sup>19</sup> Table 2 documents medications that have been associated with pancreatitis.

<b>Anticonvulsants</b> • Potassium bromide • Phenobarbital	<b>Diuretics</b> • Furosemide • Thiazide diuretics
<b>Antimicrobials</b> • Sulfonamides • Tetracyclines	<b>Others</b> • Azathioprine • Organophosphates • Estrogen • Meglumine antimonate • Salicylates
<b>Chemotherapeutics</b> • L-asparaginase • Vinca alkaloids	

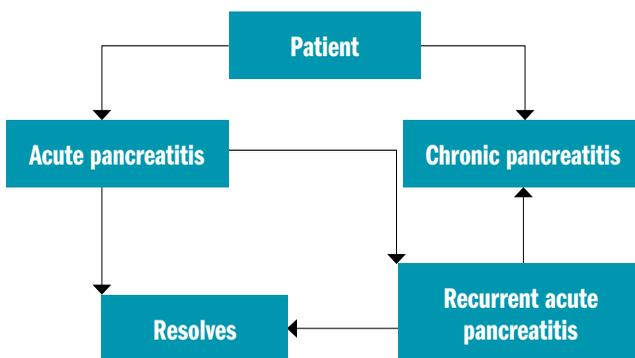
**Table 2: Drug-induced pancreatitis.**<sup>4,19-22</sup>

**MISCELLANEOUS PREDISPOSING FACTORS**

Abdominal trauma and recent abdominal surgery may predispose to pancreatitis. The pancreas is particularly vulnerable to changes in its unique microcirculation.<sup>23</sup> Similarly, hypotension may predispose<sup>4</sup> to or worsen pancreatitis. Other miscellaneous predisposing factors include hypercalcaemia<sup>2</sup>, obstruction of the pancreatic duct, and *Babesia* infections.<sup>25</sup>

**ACUTE AND CHRONIC PANCREATITIS**

Acute pancreatitis cannot be clinically distinguished from chronic pancreatitis; however, chronic pancreatitis cases tend to have milder clinical signs. Acute pancreatitis is defined as reversible inflammation of the pancreas with histological evidence of oedema, neutrophilic infiltration and necrosis.<sup>13</sup> Chronic pancreatitis, however, is defined as having irreversible changes, such as fibrosis.<sup>13</sup> There are two ways a patient may develop chronic pancreatitis, as highlighted in Figure 2. While some cases of pancreatitis can be considered chronic from the outset due to lymphoplasmacytic infiltration, other cases of chronic pancreatitis develop from failure of acute pancreatitis to completely resolve.<sup>26</sup>



**Figure 2: Relationship between acute and chronic pancreatitis.**

**CLINICAL SIGNS**

Due to the absence of pathognomonic clinical signs, overlapping clinical signs with other gastrointestinal diseases, and vague histories, pancreatitis can be considered one of the ‘great pretenders’ of small animal medicine. The majority of patients with pancreatitis, especially those with chronic disease, have mild, nonspecific clinical signs, while others can show signs of severe disease and systemic complications.<sup>27</sup>

The classic clinical signs of acute, severe pancreatitis vary in frequency between dogs and cats (see Table 3). In dogs, vomiting, abdominal pain, lethargy and dehydration are the most common clinical signs. Diarrhoea and fever are also possible. In general, clinical signs of pancreatitis are more vague in cats than in dogs, with anorexia or hyporexia, lethargy, dehydration and vomiting being the most common clinical signs.<sup>28</sup> In cats, abdominal pain, a common clinical sign in dogs, is reported in only 25% of cases.<sup>12</sup> Due to the unique pancreaticobiliary anatomy in cats, pancreatitis is often associated with triaditis.<sup>29</sup> Triaditis is a combination of pancreatitis, cholangiohepatitis and inflammatory bowel disease. Clinical signs of these three diseases are often seen together in cats. More severe clinical signs are related to systemic complications of pancreatitis, as discussed below.

<b>Canine</b>	Vomiting - 90% Abdominal pain - 58% Lethargy Dehydration
<b>Feline</b>	Inappetence - 83% Lethargy - 77% Dehydration - 65% Vomiting - 43% Icterus - 29% Abdominal pain - 25% Weight loss - 16%

**Table 3: Clinical signs of acute pancreatitis in dogs and cats.**<sup>12,28,30</sup>

**SEQUELAE/COMPLICATIONS OF PANCREATITIS**

**LOCALISED COMPLICATIONS**

Localised complications of pancreatitis result from the release of activated digestive enzymes into the pancreas and surrounding tissue, resulting in peritonitis and, possibly, necrosis of adjacent organs. Pancreatic inflammation may also extend into the endocrine pancreas and lead to development of diabetes mellitus. Hyperglycaemia in a patient with previous or current pancreatitis should prompt suspicion of diabetes and warrants further investigation and monitoring. Pancreatitis may cause both peritoneal and pleural effusions. Obstruction of the bile duct and post-hepatic hyperbilirubinaemia are additional complications of severe pancreatitis. Pancreatic abscesses and pseudocysts have also been reported as sequelae to pancreatitis. A detailed discussion of management of pancreatic pseudocysts, pancreatic abscesses and necrotic masses is beyond the scope of this review; however, readers are encouraged to read a recent review by Coleman and Robson.<sup>31</sup>

**SYSTEMIC COMPLICATIONS**

Release of digestive enzymes, or proteases, into the systemic circulation can result in hypotension, systemic inflammatory response syndrome (SIRS) and multi-organ dysfunction syndrome (MODS). Inflammatory cytokines, oxidative substances, and proteolytic enzymes allow for such extreme progression of pancreatitis and development of multiple organ failure.<sup>2,32</sup> Arrhythmias, myocardial depression, ileus, pre-renal or renal azotemia, DIC, and non-cardiogenic pulmonary oedema may develop in severe cases.<sup>32</sup>

**DIAGNOSIS – TRADITIONAL GOLD STANDARD VS CLINICAL GOLD STANDARD**

**TRADITIONAL GOLD STANDARD**

Pancreatic histopathology is considered the traditional gold standard and most reliable method for diagnosing pancreatitis.<sup>1</sup> However, pancreatic histopathology is rarely performed due to its invasive nature. Pancreatic biopsies also have a number of limitations, including the potential to miss highly localised lesions of pancreatitis,<sup>2,3</sup> a lack of standardised criteria for interpretation, and detection of subclinical pancreatitis.<sup>2</sup>

**CLINICAL GOLD STANDARD**

In the absence of a practical and clinically justifiable reason to obtain pancreatic biopsies, many clinicians, elect to pursue a clinical diagnosis of pancreatitis based on analysis of a comprehensive body of information including; signalment, history, physical examination, complete blood count (CBC), serum biochemistry, abdominal ultrasound and a pancreatic lipase assay. Recent publications support this more practical approach.<sup>33-35</sup>

**CBC AND SERUM BIOCHEMISTRY ABNORMALITIES IN PANCREATITIS**

CBC abnormalities found with pancreatitis are relatively non-specific. Patients with severe pancreatitis can develop a neutrophilia with a left shift. Thrombocytopenia and anaemia may occur, especially in the presence of DIC. Haemoconcentration, due to fluid losses may be noted initially. Pre-renal (due to dehydration) and renal azotemia elevated liver enzymes, hypoalbuminemia, hyponatraemia, hypokalaemia, hyperbilirubinaemia, hyperlipidaemia and hypocalcaemia (due to saponification of peri-pancreatic fat) may occur. Potential bloodwork findings are summarised in Table 4.

CBC	Serum biochemistry
<ul style="list-style-type: none"> <li>• Neutrophilia with left shift</li> <li>• Thrombocytopenia and mild anaemia</li> <li>• Haemoconcentration</li> <li>• Hyperproteinaemia (initially due to haemoconcentration)</li> </ul>	<ul style="list-style-type: none"> <li>• Azotemia</li> <li>• ALT and ALP elevation</li> <li>• Hyperbilirubinaemia</li> <li>• Hypocalcaemia, hyponatraemia, and/or hypokalaemia</li> <li>• Hypoalbuminaemia</li> <li>• Hyperlipidaemia</li> </ul>

Table 4: CBC and serum biochemistry abnormalities in pancreatitis.

**MOVING BEYOND TRADITIONAL LIPASE AND AMYLASE**

Although used historically for the diagnosis of pancreatitis, lipase and amylase have a poor sensitivity and specificity.<sup>34,36</sup> Serum lipase measures total lipase (ie. lipase of pancreatic, hepatic and gastric-cells origin), whereas pancreatic lipase assays measure lipase of pancreatic acinar cell origin only.<sup>37</sup> Therefore, pancreatic lipase is expected to be increased only during times of active pancreatic inflammation.

**CANINE ASSAYS**

The SNAP cPL is a rapid in-house test that is reported as either normal or abnormal. Normal results indicate a pancreatic lipase concentration <200mg/L and can rapidly rule out pancreatitis. Abnormal (or positive) results indicate a pancreatic lipase concentration<sup>3</sup> 200mg/L and should be followed by the Spec cPL.<sup>4</sup> If the sample ‘spot’ is equal in color to the reference spot, the pancreatic lipase concentration is between 200-399mg/L; this is equivocal for the diagnosis of pancreatitis. If the sample spot is darker than the reference spot, then the pancreatic lipase concentration is<sup>3</sup> 400mg/L, which is consistent with a diagnosis of pancreatitis. The Spec cPL is a quantitative, send-out test for measurement of canine pancreatic lipase; it is useful to confirm pancreatitis and can be monitored during or after therapy. The disadvantage of this test is that the results take >24 hours to return, thereby delaying a diagnosis. The VetScan cPL Rapid Test is a newer diagnostic assay that offers the combined benefit of a rapid in-house result and a specificity similar to, or greater than, the established Spec cPL assay.<sup>33</sup> There are currently no published validation studies for the VetScan cPL Rapid Test. To the authors’ knowledge, the Precision PSL, a DGGR (1,2-o-dilauryl-rac-glycero-3-glutaric acid 6’-methyl-resorufin ester) based assay, is not commercially available in the UK/ Republic of Ireland. It is non-specific for pancreatic lipase.<sup>38</sup>

**FELINE ASSAYS**

There are fewer commercially available pancreatic lipase assays available for cats. The SNAP fPL is an in-house assay. Normal results indicate a feline pancreatic lipase concentration <3.5mg/L and can rapidly rule out pancreatitis. Abnormal (or positive) results indicate a pancreatic lipase concentration<sup>3</sup> 3.5mg/L. If the sample spot is equal in color to the reference spot, then the pancreatic lipase concentration is considered between 3.5-5.4mg/L; this is equivocal for the diagnosis of pancreatitis. If the sample spot is darker than the reference spot, the pancreatic lipase concentration is considered<sup>3</sup> 5.4mg/L, which is consistent with a diagnosis of pancreatitis. The Spec fPL is a quantitative send-out assay similar to the canine Spec cPL.

**DIAGNOSTIC IMAGING**

Radiographs have a poor sensitivity and specificity for the diagnosis of pancreatitis in dogs and cats. Radiographic signs of pancreatitis include a gas-filled duodenum (duodenal stripe), displacement of the proximal duodenum

	Total lipase	SNAP cPL	Spec cPL	VetScan cPL rapid test	Precision PSL
Sensitivity (%)	54.0	73.9-100	81.0-90.9	73.9-83.3	85.7-90.9
Specificity (%)	43.0	71.1-77.8	74.1-81.1	76.9-83.8	64.0-74.3
Recommended use	-	Screening	Confirmatory	Confirmatory	Screening
In house/send out	Send out	In house	Send out	In house	Send out
Availability in UK/ROI	Yes	Yes	Yes	Yes	No

Table 5: Diagnostic assays for pancreatitis in dogs.<sup>33,36</sup>

and pylorus to the right, and evidence of abdominal effusion. The diagnostic sensitivity of ultrasound is around 68% but varies greatly depending on ultrasonographer experience.<sup>1</sup> Characteristic ultrasonographic signs of pancreatitis include enlargement or irregularity of the pancreas, hypoechoic areas within the pancreas and/or a hyperechoic mesentery surrounding the pancreas.

### TREATMENT

Mild cases are frequently managed on an outpatient basis (antiemetics and pain medication), whereas moderate-to-severe cases with systemic consequences often require in-hospital management. As with many conditions, disease severity is inversely proportional to prognosis. There are no specific treatments for canine or feline pancreatitis, and as such, supportive care is the treatment of choice.

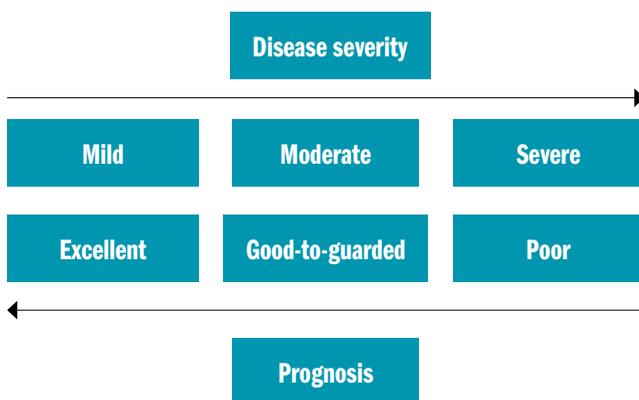


Figure 3: Relationship between disease severity and prognosis.

### FLUID THERAPY

Intravenous fluids are important for maintenance of pancreatic micro-perfusion and help to slow progression of pancreatitis. Balanced isotonic electrolyte solutions such as lactated Ringer's solution (LRS) are appropriate first choice fluids in pancreatitis. Fluid rates should be calculated to correct the fluid deficit over 12-24 hours (within the physiological demands of each patient) followed by a taper to maintenance fluid rates. Patient losses (vomiting, diarrhoea, cavitory effusions) must also be accounted for and normal blood pressure should be maintained to ensure adequate pancreatic perfusion. Electrolytes should be monitored, and supplementation should be given accordingly. Colloids may be indicated for hypotension and/or severe hypoalbuminemia.

### PLASMA TRANSFUSIONS

Plasma transfusions for pancreatitis have been explored in both human and veterinary medicine. There are two main theoretical benefits to plasma transfusions in pancreatitis. Firstly, many pancreatitis patients are hypoalbuminaemic, and therefore, a plasma transfusion may provide colloidal support. However, fresh-frozen plasma (FFP) is relatively low in albumin, and a significant volume of plasma would be required to correct or substantially improve the hypoalbuminaemia. In addition, other transfusion products such as cryo-poor plasma (CPP) are more cost-effective and higher in albumin than FFP<sup>39</sup> and are not used in the management of pancreatitis. The second argument for plasma in pancreatitis, is that plasma contains anti-proteases which are depleted in pancreatitis (eg. alpha-



macroglobulins and anti-trypsins).<sup>40</sup> On the other hand, studies have documented that, despite a decrease in alpha macroglobulins in pancreatitis the severity of decrease does not correspond with clinical severity. A recent study also documented a higher mortality rate in pancreatitis dogs receiving FFP compared to those that did not, concluding there was no benefit to administering FFP in canine pancreatitis.<sup>41</sup> Similar results have been documented in large, human clinical trials.<sup>42</sup> It is, therefore, the authors' opinion that, until further evidence is published, plasma transfusions should be reserved for pancreatitis patients with documented coagulopathies.

**ANTIEMETICS**

Antiemetics should be used to treat vomiting and reduce nausea-associated inappetence. Commonly used anti-emetics include maropitant citrate (Cerenia) and ondansetron (Zofran). Metoclopramide (Reglan) or cisapride (Propulsid) may also be indicated, especially if ileus is present.

**ANALGESIA**

Pancreatitis may cause severe abdominal pain, and analgesia is key to its successful management. It is important to recognise that clinical signs of pain are often underappreciated in feline patients, and that pain assessments must be based on behavioural assessment rather than objective measures such as heart rate.<sup>43</sup> Opioid analgesics, such as methadone, fentanyl, and

buprenorphine should be considered. Non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided.

**NUTRITION – TO FEED OR NOT TO FEED?**

Traditionally, fasting pancreatitis patients was a mainstay of acute pancreatitis treatment,<sup>1</sup> based on the theory that it this would avoid pancreatic stimulation and premature activation of zymogens. However, there is now a large body of data in human medicine that documents decreased morbidity and mortality from pancreatitis with early enteral nutrition. Based on clinical evidence in humans, experimental animal studies, and preliminary studies in dogs and cats, early enteral feeding during pancreatitis is encouraged.<sup>44</sup> A recent clinical practice review concluded that enteral nutrition in dogs and cats with acute pancreatitis is beneficial and well tolerated.<sup>44</sup> Enteral feeding is strongly recommended in cats to prevent complications of inappetence such as hepatic lipidosis. A detailed discussion of feeding recommendations for pancreatitis is beyond the scope of this review; however, readers are encouraged to read a recent review by Justin Shmalberg.<sup>5</sup>

**OTHER MEDICATIONS**

Proton pump inhibitors (omeprazole) or H2-receptor antagonists (famotidine, ranitidine) are useful adjunctive medications and may decrease the risk of gastric or intestinal ulceration or oesophagitis.

**REFERENCES ON REQUEST**

**READER QUESTIONS AND ANSWERS**

**1: WHAT IS THE MOST COMMON CLINICAL SIGN OF ACUTE PANCREATITIS IN DOGS?**

- A Abdominal pain
- B Vomiting
- C Diarrhoea
- D Inappetence

**2: WHAT IS THE MOST COMMON CLINICAL SIGN OF ACUTE PANCREATITIS IN CATS?**

- A Abdominal pain
- B Vomiting
- C Diarrhoea
- D Inappetence

**3: WHICH OF THE FOLLOWING TESTS HAS THE HIGHEST SPECIFICITY FOR THE DIAGNOSIS OF PANCREATITIS IN DOGS?**

- A Abdominal ultrasound
- B SNAP cPL
- C Spec cPL
- D Serum lipase

**4: WHICH OF THE FOLLOWING IS NOT AN APPROPRIATE ANALGESIC FOR PANCREATITIS?**

- A Methadone
- B Fentanyl
- C Buprenorphine
- D Carprofen

**5: WHICH OF THE FOLLOWING STATEMENTS IS CORRECT?**

- A All cases of pancreatitis have a good prognosis with medical management
- B Patients with pancreatitis should be fasted for 24 hours
- C All cases of pancreatitis require in-hospital management
- D Enteral nutrition is preferred over parenteral nutrition in the management of pancreatitis

**ANSWERS: 1:B; 2:D; 3:C; 4:D; 5:D**