REVIEW

Diagnosis of pancreatitis in dogs and cats

P. G. Xenoulis

Clinic of Medicine, Faculty of Veterinary Medicine, University of Thessaly, Karditsa 43100, Greece

Animal Medical Center of Athens, Athens, Greece

Pancreatitis is the most common disorder of the exocrine pancreas in both dogs and cats. Ante-mortem diagnosis of canine and feline pancreatitis can be challenging. The clinical picture of dogs and cats with pancreatitis varies greatly (from very mild to severe or even fatal) and is characterised by non-specific findings. Complete blood count, serum biochemistry profile and urinalysis should always be performed in dogs and cats suspected of having pancreatitis, although findings are not-specific for pancreatitis. Serum amylase and lipase activities and trypsin-like immunoreactivity (TLI) concentrations have no or only limited clinical value for the diagnosis of pancreatitis in either dogs or cats. Conversely, serum pancreatic lipase immunoreactivity (PLI) concentration is currently considered to be the clinicopathological test of choice for the diagnosis of canine and feline pancreatitis. Abdominal radiography is a useful diagnostic tool for the exclusion of other diseases that may cause similar clinical signs to those of pancreatitis. Abdominal ultrasonography can be very useful for the diagnosis of pancreatitis, but this depends largely on the clinician's experience. Histopathological examination of the pancreas is considered the gold standard for the diagnosis and classification of pancreatitis, but it is not without limitations. In clinical practice, a combination of careful evaluation of the animal's history, serum PLI concentration and abdominal ultrasonography, together with pancreatic cytology or histopathology when indicated or possible, is considered to be the most practical and reliable means for an accurate diagnosis or exclusion of pancreatitis compared with other diagnostic modalities.

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INTRODUCTION

Exocrine pancreatic disorders are common in clinical practice and pancreatitis is by far the most common disorder of the exocrine pancreas in both dogs and cats. Strictly speaking, pancreatitis refers to inflammation (i.e. infiltration with inflammatory cells) of the exocrine pancreas. However, the term pancreatitis is commonly expanded to also include diseases of the exocrine pancreas characterised mainly by necrosis (necrotising pancreatitis) or irreversible structural changes such as fibrosis (chronic pancreatitis), sometimes with only minimal inflammatory component. Pancreatitis is generally divided into acute and chronic forms based on the absence or presence of permanent histopathological lesions, respectively, such as pancreatic fibrosis and/or atrophy (Xenoulis *et al.* 2008). The categorisation of pancreatitis into acute and chronic has potential diagnostic, therapeutic, and prognostic implications.

Despite recent advances in diagnostics, it is increasingly recognised that accurate clinical diagnosis of pancreatitis can be challenging. New diagnostic modalities as well as new knowledge regarding older diagnostic modalities are becoming available with increasing frequency. Proper use and correct interpretation of the results of these diagnostic modalities is crucial for a correct diagnosis. Although the diagnostic evaluation of dogs and cats suspected of having pancreatitis should always take into account the signalment, clinical presentation and general clinicopathological findings, this review will mainly focus on the diagnostic modalities that are used to specifically evaluate pancreatic structure, function and pathology.

SIGNALMENT AND RISK FACTORS

Dogs and cats of any age, breed or sex can develop pancreatitis. Certain age groups and breeds might be predisposed. Most dogs and cats that are presented with pancreatitis are middle aged to old (usually >5 years of age), although the age range is from a few months to >15 years (Akol *et al.* 1993, Cook *et al.* 1993, Hess *et al.* 1998, Ferreri *et al.* 2003, Watson *et al.* 2010). With regard to breed predisposition, differences likely exist in different geographic regions. Miniature schnauzers and terrier breeds (especially Yorkshire terriers) are considered to be at increased risk mainly in the USA (Cook *et al.* 1993, Hess *et al.* 1998, Lem *et al.* 2008). Cocker spaniels, Cavalier King Charles spaniels, Border collies and boxers have been reported to be at increased risk for chronic pancreatitis in the UK (Watson *et al.* 2007). No significant breed predisposition has been identified in cats (Akol *et al.* 1993, Hill & Van Winkle 1993, Ferreri *et al.* 2003, De Cock *et al.* 2007).

In the majority of cases, pancreatitis is considered idiopathic in both dogs and cats. However, several pathological conditions (e.g. hypertriglyceridaemia, endocrine disease, adverse drug reactions, prior surgery, infections and dietary factors) have all been identified as potential risk factors for pancreatitis in dogs, while in cats risk factors are even less clear. Although a cause-and-effect relationship has not been established for most of those factors, their presence along with compatible clinical signs should raise the suspicion for pancreatitis. The pathophysiology, causes and risk factors for pancreatitis are discussed elsewhere in this issue as well as in other recent publications (Mansfield 2012a,b, Watson 2012, Xenoulis & Steiner 2013).

CLINICAL SIGNS AND PHYSICAL EXAMINATION FINDINGS

The perception of the clinical presentation of dogs and cats with pancreatitis has changed dramatically over the last decade. It is now widely accepted that the clinical presentation of dogs and cats with pancreatitis varies greatly. There is mounting evidence that many dogs and cats with pancreatitis, especially chronic pancreatitis, have subclinical disease, whereas others might only display mild and non-specific clinical signs such as intermittent anorexia and weakness with no gastrointestinal signs. Diagnosis of pancreatitis is often missed in those animals mainly due to low level of suspicion for the disease. On the other hand, dogs and cats with severe acute pancreatitis might be presented with cardiovascular shock, disseminated intravascular coagulation (DIC) or multi-organ failure and die within hours of the development of clinical signs.

There is no single clinical sign or combination of clinical signs that is pathognomonic for pancreatitis in dogs. Dogs with severe acute pancreatitis are typically presented with an acute onset of anorexia, weakness, vomiting, diarrhoea and/or abdominal pain (Hess *et al.* 1998, Weatherton & Streeter 2009). Dogs may display one or more of these clinical signs and in various combinations. Dehydration, abdominal pain, icterus, fever or hypothermia, bleeding diathesis or ascites may be identified in some dogs on physical examination (Hess *et al.* 1998). Severe systemic complications (e.g. cardiovascular shock, DIC or multi-organ failure) might occur in patients with severe pancreatitis (Ruaux 2000, Weatherton & Streeter 2009). Dogs with chronic pancreatitis are typically presented with intermittent clinical signs that are less specific and milder than those of dogs with acute pancreatitis. These usually include anorexia and weakness, while sometimes weight loss, vomiting, diarrhoea or abdominal pain may also be present (Watson *et al.* 2010, Bostrom *et al.* 2013). It is important to note that additional clinical signs are often present as a consequence of concurrent or complicating diseases (e.g. polyuria/polydipsia in animals with diabetes mellitus or polyphagia and weight loss in dogs with exocrine pancreatic insufficiency) (Hess *et al.* 1998, Watson *et al.* 2010, Bostrom *et al.* 2013). This is of particular importance especially in dogs with mild or chronic pancreatitis because clinical signs caused by pancreatitis *per se* are often subtle or absent, while clinical signs of concurrent diseases predominate and may mislead the clinician.

Clinical signs in cats with pancreatitis are similar to those described in dogs. An important difference is that the majority of cats with pancreatitis are presented for anorexia and/or lethargy. Gastrointestinal clinical signs are seen less commonly and include vomiting, weight loss and diarrhoea (Akol *et al.* 1993, Hill & Van Winkle 1993, Kimmel *et al.* 2001). The most common physical examination findings include dehydration, pallor and icterus. Tachypnoea and/or dyspnoea, hypothermia or fever, tachycardia, signs of abdominal pain and a palpable abdominal mass may also be noted (Akol *et al.* 1993, Hill & Van Winkle 1993, Kimmel *et al.* 2001). Similar to dogs, severe systemic complications (e.g. DIC, pulmonary thromboembolism, cardiovascular shock and multi-organ failure) may occasionally be seen in cats with severe pancreatitis (Schermerhorn *et al.* 2004).

ROUTINE CLINICAL PATHOLOGY

Results of complete blood count (CBC), serum biochemistry profile and urinalysis in dogs and cats with pancreatitis are non-specific and therefore non-diagnostic. However, these tests should always be performed in animals with suspected pancreatitis because they are useful for the diagnosis or exclusion of other diseases, and also give important information about the general condition of the patient. In addition, routine clinical pathology may help estimate the severity of pancreatitis to determine the optimal therapeutic plan for each individual patient.

The results of the CBC, serum biochemistry profile and urinalysis are often within normal limits in dogs and cats with pancreatitis, especially in mild cases. On the other hand, animals with pancreatitis can be presented with almost any kind of haematological abnormality, including anaemia or haemoconcentration, leukocytosis or leucopenia and thrombocytopenia (Akol *et al.* 1993, Hill & Van Winkle 1993, Hess *et al.* 1998, Kimmel *et al.* 2001, Ferreri *et al.* 2003). Clinicopathological abnormalities, when present, are variable and unpredictable (Akol *et al.* 1993,

Hill & Van Winkle 1993, Hess *et al.* 1998, Kimmel *et al.* 2001, Ferreri *et al.* 2003, Son *et al.* 2010). Different combinations of increases in liver enzyme activities and hyperbilirubinaemia are common and therefore, when present, should raise the suspicion for pancreatitis. In some cases, these findings might be associated with extrahepatic biliary tract obstruction (Mayhew *et al.* 2002, 2006, Son *et al.* 2010). In cats, they might also be associated with concurrent cholangitis or hepatic lipidosis. Increases in serum creatinine and blood urea nitrogen (BUN) concentrations are variably present and most often associated with dehydration due to vomiting, diarrhoea and/or decreased water intake. In severe cases, azotaemia might be the result of concurrent renal failure. Other possible findings include hypoalbuminaemia, hypertriglyceridaemia, hypercholesterolaemia and hyperglycaemia or hypoglycaemia. Electrolyte abnormalities are commonly present and variable, with hypokalaemia, hypochloraemia and hyponatraemia being the most common. Hypocalcaemia might also be present and it is seen more commonly in cats than in dogs (Kimmel *et al.* 2001). Evidence of coagulopathy, such as prolonged activated clotting time (ACT) and prothrombin (PT) and partial thromboplastin (PTT) times, is seen in some cases, and may or may not be associated with spontaneous bleeding. In other cases, there might be evidence suggestive of DIC, such as thrombocytopenia, prolongation of clotting times (ACT, PT, PTT) and a positive d-dimer test.

Serum tests for pancreatic function and pathology

The search for a sensitive and specific serum test for pancreatitis started over 5 decades ago. Several serum tests have been developed and evaluated since then, but most have shown no or only limited usefulness for the diagnosis of pancreatitis in dogs and cats. It needs to be mentioned that the evaluation of the diagnostic accuracy of new diagnostic tests is always predicated upon having an acceptable gold standard. Although histopathology of the pancreas is often used as a gold standard for the diagnosis of canine and feline pancreatitis, it cannot be considered an ideal gold standard (see section on histopathology) (Xenoulis & Steiner 2012). Therefore, the results of the studies discussed in the following sections should be interpreted with caution and the understanding that they rely upon an imperfect gold standard. It also needs to be mentioned that it is particularly difficult to determine a single number that corresponds to the exact sensitivity of a diagnostic test for pancreatitis, because this varies depending upon several factors, including the type of study, the criteria for pancreatitis used (i.e. based on histopathological confirmation, ultrasonographic findings, or overall clinical information available), the type of pancreatitis (i.e. acute or chronic, mild or severe), the cut-off values used, etc. Therefore, direct comparison of the results among different studies is often challenging. Table 1 provides an overview of selected studies evaluating the sensitivity and/or specificity of different laboratory tests for the diagnosis of pancreatitis in dogs and cats.

Pancreatic lipase immunoreactivity (PLI) assays

The PLI assays are currently considered the most sensitive and specific serum tests for the diagnosis of pancreatitis in both dogs and cats. The advantages of the PLI assays over the traditional lipase activity assays rely on two facts: (1) pancreatic lipase is exclusively of pancreatic origin and (2) in contrast to the traditional activity assays for lipase, which indiscriminately measure the activities of lipases of multiple origins origin, immunoassays used to measure pancreatic lipase concentration in serum (i.e. the PLI assays) quantify exclusively lipase of pancreatic origin based on its unique structure (Steiner 2000, Steiner *et al.* 2002, 2006, Hoffmann 2008, Neilson-Carley *et al.* 2011). Therefore, the PLI assays have inherent advantages over the traditional serum lipase activity assays that make them more suitable for specific evaluation of the exocrine pancreas in dogs and cats.

The originally developed and analytically validated immunoassays for the specific measurement of serum pancreatic lipase in dogs (canine PLI) and cats (feline PLI) (Steiner *et al.* 2003, 2004, Steiner & Williams 2003) have been replaced by more widely available immunoassays (Spec cPL® for dogs and Spec fPL® for cats) that demonstrate a similar clinical performance with the original PLI assays (Steiner *et al.* 2008, Huth *et al.* 2010). The reference interval for Spec cPL is 0 to 200 µg/L and for Spec fPL 0 to 3·5 µg/L. Both assays incorporate a gray zone in the interpretation of the results (201 to 399 µg/L for Spec cPL and 3·6 to 5·3 µg/L for Spec fPL); values in the gray zone are non-diagnostic and further testing or retesting is recommended. Concentrations ≥400 µg/L (Spec cPL) or ≥5·4 µg/L (Spec fPL) are considered highly suggestive of pancreatitis. It needs to be mentioned that the implementation of cut-off values for the Spec PL assays was originally somewhat arbitrary but these cut-off values have now been used in several studies and are considered clinically useful.

Canine PLI: Both clinical (McCord *et al.* 2012) and histopathological (Steiner *et al.* 2008, Watson *et al.* 2010, Trivedi *et al.* 2011) studies on the sensitivity of cPLI for canine pancreatitis have been published and all generally agree that serum cPLI is the most sensitive and specific serum marker for pancreatitis in dogs (Table 1). In the only multi-institutional clinical study on the sensitivity of serum cPLI (Spec cPL) currently available that included 84 dogs, the sensitivity of cPLI was reported to range between 72 and 78% (McCord *et al.* 2012). Three necropsy studies have also determined the sensitivity of cPLI (Steiner *et al.* 2008, Watson *et al.* 2010, Trivedi *et al.* 2011). However, it is more challenging to accurately interpret and determine the clinical significance of the results of those studies, because the diagnosis of pancreatitis was primarily based on histopathological criteria. Therefore, clinically healthy dogs with histopathological lesions of the pancreas but clinically insignificant disease were also included in those studies (Steiner *et al.* 2008, Trivedi *et al.* 2011). It is of note that in the most recent of those studies (Trivedi *et al.* 2011), in which 70 dogs euthanased for a variety of reasons were examined, 56 (89%) of 63 dogs that had histopathological evidence of pancreatitis had only mild lesions. In these three necropsy studies, the sensitivity of cPLI ranged from 21% for mild (and most likely clinically insignificant) pancreatitis to 71% for histopathologically moderate to severe pancreatitis (Table 1). The wide overall range of sensitivities reported for cPLI (21 to 78%) is also seen with other markers for pancreatitis and

Table 1. Selected studies evaluating the sensitivity and/or specificity of different laboratory tests for the diagnosis of pancreatitis in dogs and cats

Study	Species	Number of animals	Gold standard	Spec PL		Lipase		Amylase		TLI	
				Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
Steiner *et al.* (2008)	Canine	22	Pathologic findings	64/73	–	14/32	–	18/41	–	36	–
Watson *et al.* (2010)	Canine	14	Histopathology	26/58	–	28/44	–	14/67	–	17	–
Trivedi *et al.* (2011)	Canine	70	Histopathology – mild pancreatitis	21/43	100/86	54	43	7	100	30	100
			Moderate/severe pancreatitis	71/71		71		14		29	
Neilson-Carley *et al.* (2011)	Canine	40	Histopathology	–	98/95	–	–	–	–	–	–
McCord *et al.* (2012)	Canine	84	Clinical criteria	72 to 78/87 to 94	81 to 88/66 to 77	52 to 56	77 to 81	43 to 54	89 to 93	–	–
Mansfield *et al.* (2012)	Canine	32	Histopathology	33/58	90/80	–	–	–	–	–	–
Forman *et al.* (2004)	Feline	29	Histopathology – mild pancreatitis	54	67 to 100%	–	–	–	–	8%	75 to 100%
			Moderate/severe pancreatitis	100		–	–	–	–	80	
Forman *et al.* (2009)	Feline	182	Clinical criteria	79	82	–	–	–	–	–	–

PL Pancreatic lipase, TLI Trypsin-like immunoreactivity
Spec cPL: Whenever two values are separated by a slash, the first value represents the cut-off for pancreatitis (200 for cPLI and 400 for Spec cPL) and the second value represents the upper limit of the reference interval (102.1 for cPLI and 200 for Spec cPL)
Amylase and lipase: Whenever two values are separated by a slash, the first value represents a suggested cut-off for pancreatitis that is three times the upper limit of the reference interval and the second value represents the upper limit of the reference interval

reflects the inherent differences in the study design, the methodology and the dog population used in each study. However, in the above-mentioned studies, cPLI consistently showed the best performance (sensitivity and specificity) compared with other serum markers evaluated (Steiner *et al*. 2008, Watson *et al*. 2010, Trivedi *et al*. 2011, McCord *et al*. 2012).

Based on some evidence from recent studies (Steiner *et al*. 2008, Watson *et al*. 2010, Trivedi *et al*. 2011) and the fact that histopathological lesions associated with chronic pancreatitis such as pancreatic fibrosis and atrophy are not expected to be associated with leakage of pancreatic enzymes (Neilson-Carley *et al*. 2011), the sensitivity of cPLI is believed to be lower for chronic pancreatitis than for acute pancreatitis. In one study of 14 dogs with chronic pancreatitis (Watson *et al*. 2010), the sensitivity of cPLI ranged between 26 and 58% (depending on the cut-off value), further supporting this hypothesis. However, the clinical significance of chronic pancreatitis in those cases is questionable as the majority of dogs had concurrent diseases and were evaluated for reasons that were likely unrelated to clinical disease resulting from chronic pancreatitis.

Similar to its sensitivity, serum cPLI is considered to have the highest specificity for pancreatitis compared with any other serum test currently available, with specificities ranging between 81 and 100% (Strombeck *et al*. 1981, Simpson *et al*. 1989, Mansfield & Jones 2000a, Steiner *et al*. 2001b, 2009, Neilson-Carley *et al*. 2011, Trivedi *et al*. 2011, Mansfield *et al*. 2012, McCord *et al*. 2012). In the multi-institutional clinical study mentioned earlier, the specificity of this assay in a cohort of dogs with a clinical presentation consistent with pancreatitis was reported to range between 81 and 88% (McCord *et al*. 2012). However, this study may have underestimated specificity because a result was judged to be false positive if there were no other clinical supporting data available, yet histopathology of multiple sections of the pancreas was not available. In two necropsy studies that included dogs that died or were euthanased for a variety of reasons and had a normal pancreas on histopathology, serum Spec cPL showed a specificity of 100% (Trivedi *et al*. 2011) and 90% (Mansfield *et al*. 2012) using the recommended cut-off of 400 µg/L. In another necropsy study, in which 40 dogs were euthanased for a variety of reasons and had a normal pancreas on histopathology, the specificity of Spec cPL using the recommended cut-off of 400 µg/L was 98% (Neilson-Carley *et al*. 2011). It is important to note, however, that dogs included in the above-mentioned necropsy studies did not all have clinical signs of or a clinical suspicion for pancreatitis, and therefore, many of these dogs would not normally undergo diagnostic testing for pancreatitis. In another study of 25 dogs with clinical signs compatible with pancreatitis (i.e. vomiting) that ended up having gastritis, only 1 dog had a possible false positive result, suggesting a specificity of 96% (Steiner 2000). Experimentally induced chronic renal failure (Steiner *et al*. 2001b) and long-term prednisone administration (Steiner *et al*. 2009) were not found to have any clinically significant effect on serum cPLI concentration. Similarly, pancreatic sampling by ultrasound-guided fine-needle aspiration (FNA) or surgical biopsy did not cause any increase in serum cPLI concentrations in healthy dogs (Cordner *et al*. 2010). It remains to be determined whether pancreatic sampling of a diseased pancreas would also have no effect and it is currently recommended that determination of serum cPLI concentration is best performed before sampling of pancreatic tissue. Finally, there have been anecdotal concerns that high cPLI concentrations might occasionally be associated with pancreatic inflammation that is not clinically important or in cases where pancreatitis is not the problem of primary clinical significance (e.g. when a foreign body is present in the proximal small intestine). Therefore, it remains to be determined whether serum cPLI concentration can detect histopathologically mild pancreatitis that might be of minor clinical importance. In either case, a final diagnosis of pancreatitis should ideally not be based solely on the results of PLI, but rather, on a careful consideration of the general clinical and clinicopathological picture of the animal and the results of ultrasonography, pancreatic cytology or histopathology.

Canine SNAP PL: A rapid, in-clinic, semi-quantitative, visually read test for the estimation of canine pancreatic lipase in serum has recently been developed (Beall *et al*. 2011). This test incorporates a reference spot that corresponds to the upper limit of the reference interval and a sample spot that is visually compared with the reference spot (Beall *et al*. 2011). Therefore, the results of this rapid assay are considered either normal (less intense than the reference spot) or abnormal (equally to or more intense than the reference spot). In the latter case, the actual PLI concentration may be in the gray zone (200 to 400 µg/L) or consistent with the diagnosis of pancreatitis (>400 µg/L for Spec cPL) (Beall *et al*. 2011). This cannot be determined with certainty, however, using the in-clinic assay and further testing using the quantitative reference method is recommended.

A recent validation study showed that there is a 90 to 100% agreement between the SNAP cPL and the reference Spec cPL (Beall *et al*. 2011). A recent multi-institutional study reported that SNAP cPL has a sensitivity between 91 and 94% and a specificity between 71 and 78% for pancreatitis (McCord *et al*. 2012). However, the main use of this diagnostic tool is to rule-out pancreatitis (i.e. a normal result makes diagnosis of pancreatitis very unlikely) and therefore, the sensitivity of this test is more important than its specificity. Abnormal results could be seen in a dog with a Spec cPL concentration in the gray zone or consistent with the diagnosis of pancreatitis and further testing using the quantitative Spec cPL assay would be necessary in such cases. Diagnosis of pancreatitis cannot be based on the result of the SNAP cPL alone.

Feline PLI: Studies in cats with both experimental and spontaneous pancreatitis have repeatedly shown that serum fPLI concentration is the most sensitive and specific serum marker for feline pancreatitis currently available (Parent *et al*. 1995, Swift *et al*. 2000, Gerhardt *et al*. 2001, Forman *et al*. 2004, Allen *et al*. 2006, Zavros *et al*. 2008, Forman *et al*. 2009). In a recent clinical study in abstract form that included 182 cats, the sensitivity of serum Spec fPL concentration was reported at 79% (Forman *et al*. 2009). In another study that included primarily cats with chronic pancreatitis that also had an acute histopathological

component, serum fPLI was found to be 100% sensitive for histopathologically moderate to severe pancreatitis (Forman *et al.* 2004). In the same study, the sensitivity of fPLI was 54% for histopathologically mild pancreatitis, with an overall sensitivity of 67%. For comparison, the overall sensitivity of fTLI in the same study was only 28%. Similar to dogs, histopathological lesions associated with chronic pancreatitis such as pancreatic fibrosis and atrophy are not expected to be associated with leakage of pancreatic enzymes, and therefore, the sensitivity of fPLI is believed to be lower for chronic pancreatitis (without a concurrent acute pancreatitis) than for acute pancreatitis. Therefore, as in dogs, false negative results cannot be excluded especially in cats with chronic or mild pancreatitis. However, the clinical significance of mild chronic pancreatitis remains to be determined.

Similar to its sensitivity, the specificity of serum fPLI concentration for feline pancreatitis is very high, ranging between 67 and 100% (Forman *et al.* 2004, 2009). In a large clinical study in abstract form that included 182 cats, the specificity of fPLI was 82% (Forman *et al.* 2009). In another study also in abstract form, azotaemia as a result of experimentally induced chronic renal failure did not have any clinically significant effect on serum fPLI concentrations (Xenoulis *et al.* 2009). Similar to dogs, laparoscopic pancreatic biopsy in healthy cats did not have any significant effect on serum fPLI concentrations (Cosford *et al.* 2010). It is unknown whether pancreatic biopsy of an inflamed pancreas would lead to an increase of serum fPLI concentration. Finally, in a recent study, endoscopic retrograde cholangiopancreatography (ERCP) was found to cause temporary increases in serum fPLI concentrations in some of the cats studied but without any clinical sings (Spillmann *et al.* 2013). The clinical significance of these findings remains to be determined.

Feline SNAP PL: The SNAP fPL test has recently been released and is based on the same principles as the canine SNAP cPL test (see preceding text). Although studies on the validation and clinical performance characteristics for the diagnosis of pancreatitis of the SNAP fPL have not been reported in the literature yet, the manufacturer indicates that this test has an 82 to 92% agreement with the Spec fPL assay. Therefore, the sensitivity of the SNAP fPL should theoretically be high and similar to the one reported for Spec fPL (see preceding text). Consequently, a normal SNAP fPL result is a good indicator that pancreatitis is unlikely. However, abnormal results could be in the gray zone or consistent with the diagnosis of pancreatitis and further testing using the quantitative Spec fPL assay is necessary. As in dogs, diagnosis of pancreatitis cannot be based on the results of the SNAP fPL alone.

Trypsin-like immunoreactivity (TLI)

TLI assays are immunoassays that measure trypsinogen and, to a lesser degree, trypsin concentrations in serum and have been shown to be of limited usefulness for the diagnosis of canine and feline pancreatitis. Serum canine TLI (cTLI) concentrations increase after experimental induction of pancreatitis in dogs, but decrease to concentrations within the reference interval as early as 3 days after induction of pancreatitis in some dogs (Simpson *et al.* 1989). In addition, cTLI has been shown to increase significantly after ERCP, but this increase in transient and is not associated with clinical evidence of acute pancreatitis (Spillmann *et al.* 2004). The sensitivity of serum cTLI for the diagnosis of spontaneous pancreatitis is low (36 to 47%), possibly due to the short half-life of trypsinogen in serum (Mansfield & Jones 2000a, Steiner *et al.* 2001a, 2008). In addition, although there is strong evidence that trypsinogen is exclusively of pancreatic origin (Simpson *et al.* 1991), it is cleared by glomerular filtration, and serum cTLI concentration can be increased in dogs with renal failure (Simpson *et al.* 1989, Mansfield & Jones 2000a). This clearly affects the specificity of the test and complicates the interpretation of increased cTLI concentrations in dogs with azotaemia (which is not uncommon in dogs with pancreatitis). A clearly increased serum cTLI concentration in a dog that is not azotaemic is indicative of pancreatitis. However, pancreatitis cannot be excluded on the basis of a normal serum cTLI concentration within the reference interval.

In cats with experimentally induced pancreatitis, feline TLI (fTLI) concentration increases sharply after induction of pancreatitis, but returns below the cut-off value within 48 hours (Zavros *et al.* 2008). Feline TLI has been evaluated for the diagnosis of spontaneous pancreatitis in cats and several cut-off values have been suggested (Swift *et al.* 2000, Gerhardt *et al.* 2001, Allen *et al.* 2006). When cut-off values allowing adequate specificity of the assay are used (i.e. 100 µg/L), the sensitivity of fTLI for the diagnosis of pancreatitis in cats is suboptimal (28 to 64%). In addition, the specificity of fTLI has been questioned, because mildly increased serum fTLI concentrations have been reported in cats with no demonstrable pancreatic disease (although focal lesions might have been missed on pancreatic biopsy) but had other gastrointestinal disorders [e.g. inflammatory bowel disease (IBD) or gastrointestinal lymphoma] or azotaemia (Swift *et al.* 2000, Simpson *et al.* 2001, Allen *et al.* 2006). Similar to dogs, a clearly increased serum fTLI concentration in a cat that is not azotaemic is indicative of pancreatitis. However, pancreatitis cannot be excluded on the basis of a normal serum fTLI concentration.

Serum amylase and lipase activities

Serum amylase and lipase activities have long been considered markers for pancreatitis in dogs (Strombeck *et al.* 1981, Jacobs *et al.* 1985). Although serum activities of these two enzymes increase during experimental canine pancreatitis, several studies have shown that these markers, when measured with the traditional methods, are not useful and should not be used for the diagnosis of spontaneous canine pancreatitis due to their low sensitivity and specificity (Brobst *et al.* 1970, Mia *et al.* 1978, Strombeck *et al.* 1981, Jacobs *et al.* 1985, Simpson *et al.* 1989, 1991, Steiner *et al.* 2008). Many tissues other than the pancreas (e.g. gastric mucosa, hepatic parenchyma and many others) synthesise amylases and lipases (Simpson *et al.* 1991, Steiner *et al.* 2006). This leads to the establishment of wide reference intervals for amylase and lipase activity assays that are at least partially associated with the low sensitivity of those assays for pancreatitis. Furthermore, traditional catalytic assays are not able

to differentiate amylases and lipases according to their tissue of origin. Specifically for amylase, it is not even certain that organ-specific isoenzymes exist in dogs and cats (Williams 1996). This leads to a low specificity of serum amylase and lipase activities for pancreatitis (Strombeck *et al.* 1981, Mansfield & Jones 2000a).

In one study, approximately 50% of dogs with an increased serum activity of either amylase or lipase did not have pancreatitis based on histopathological examination of the pancreas (Strombeck *et al.* 1981). In another more recent study that investigated the specificity and sensitivity of a new serum lipase activity assay, the specificity was similar (53%) (Graca *et al.* 2005). The main non-pancreatic conditions associated with increased serum amylase and/or lipase activities include renal, hepatic, intestinal, and neoplastic diseases, as well as corticosteroid administration (only for lipase activity). It has been suggested that only increases of amylase and lipase activities of more than three to five times the upper limit of the reference interval should be considered suggestive of pancreatitis in dogs, in order to increase the specificity of these assays (Williams 1996, Steiner 2003). However, it has been shown that such increases can result from non-pancreatic disorders (Strombeck *et al.* 1981, Polzin *et al.* 1983, Williams 1996, Mansfield & Jones 2000a). Therefore, increased serum amylase and/or lipase activities do not confirm the presence of pancreatitis and more specific tests need to be utilised. The sensitivity of serum amylase and lipase activities for spontaneous canine pancreatitis varies but is generally low (32 to 73% for lipase activity and 41 to 69% for amylase activity) and it is even lower when a cut-off value of three or five times the upper limit of the respective reference interval is used (14% for lipase activity and 18% for amylase activity in one study) (Hess *et al.* 1998, Steiner *et al.* 2001a, 2008). Thus, many dogs with pancreatitis may have serum activities of these enzymes within the reference interval and, therefore, serum amylase and/or lipase activities within the reference interval cannot rule out pancreatitis (Strombeck *et al.* 1981, Hess *et al.* 1998).

Serum lipase activity increases and serum amylase activity decreases in experimentally induced acute pancreatitis in cats (Kitchell *et al.* 1986, Karanjia *et al.* 1990, Zavros *et al.* 2008). Although well-designed clinical studies are lacking, both serum lipase and amylase activities do not appear to be of any clinical value in the diagnosis of spontaneous feline pancreatitis (Hill & Van Winkle 1993, Simpson *et al.* 1994, Parent *et al.* 1995). Therefore, these two tests are not recommended for the diagnosis of pancreatitis in cats (Hill & Van Winkle 1993, Simpson *et al.* 1994).

Recently, a new lipase activity assay (DGGR) using the substrate 1,2-*o*-dilauryl-rac-glycero glutaric acid-(6′methyl resorufin)-ester was validated for use in dogs (Graca *et al.* 2005). A more recent study has evaluated the use of the DGGR lipase activity assay for the diagnosis of pancreatitis in cats and has found that, when specific cut-offs are used, there is substantial agreement between this assay and the Spec fPL assay (Oppliger *et al.* 2013). Specifically, in this study of 250 cats, the best agreement (κ=0·755) was found for a cut-off of DGGR lipase of >34 U/L. A similar study in 142 dogs also found high agreement between the DGGR lipase assay and the Spec cPL assay, with the best agreement (κ=0.80) for a cut-off of DGGR lipase of >216 U/L (Kook *et al.* 2014). Based on these initial results, the DGGR lipase activity assay shows promise as a test to aid in diagnosis of feline and canine pancreatitis. However, more studies are necessary in different populations of cats and dogs comparing the specificity and sensitivity of the DGGR lipase assay to other tests used for the diagnosis of pancreatitis.

Other diagnostic markers

Several other diagnostic markers for pancreatitis have been developed and studied, but none of those can currently be recommended for the routine diagnosis of canine and feline pancreatitis in clinical practice, either because their diagnostic performance has not been sufficiently evaluated clinically or because they have been shown to have a low sensitivity and/or specificity. In addition, the availability of most of these diagnostic tests is currently limited. Such tests include serum concentrations of pancreatic elastase-1 (Mansfield *et al.* 2011), phospholipase A2 (Westermarck & Rimaila-Pärnänen 1983), trypsin-α_1-anti-trypsin complexes (Suchodolski *et al.* 2001, Steiner *et al.* 2008), α_2-macroglobulin (Ruaux *et al.* 1999), plasma and urine concentrations of trypsinogen activation peptide (TAP) (Mansfield & Jones 2000a,b, Mansfield *et al.* 2003, Allen *et al.* 2006) and lipase activity in peritoneal fluid (De Arespacochaga *et al.* 2006). Of these markers, serum pancreatic elastase-1 and TAP concentrations seem to hold some promise and might prove helpful for the diagnosis or the assessment of severity of pancreatitis in the future.

DIAGNOSTIC IMAGING

Abdominal radiography

Abdominal radiography is of no value for the diagnosis of canine and feline pancreatitis because, in the majority of cases, abdominal radiographs are normal or only show non-specific findings (Gibbs *et al.* 1972, Suter & Lowe 1972, Akol *et al.* 1993, Hill & Van Winkle 1993, Hess *et al.* 1998, Gerhardt *et al.* 2001, Ferreri *et al.* 2003). In a group of 70 dogs with fatal acute pancreatitis, the sensitivity of abdominal radiography for pancreatitis was only 24% (Hess *et al.* 1998). In addition, radiographic abnormalities observed in dogs and cats with pancreatitis can be present in other conditions and are therefore non-specific for pancreatitis. Such findings include an increased soft tissue opacity and decreased serosal detail in the cranial right abdomen, displacement of the stomach and/or duodenum from their normal positions, gaseous dilation of bowel loops adjacent to the pancreas and abdominal effusion (Gibbs *et al.* 1972, Suter & Lowe 1972, Hill & Van Winkle 1993, Hess *et al.* 1998, Gerhardt *et al.* 2001, Saunders *et al.* 2002, Ferreri *et al.* 2003). When pancreatitis is in the list of differential diagnoses, radiography should always be followed up by more sensitive and specific serum tests and/or imaging methods in order to confidently diagnose or rule out pancreatitis. However, radiography remains a logical initial approach for patients suspected of having pancreatitis because it is relatively inexpensive and useful for the diagnosis and/or to rule out other diseases that cause similar clinical sings.

Abdominal ultrasound

Abdominal ultrasound is considered the imaging method of choice for the diagnosis of pancreatitis in dogs and cats. Furthermore, abdominal ultrasound is helpful for the diagnosis or rule out of other diseases that cause similar clinical sings. There is only a limited number of studies that have systematically evaluated the performance of abdominal ultrasonography for the diagnosis of pancreatitis in dogs and cats, and most of these studies are more than a decade old. Since then, there have been significant advances in both the quality of the equipment and the expertise of the radiologists, and the level of suspicion for canine and feline pancreatitis in small animal medicine has increased. Therefore, the performance of ultrasonography is expected to have improved since the original reports were published. However, although abdominal ultrasound is considered to be both relatively sensitive and specific for the diagnosis of canine and feline pancreatitis, its exact sensitivity and specificity is largely unknown. When interpreting the results of studies investigating the clinical performance of abdominal ultrasound for the diagnosis of pancreatitis, it is important to realise that abdominal ultrasonography is typically evaluated based upon an imperfect gold standard (i.e. histopathology).

It is of utmost significance to underline the fact that the performance of abdominal ultrasonography in the diagnosis of pancreatitis is highly dependent on the expertise of the ultrasonographer and the quality of the equipment used. In most reported studies, abdominal ultrasonography has been performed at teaching hospitals by board certified radiologists, and therefore, the performance of abdominal ultrasound for pancreatitis is expected to be considerably lower when less experienced clinicians are performing the ultrasound examination and the equipment used is of lower quality. In addition, the lack of standardised criteria for the ultrasonographic evaluation of the pancreas in dogs and cats leads to great variation in the interpretation of imaging results even among radiologists and makes the need for specialised ultrasonographers even greater.

The sensitivity of abdominal ultrasound has been reported to be about 68% in dogs with severe acute pancreatitis (Hess *et al.* 1998) and between 11 and 67% in cats with pancreatitis (Swift *et al.* 2000, Saunders *et al.* 2002, Ferreri *et al.* 2003, Forman *et al.* 2004). This high range of sensitivities likely reflects differences in the level of suspicion or the skills of the ultrasonographer, the equipment used and the severity of lesions and highlights the lack of standardised diagnostic criteria. The sensitivity of abdominal ultrasound reported in the earlier studies indicates that a normal pancreas on ultrasound examination is not sufficient to rule out pancreatitis in either dogs or cats. This is particularly true in cases of chronic or mild pancreatitis, where pancreatic changes are mild and often not detected during ultrasound examination. In one study in a small number of dogs with chronic pancreatitis, finding any change in the pancreas on ultrasound examination led to a sensitivity of only 56% (Watson *et al.* 2010).

The specificity of abdominal ultrasound for canine and feline pancreatitis has been traditionally thought to be relatively high, although this has not been systematically investigated in well-designed studies. Other diseases of the pancreas (e.g. neoplasia, hyperplastic nodules, oedema due to portal hypertension or hypoalbuminaemia) may display similar ultrasonographic findings and cannot be differentiated from pancreatitis in many cases (Lamb *et al.* 1995, Lamb 1999a, Hecht & Henry 2007, Hecht *et al.* 2007). In a recent study where ultrasonography was performed in 26 dogs and cats with suspected gastrointestinal disease, 6 (23.1%) of the animals had ultrasonographic evidence consistent with pancreatitis, while histopathology revealed either a normal pancreas or pancreatic hyperplasia (Webb & Trott 2008). In the same study, there was only a 22 and 33% agreement between the ultrasound report and pancreatic histopathology in dogs and cats, respectively. These data raise concerns regarding the accuracy of ultrasonography in evaluating the pancreas and underscore the importance of not overinterpreting ultrasonographic findings. However, the findings of this particular study should be evaluated with caution because pancreatic lesions suggestive of pancreatitis might have been missed on histopathology. In another more recent study, a significant agreement existed between the use of serum fPLI concentration and abdominal ultrasonography for the diagnosis of traumatic pancreatitis in a group of cats with high-rise syndrome (Zimmermann *et al.* 2013). Finally, another recent study of a group of cats with pancreatitis that used serum fPLI as the standard for diagnosis of pancreatitis showed that pancreatic ultrasonography had a sensitivity of 84% and a specificity of 75% for diagnosing pancreatitis (Williams *et al.* 2013). Specific ultrasonographic changes (such as peripancreatic fat echogenicity, pancreatic thickness, pancreatic margins) were evaluated in that study and the usefulness of each one of those findings described.

Ultrasonographic findings in dogs and cats with pancreatitis include hypoechoic areas within the pancreas (possibly indicating necrosis or fluid accumulation), increased echogenicity of the surrounding mesentery (due to necrosis of the peripancreatic fat), enlargement and/or irregularity of the pancreas, dilation of the pancreatic or biliary duct and abdominal effusion (Fig 1) (Hess *et al.* 1998, Lamb 1999b, Swift *et al.* 2000, Saunders *et al.* 2002, Ferreri *et al.* 2003, Hecht & Henry 2007). Specifically in cats, it was suggested that the presence of a thick left limb of the pancreas, severely irregular pancreatic margins and hyperechoic peripancreatic fat in cats with appropriate clinical signs and increased serum fPLI concentrations are highly supportive of pancreatitis (Williams *et al.* 2013). On occasion, hyperechoic areas of the pancreas can be identified, possibly indicating the presence of pancreatic fibrosis. Cavitary lesions, a thickened duodenum, biliary obstruction or mass-like lesions might also be noted (Hecht & Henry 2007). It has been suggested that a dilation of the pancreatic duct is suggestive of pancreatitis in cats, but recent studies have not confirmed this hypothesis (Hecht *et al.* 2006).

Other imaging modalities

Contrast-enhanced computed tomography (CECT) is an extremely valuable tool for the evaluation of human patients with suspected pancreatitis (Bollen 2012). The computed tomographic anatomy of the canine pancreas has been described (Probst & Kneissl 2001) but, the usefulness of computed tomography for the diagnosis of pancreatitis in dogs has not been thoroughly

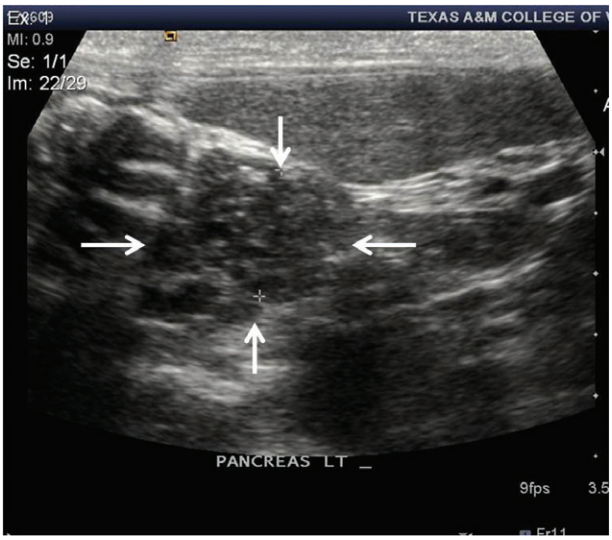

FIG 1. Ultrasonographic appearance of the pancreas of a cat with pancreatitis. The pancreas is enlarged and appears heterogeneous, with hypoechoic areas and hyperechoic surrounding fat. These findings are highly suggestive of pancreatitis (Courtesy of Dr. B. Young, Texas A&M University). Reprinted from Reference, Xenoulis P.G. & Steiner J.M. (2013) with permission from Elsevier

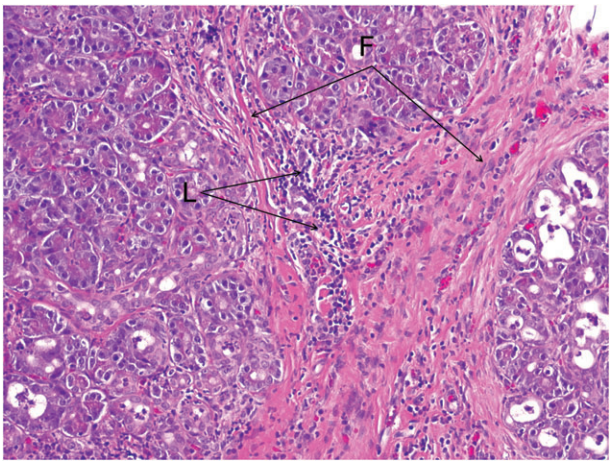

FIG 2. Histopathological appearance of the pancreas of a cat with chronic pancreatitis. There is extensive fibrosis (F) and lymphocytic infiltration (L). Haematoxylin and eosin; magnification: 200×

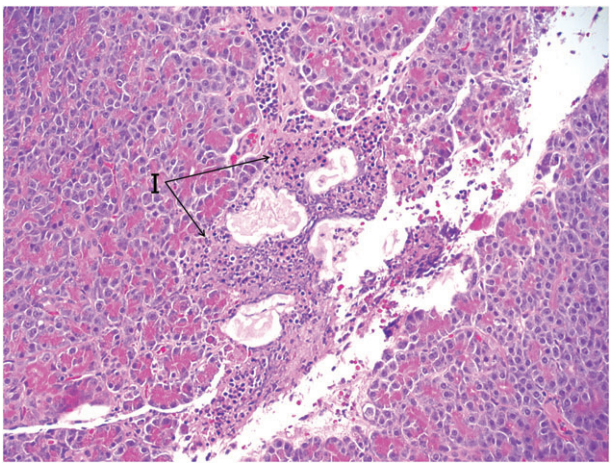

FIG 3. Histopathological appearance of the pancreas of a cat with acute pancreatitis. There are areas of inflammatory infiltration (I) but there is no evidence of fibrosis or other permanent histopathological changes. Haematoxylin and eosin; magnification: 200×

investigated to date. A report of the use of CECT in two cases of canine pancreatitis (Jaeger *et al.* 2003) showed some encouraging results. However, a recent study in which the findings of different imaging modalities in dogs with acute abdomen were compared showed that contrast-enhanced multi-detector helical computed tomography (CE-MDCT) had low sensitivity for diagnosing pancreatitis in a small number of cases (n=7) (Shanaman *et al.* 2013). In cats, computed tomography performed in cases with histologically confirmed pancreatitis showed disappointing results (Forman *et al.* 2004). Other imaging methods (e.g. ERCP, endoscopic ultrasonography) have been used in healthy dogs and cats as well as in dogs and cats with pancreatitis with varying results (Spillmann *et al.* 2005a,b, 2013, Schweighauser *et al.* 2009). Also, a recent study evaluated the usefulness of magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP) for the diagnosis of pancreatitis in cats and reported promising results (Marolf *et al.* 2012). However, due to the lack of standardised criteria for the diagnosis of pancreatitis, the complexity of these imaging modalities, the necessity for general anaesthesia, the limited availability and the cost of the equipment, none of the above-mentioned methods can currently be recommended for the routine diagnosis of canine or feline pancreatitis. It is possible that after proper and meticulous evaluation, some of these methods will be used in the future for the diagnosis of pancreatitis in cases where all other diagnostic approaches result in equivocal results.

Histopathology of the pancreas

At present, histopathological examination of the pancreas is considered the gold standard for the diagnosis of pancreatitis, as well as the definitive differentiation between acute and chronic pancreatitis in dogs and cats. Histopathological scoring systems for the evaluation of severity of pancreatitis have been proposed for both dogs and cats (Newman *et al.* 2004, 2006, De Cock *et al.* 2007, Watson *et al.* 2007). However, in contrast to humans, histopathological criteria for the classification of pancreatitis have not been universally standardised in veterinary medicine and substantial confusion exists regarding both classification and terminology of canine and feline pancreatitis. The presence of permanent histopathological changes (namely fibrosis and acinar atrophy) is generally considered suggestive of chronic pancreatitis (Fig 2), while the absence of such changes in an inflamed pancreas indicates acute pancreatitis (Fig 3) (Newman *et al.* 2004, Watson *et al.* 2007, Bostrom *et al.* 2013). The predominant inflammatory cellular infiltrate (neutrophils or lymphocytes) is often used to further divide pancreatitis into suppurative or lymphocytic, and some authors consider a suppurative inflammation compatible with acute disease and lymphocytic infiltration compatible with chronic disease (Hill & Van Winkle 1993,

Ferreri *et al.* 2003). A significant degree of necrosis is usually used to characterise the pancreatitis as necrotising. It should be noted that the histopathological distinction between acute and chronic pancreatitis is not always clear, and many animals have histopathological evidence of both acute and chronic pancreatitis.

Although still considered the gold standard for the diagnosis of pancreatitis, there is accumulating evidence that pancreatic histopathology is associated with several and important limitations, and therefore, cannot be considered an ideal gold standard. First, determining the clinical significance of histopathological findings is often challenging. In a necropsy study, 64% of 73 dogs that were presented for necropsy for various reasons had microscopic evidence of pancreatitis (Newman *et al.* 2004). In another study, histopathological lesions of pancreatitis were found in 67% of all cats examined, including 45% of healthy cats (De Cock *et al.* 2007). Currently, there are no standardised criteria that distinguish microscopic findings leading to clinical disease from those that do not, and it is possible that clinically insignificant pancreatic lesions could lead to a false diagnosis of clinical pancreatitis. On the other hand, exclusion of pancreatitis based on histopathology can be difficult because inflammatory lesions of the pancreas are often highly localised and can easily be missed (Hill & Van Winkle 1993, Saunders *et al.* 2002, Newman *et al.* 2004, De Cock *et al.* 2007, Pratschke *et al.* 2014). Therefore, multiple sections of the pancreas must be evaluated in order to increase the likelihood of finding microscopic lesions, although this is not always feasible in clinical practice. The absence of histopathological findings of pancreatitis must be evaluated with caution, especially when only one section of the pancreas has been examined (Newman *et al.* 2004, De Cock *et al.* 2007). Finally, pancreatic biopsy requires invasive procedures that are expensive and potentially detrimental in patients with pancreatitis that are haemodynamically unstable (Webb & Trott 2008, Cordner *et al.* 2010). Therefore, pancreatic biopsy is rarely performed in clinical practice for the diagnosis of pancreatitis, unless a laparotomy is performed for other reasons. Nevertheless, in contrast to what was believed in the past, a large number of studies have shown that pancreatic biopsy per se is a rather safe procedure and can be used for the diagnosis of pancreatitis in dogs and cats (Westermark *et al.* 1993, Wiberg *et al.* 1999, Harmoinen *et al.* 2002, Webb & Trott 2008, Cordner *et al.* 2010, Cosford *et al.* 2010). In a recent retrospective study (Pratschke *et al.* 2014), the most common complications following surgical biopsy of the pancreas included vomiting, abdominal pain, nausea, anorexia, and lethargy.

Gross lesions of the pancreas (e.g. peripancreatic fat necrosis, pancreatic haemorrhage and congestion, pancreatic oedema, dull granular capsular surface) are present in some dogs and cats with pancreatitis but this finding is neither sensitive nor specific for pancreatitis (Fig 4) (Hill & Van Winkle 1993, Saunders *et al.* 2002, Steiner *et al.* 2008). When present, gross lesions of the pancreas are preferred sites for biopsy. However, gross pathological lesions are often absent in dogs and cats with pancreatitis or may be the result of neoplasia or nodular hyperplasia (Hill & Van Winkle 1993, Saunders *et al.* 2002, Newman *et al.* 2004).

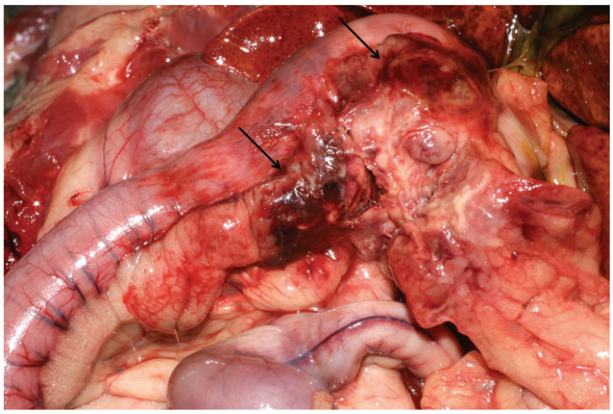

FIG 4. Gross appearance of the pancreas of a dog with acute pancreatitis. The pancreas appears severely haemorrhagic, necrotic and oedematous (arrows) (Courtesy of Dr. B. Porter, Texas A&M University). Reprinted from Reference, Xenoulis P.G. & Steiner J.M. (2013) with permission from Elsevier

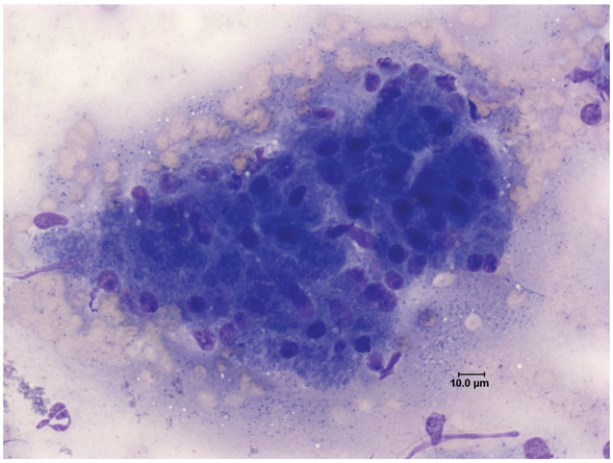

FIG 5. Cytological appearance of a fine-needle aspirate from a normal canine pancreas. Acinar cells can be seen in the form of a multi-cellular cluster. Diff-quick; magnification 500× (Courtesy of Dr. P. J. Armstrong, University of Minnesota). Reprinted from Reference, Xenoulis P.G. & Steiner J.M. (2013) with permission from Elsevier

Because concurrent inflammation of the intestines and/or liver appears to be a common problem in cats (Weiss *et al.* 1996, Callahan Clark *et al.* 2011) and may also occur in dogs, intestinal and hepatic biopsies should be collected in patients (especially cats) suspected of having pancreatitis that are undergoing exploratory laparotomy or laparoscopy. Likewise, cats with IBD and/or cholangitis that undergo laparotomy or laparoscopy should also have their pancreas evaluated.

Cytology of the pancreas

FNA of the pancreas and cytological examination of the aspirated material is a minimally invasive technique that is increasingly used for the diagnosis of pancreatitis in dogs and cats (Bjorneby & Kari 2002). To date, there are no studies that have evaluated the sensitivity and specificity of this diagnostic modality for the diagnosis of canine or feline pancreatitis. It is logical to assume

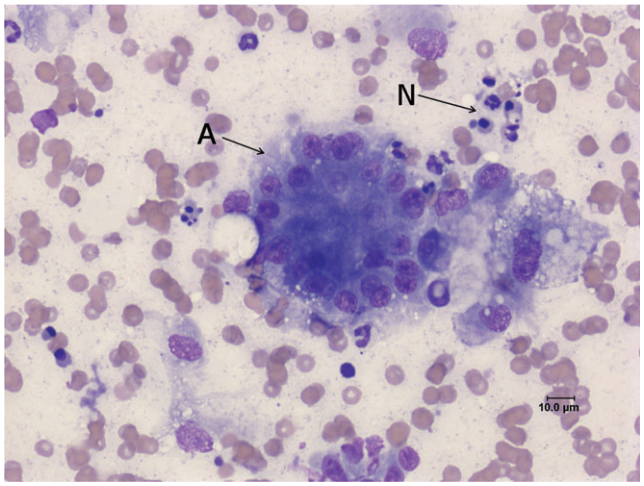

FIG 6. Cytologic appearance of a fine-needle aspirate from a canine pancreas with suspected pancreatitis. There is mild to moderate neutrophilic inflammation (N) with neutrophilic degeneration. A cluster of normal acinar cells (A) can also be seen. Diff-quick; magnification 500× (Courtesy of Dr. P.J. Armstrong, University of Minnesota). Reprinted from Reference, Xenoulis P.G. & Steiner J.M. (2013) with permission from Elsevier

that the finding of inflammatory cells within the aspirated material from the pancreas should be specific for pancreatitis. Pancreatic acinar cells constitute the majority of the cells found in FNA smears from a normal pancreas (Fig 5) (Bjorneby & Kari 2002). In animals with acute pancreatitis, the cytological picture is mainly characterised by hypercellularity and the presence of entire and degenerate neutrophils and degenerate pancreatic acinar cells (Fig 6). In animals with chronic pancreatitis, small numbers of lymphocytes and neutrophils are usually present, and the specimen is often characterised by low cellularity, possibly due to replacement of the normal pancreatic tissue by fibrotic tissue (Bjorneby & Kari 2002). It should be highlighted that, as for histopathology, highly localised lesions might be missed. Thus, negative FNA cytology results are not sufficient to rule out pancreatitis.

FNA of the pancreas is usually performed either under ultrasonographic guidance or during laparotomy (Bjorneby & Kari 2002). Although considered relatively innocuous, the safety of pancreatic FNA has not been evaluated in dogs and cats with pancreatic diseases. Pancreatic sampling by ultrasound-guided FNA or surgical biopsy did not cause increases in serum cPLI concentrations or clinically detectable pancreatitis in healthy dogs (Cordner *et al.* 2010). Endoscopic ultrasound-guided FNA of the pancreas has also been described in medium-sized healthy dogs and reported to be feasible and safe (Kook *et al.* 2012).

ASSESSMENT AND PREDICTION OF THE SEVERITY OF PANCREATITIS

Assessment of the severity of human acute pancreatitis is based on the application of standardised severity scores that are frequently modified and updated (Bradley 1993, Papachristou *et al.* 2007, Pavlidis *et al.* 2010). Prediction of the severity of pancreatitis constitutes a very important component of the diagnosis of pancreatitis, because it allows prediction of the likelihood of complications and morbidity and helps determine the optimal therapeutic plan before the patient enters a critical stage. It has been hypothesised that the severity of a pancreatitis episode can be determined by events that occur within the first 24 to 48 hours of the episode (Papachristou *et al.* 2007). These events are reflected through clinical, clinicopathological and imaging findings that can be used to predict the severity of the pancreatitis (Papachristou *et al.* 2007, Pavlidis *et al.* 2010).

In veterinary medicine, no well-established and universally accepted severity scores for pancreatitis have been described. Serum PLI and TLI concentrations are believed to lack prognostic significance because they correlate poorly with histopathological severity (Steiner *et al.* 2008). However, in a recent study, serum fPLI concentrations as well as dyspnoea and hyperkalaemia at the time of admission were found to be significant and independent prognostic indicators for outcome in cats hospitalised because of pancreatitis (Stockhaus *et al.* 2013). Currently, severity of canine and feline pancreatitis is determined based on the clinician's clinical judgment, and typically a diagnosis of severe pancreatitis is made after the animal has entered a critical stage. In general, evidence of systemic complications (e.g. oliguria, renal azotaemia, icterus, severely increased hepatic enzyme activities, hypocalcaemia, hypoglycaemia, severe hyperglycaemia, hyperkalaemia, leukocytosis, shock or DIC) are considered indicators of severe disease and a poor prognosis (Ruaux & Atwell 1998, Kimmel *et al.* 2001, Mansfield *et al.* 2008). In a recent study (Tvarijonaviciute *et al.* 2014), serum paraoxonase 1 activity together with triglyceride and C-reactive protein concentrations were suggested to represent potential of disease severity. However, prediction of the severity of pancreatitis has not been sufficiently studied in dogs and cats. Further studies are needed to establish the use of convenient and valuable clinical severity scores for pancreatitis in these species.

Although not directly related to severity of pancreatitis, results of two recent studies from the UK suggest that some dogs and cats with IBD have increased serum PLI concentrations. In one of those studies, increased serum cPLI concentrations in dogs with IBD were associated with a negative outcome; specifically, increased serum cPLI concentration was identified as the only variable that significantly affected survival in these dogs (Kathrani *et al.* 2009). In the other study, increased serum fPLI concentrations in cats with IBD were significantly associated with hypoalbuminaemia and hypocobalaminaemia also suggesting more severe clinical disease (Bailey *et al.* 2010).

Conclusive remarks

No single diagnostic modality is 100% reliable for the diagnosis of canine or feline pancreatitis. Maintaining a high level of suspicion for pancreatitis, especially in animals that are presented with mild and non-specific clinical signs, is of utmost importance for a correct diagnosis. In addition, other diseases that cause similar clinical signs should be judiciously excluded. Careful evaluation of the animal's history, physical examina-

tion and routine clinical pathology findings, as well as the use of highly specific and sensitive tests (serum PLI concentration, abdominal ultrasonography, cytology and/or histopathology), is crucial for an accurate diagnosis of pancreatitis. In clinical practice, a combination of the clinical picture of the patient, serum PLI concentration and abdominal ultrasonography is considered to be the most practical and reliable means for an accurate diagnosis or exclusion of pancreatitis compared with other diagnostic modalities.

References

Akol, K. G., Washabau, R. J., Saunders, H. M., *et al.* (1993) Acute pancreatitis in cats with hepatic lipidosis. *Journal of Veterinary Internal Medicine* **7**, 205-209

Allen, H. S., Steiner, J., Broussard, J., *et al.* (2006) Serum and urine concentrations of trypsinogen-activation peptide as markers for acute pancreatitis in cats. *Canadian Journal of Veterinary Research* **70**, 313-316

Bailey, S., Benigni, L., Eastwood, J., *et al.* (2010) Comparisons between cats with normal and increased fPLI concentrations in cats diagnosed with inflammatory bowel disease. *Journal of Small Animal Practice* **51**, 484-489

Beall, M. J., Cahill, R., Pigeon, K., *et al.* (2011) Performance validation and method comparison of an in-clinic enzyme-linked immunosorbent assay for the detection of canine pancreatic lipase. *Journal of Veterinary Diagnostic Investigation* **23**, 115-119

Bjorneby, J. M. & Kari, S. (2002) Cytology of the pancreas. *Veterinary Clinics of North America – Small Animal Practice* **32**, 1293-1312

Bollen, T. L. (2012) Imaging of acute pancreatitis: update of the revised Atlanta classification. *Radiology Clinincs of North America* **50**, 429-445

Bostrom, B. M., Xenoulis, P. G., Newman, S. J., *et al.* (2013) Chronic pancreatitis in dogs: a retrospective study of clinical, clinicopathological, and histopathological findings in 61 cases. *Veterinary Journal* **195**, 73-79

Bradley, E. L. (1993) A clinically based classification system for acute pancreatitis. *Archives of Surgery* **128**, 586-590

Brobst, D., Ferguson, A. B. & Carter, J. M. (1970) Evaluation of serum amylase and lipase activity in experimentally induced pancreatitis in the dog. *Journal of the American Veterinary Medical Association* **157**, 1697-1702

Callahan Clark, J. E., Haddad, J. L., Brown, D. C., *et al.* (2011) Feline cholangitis: a necropsy study of 44 cats (1986-2008). *Journal of Feline Medicine and Surgery* **13**, 570-576

Cook, A. K., Breitschwerdt, E. B., Levine, J. F., *et al.* (1993) Risk factors associated with acute pancreatitis in dogs: 101 cases (1985-1990). *Journal of the American Veterinary Medical Association* **203**, 673-679

Cordner, A. P., Armstrong, P. J., Newman, S. J., *et al.* (2010) Effect of pancreatic tissue sampling on serum pancreatic enzyme levels in clinically healthy dogs. *Journal of Veterinary Diagnostic Investigation* **22**, 702-707

Cosford, K. L., Shmon, C. L., Myers, S. L., *et al.* (2010) Prospective evaluation of laparoscopic pancreatic biopsies in 11 healthy cats. *Journal of Veterinary Internal Medicine* **24**, 104-113

De Arespacochaga, A. G., Hittmair, K. M. & Schwendenwein, I. (2006) Comparison of lipase activity in peritoneal fluid of dogs with different pathologies – a complementary diagnostic tool in acute pancreatitis? *Journal of Veterinary Medicine Series A-Physiology Pathology Clinical Medicine* **53**, 119-122

De Cock, H. E., Forman, M. A., Farver, T. B., *et al.* (2007) Prevalence and histopathologic characteristics of pancreatitis in cats. *Veterinary Pathology* **44**, 39-49

Ferreri, J. A., Hardam, E., Kimmel, S. E., *et al.* (2003) Clinical differentiation of acute necrotizing from chronic nonsuppurative pancreatitis in cats: 63 cases (1996-2001). *Journal of the American Veterinary Medical Association* **223**, 469-474

Forman, M. A., Marks, S. L., De Cock, H. E., *et al.* (2004) Evaluation of serum feline pancreatic lipase immunoreactivity and helical computed tomography versus conventional testing for the diagnosis of feline pancreatitis. *Journal of Veterinary Internal Medicine* **18**, 807-815

Forman, M. A., Shiroma, J., Armstrong, P. J., *et al.* (2009) Evaluation of feline pancreas-specific lipase (Spec fPL™) for the diagnosis of feline pancreatitis. *Journal of Veterinary Internal Medicine* **23**, 733-734 [Abstract]

Gerhardt, A., Steiner, J. M., Williams, D. A., *et al.* (2001) Comparison of the sensitivity of different diagnostic tests for pancreatitis in cats. *Journal of Veterinary Internal Medicine* **15**, 329-333

Gibbs, C., Denny, H. R., Minter, H. M., *et al.* (1972) Radiological features of inflammatory conditions of the canine pancreas. *Journal of Small Animal Practice* **13**, 531-544

Graca, R., Messick, J., McCullough, S., *et al.* (2005) Validation and diagnostic efficacy of a lipase assay using the substrate 1,2-o-dilauryl-rac-glycero glutaric acid-(6´ methyl resorufin)-ester for the diagnosis of acute pancreatitis in dogs. *Veterinary Clinical Pathology* **34**, 39-43

Harmoinen, J., Saari, S., Rinkinen, M., *et al.* (2002) Evaluation of pancreatic forceps biopsy by laparoscopy in healthy beagles. *Veterinary Therapeutics* **3**, 31-36.

Hecht, S. & Henry, G. (2007) Sonographic evaluation of the normal and abnormal pancreas. *Clinical Techniques in Small Animal Practice* **22**, 115-121

Hecht, S., Penninck, D. G., Mahony, O. M., *et al.* (2006) Relationship of pancreatic duct dilation to age and clinical findings in cats. *Veterinary Radiology and Ultrasound* **47**, 287-294

Hecht, S., Penninck, D. G. & Keating, J. H. (2007) Imaging findings in pancreatic neoplasia and nodular hyperplasia in 19 cats. *Veterinary Radiology and Ultrasound* **48**, 45-50

Hess, R. S., Saunders, H. M., Van Winkle, T. J., *et al.* (1998) Clinical, clinicopathologic, radiographic, and ultrasonographic abnormalities in dogs with fatal acute pancreatitis: 70 cases (1986-1995). *Journal of the American Veterinary Medical Association* **213**, 665-670

Hill, R. C. & Van Winkle, T. J. (1993) Acute necrotizing pancreatitis and acute suppurative pancreatitis in the cat. A retrospective study of 40 cases (1976-1989). *Journal of Veterinary Internal Medicine* **7**, 25-33

Hoffmann, W. E. (2008) Diagnostic enzymology of domestic animals. In: Clinical Biochemistry of Domestic Animals. 6th edn. Eds J. J. Kaneko, J. W. Harvey and M. L. Bruss. Burlington, Vermont, Canada: Academic Press. pp 351-378

Huth, S. P., Relford, R., Steiner, J. M., *et al.* (2010) Analytical validation of an ELISA for measurement of canine pancreas-specific lipase. *Veterinary Clinical Pathology* **39**, 346-353

Jacobs, R. M., Murtaugh, R. J. & DeHoff, W. D. (1985) Review of the clinicopathological findings of acute pancreatitis in the dog: use of an experimental model. *Journal of the American Animal Hospital Association* **21**, 795-800

Jaeger, J. Q., Mattoon, J. S., Bateman, S. W., *et al.* (2003) Combined use of ultrasonography and contrast enhanced computed tomography to evaluate acute necrotizing pancreatitis in two dogs. *Veterinary Radiology and Ultrasound* **44**, 72-79

Karanjia, N. D., Lutrin, F. J., Chang, Y. B., *et al.* (1990) Low dose dopamine protects against hemorrhagic pancreatitis in cats. *Journal of Surgical Research* **48**, 440-443

Kathrani, A., Steiner, J.M., Suchodolski, J., *et al.* (2009) Elevated canine pancreatic lipase immunoreactivity concentration in dogs with inflammatory bowel disease is associated with a negative outcome. *Journal of Small Animal Practice* **50**, 126-132.

Kimmel, S. E., Washabau, R. J. & Drobatz, K. J. (2001) Incidence and prognostic value of low plasma ionized calcium concentration in cats with acute pancreatitis: 46 cases (1996-1998). *Journal of the American Veterinary Medical Association* **219**, 1105-1109

Kitchell, B. E., Strombeck, D. R., Cullen, J., *et al.* (1986) Clinical and pathologic changes in experimentally induced acute pancreatitis in cats. *American Journal of Veterinary Research* **47**, 1170-1173

Kook, P. H., Baloi, P., Ruetten, M., *et al.* (2012) Feasibility and safety of endoscopic ultrasound-guided fine needle aspiration of the pancreas in dogs. *Journal of Veterinary Internal Medicine* **26**, 513-517

Kook, P. H., Kohler, N., Hartnack, S., *et al.* (2014) Agreement of serum Spec cPL with the 1,2-o-dilauryl-rac-glycero glutaric acid-(6'-methylresorufin) ester (DGGR) lipase assay and with pancreatic ultrasonography in dogs with suspected pancreatitis. *Journal of Veterinary Internal Medicine* **28**, 863-870

Lamb, C. R. (1999a) Pancreatic edema in dogs with hypoalbuminemia or portal hypertension. *Journal of Veterinary Internal Medicine* **13**, 498-500

Lamb, C. R. (1999b) Recent developments in diagnostic imaging of the gastrointestinal tract of the dog and cat. *Veterinary Clinics of North America – Small Animal Practice* **29**, 307-342

Lamb, C. R., Simpson, K. W., Boswood, A., *et al.* (1995) Ultrasonography of pancreatic neoplasia in the dog: a retrospective review of 16 cases. *Veterinary Record* **137**, 65-68

Lem, K. Y., Fosgate, G. T., Norby, B., *et al.* (2008) Associations between dietary factors and pancreatitis in dogs. *Journal of the American Veterinary Medical Association* **233**, 1425-1431

Mansfield C. (2012a) Pathophysiology of acute pancreatitis: potential application from experimental models and human medicine to dogs. *Journal of Veterinary Internal Medicine* **26**, 875-887.

Mansfield C. (2012b) Acute pancreatitis in dogs: advances in understanding, diagnostics, and treatment. *Topics in Companion Animal Medicine* **27**, 123-32.

Mansfield, C. S. & Jones, B. R. (2000a) Plasma and urinary trypsinogen activation peptide in healthy dogs, dogs with pancreatitis and dogs with other systemic diseases. *Australian Veterinary Journal* **78**, 416-422

Mansfield, C. S. & Jones, B. R. (2000b) Trypsinogen activation peptide in the diagnosis of canine pancreatitis. *Journal of Veterinary Internal Medicine* 14, 346 [Abstract]

Mansfield, C. S., Jones, B. R., & Spillmann, T. (2003) Assessing the severity of canine pancreatitis. *Research in Veterinary Science* **74**, 137-144

Mansfield, C. S., James, F. E. & Robertson, I. D. (2008) Development of a clinical severity index for dogs with acute pancreatitis. *Journal of the American Veterinary Medical Association* **233**, 936-944

Mansfield, C. S., Watson, P. J. & Jones, B. R. (2011) Specificity and sensitivity of serum canine pancreatic elastase-1 concentration in the diagnosis of pancreatitis. *Journal of Veterinary Diagnostic Investigation* **23**, 691-697

Mansfield, C. S., Anderson, G. A. & O'Hara, A. J. (2012) Association between canine pancreatic-specific lipase and histologic exocrine pancreatic inflammation in dogs: assessing specificity. *Journal of Veterinary Diagnostic Investigation* **24**, 312-318

Marolf, A. J., Kraft, S. L., Dunphy, T. R., *et al*. (2012) Magnetic resonance (MR) imaging and MR cholangiopancreatography findings in cats with cholangitis and pancreatitis. *Journal of Feline Medicine and Surgery,* doi: 10.1177/1098612X12466084

Mayhew, P. D., Holt, D. E., McLear, R. C., *et al*. (2002) Pathogenesis and outcome of extrahepatic biliary obstruction in cats. *Journal of Small Animal Practice* **43**, 247-253

Mayhew, P. D., Richardson, R. W., Mehler, S. J., *et al*. (2006) Choledochal tube stenting for decompression of the extrahepatic portion of the biliary tract in dogs: 13 cases (2002-2005). *Journal of the American Veterinary Medical Association* **228**, 1209-1214

McCord, K., Morley, P. S., Armstrong, J., *et al*. (2012) A multi-institutional study evaluating the diagnostic utility of the spec cPL™ and SNAP® cPL™ in clinical acute pancreatitis in 84 dogs. *Journal of Veterinary Internal Medicine* **26**, 888-896

Mia, A. S., Koger, H. D. & Tierney, M. M. (1978) Serum values of amylase and pancreatic lipase in healthy mature dogs and dogs with experimental pancreatitis. *American Journal of Veterinary Research* **39**, 965-969

Neilson-Carley, S. C., Robertson, J. E., Newman, S. J., *et al*. (2011) Specificity of a canine pancreas-specific lipase assay for diagnosing pancreatitis in dogs without clinical or histologic evidence of the disease *American Journal of Veterinary Research* **72** 302-307

Newman, S., Steiner, J., Woosley, K., *et al*. (2004) Localization of pancreatic inflammation and necrosis in dogs. *Journal of Veterinary Internal Medicine* **18**, 488-493

Newman, S. J., Steiner, J. M., Woosley, K., *et al*. (2006) Histologic assessment and grading of the exocrine pancreas in the dog. *Journal of Veterinary Diagnostic Investigation* **18**, 115-118

Oppliger, S., Hartnack, S., Riond, B., *et al*. (2013) Agreement of the serum Spec fPL™ and 1,2-o-dilauryl-rac-glycero-3-glutaric acid-(6´-methylresorufin) ester lipase assay for the determination of serum lipase in cats with suspicion of pancreatitis. *Journal of Veterinary Internal Medicine* **27**, 1077-1082

Papachristou, G. I., Clermont, G., Sharma, A., *et al*. (2007) Risk and markers of severe acute pancreatitis. *Gastroenterology Clinics of North America* **36**, 277-296

Parent, C., Washabau, R. J., Williams, D. A., *et al*. (1995) Serum trypsin-like immunoreactivity, amylase and lipase in the diagnosis of feline acute pancreatitis. *Journal of Veterinary Internal Medicine* **9**, 194 [Abstract]

Pavlidis, T. E., Pavlidis, E. T. & Sakantamis, A. K. (2010) Advances in prognostic factors in acute pancreatitis: a mini-review. *Hepatobiliary & Pancreatic Diseases International* **9**, 482-486

Polzin, D. J., Osborne, C. A., Stevens, J. B., *et al*. (1983) Serum amylase and lipase activities in dogs with chronic primary renal failure. *American Journal of Veterinary Research* **44**, 404-410

Pratschke, K. M., Ryan, J., McAlinden, A., *et al*. (2014) Pancreatic surgical biopsy in 24 dogs and 19 cats: postoperative complications and clinical relevance of histological findings. *Journal of Small Animal Practice* **56**, 60-66

Probst, A. & Kneissl, S. (2001) Computed tomographic anatomy of the canine pancreas. *Veterinary Radiology & Ultrasound* **42**, 226-230

Ruaux, C. G. (2000) Pathophysiology of organ failure in severe acute pancreatitis in dogs. *Compendium on Continuing Education for the Practicing Veterinarian* **22**, 531-535

Ruaux, C. G. & Atwell, R. B. (1998) A severity score for spontaneous canine acute pancreatitis. *Australian Veterinary Journal* **76**, 804-808

Ruaux, C. G., Lee, R. P. & Atwell, R. B. (1999) Detection and measurement of canine alpha-macroglobulins by enzyme immuno-assay. *Research in Veterinary Science* **66**, 185-190

Saunders, H. M., VanWinkle, T. J., Drobatz, K., *et al*. (2002) Ultrasonographic findings in cats with clinical, gross pathologic, and histologic evidence of acute pancreatic necrosis: 20 cases (1994-2001). *Journal of the American Veterinary Medical Association* **221**, 1724-1730

Schermerhorn, T., Pembleton-Corbett, J. R. & Kornreich, B. (2004) Pulmonary thromboembolism in cats. *Journal of Veterinary Internal Medicine* **18**, 533-535

Schweighauser, A., Gaschen, F., Steiner, J., *et al*. (2009) Evaluation of endosonography as a new diagnostic tool for feline pancreatitis. *Journal of Feline Medicine and Surgery* **11**, 492-498

Shanaman, M.M., Schwarz, T., Gal, A., *et al*. (2013) Comparison between survey radiography, b-mode ultrasonography, contrast-enhanced ultrasonography and contrast-enhanced multi-detector computed tomography findings in dogs with acute abdominal signs. *Veterinary Radiology & Ultrasound*, doi: 10.1111/vru.12079 [Epub ahead of print]

Simpson, K. W., Batt, R. M., McLean, L., *et al*. (1989) Circulating concentrations of trypsin-like immunoreactivity and activities of lipase and amylase after pancreatic duct ligation in dogs. *American Journal of Veterinary Research* **50**, 629-632

Simpson, K. W., Simpson, J. W., Lake, S., *et al*. (1991) Effect of pancreatectomy on plasma activities of amylase, isoamylase, lipase and trypsin-like immunoreactivity in dogs. *Research in Veterinary Science* **51**, 78-82

Simpson, K. W., Shiroma, J. T., Biller, D. S., *et al*. (1994) Ante mortem diagnosis of pancreatitis in four cats. *Journal of Small Animal Practice* **35**, 93-99

Simpson, K. W., Fyfe, J., Cornetta, A., *et al*. (2001) Subnormal concentrations of serum cobalamin (vitamin B12) in cats with gastrointestinal disease. *Journal of Veterinary Internal Medicine* **15**, 26-32

Son, T. T., Thompson, L., Serrano, S., *et al*. (2010) Surgical intervention in the management of severe acute pancreatitis in cats: 8 cases (2003-2007). *Journal of Veterinary Emergency and Critical Care* **20**, 426-435

Spillmann T, Happonen I, Sankari S, *et al*. (2004) Evaluation of serum values of pancreatic enzymes after endoscopic retrograde pancreatography in dogs. *American Journal of Veterinary Research* **65**, 616-619.

Spillmann, T., Happonen, I., Kahkonen, T., *et al*. (2005a) Endoscopic retrograde cholangio-pancreatography in healthy beagles. *Veterinary Radiology and Ultrasound* **46**, 97-104

Spillmann, T., Schnell-Kretschmer, H., Dick, M., *et al*. (2005b) Endoscopic retrograde cholangio-pancreatography in dogs with chronic gastrointestinal problems. *Veterinary Radiology & Ultrasound* **46**, 293-299

Spillmann, T., Willard, M.D., Ruhnke, I., *et al*. (2013) Feasibility of endoscopic retrograde cholangiopancreatography in healthy cats. *Veterinary Radiology & Ultrasound*, doi: 10.1111/vru.12086 [Epub ahead of print]

Steiner, J. M. (2000) Canine digestive lipases. PhD Thesis. Texas, USA: A&M University. pp 1-251

Steiner, J. M. (2003) Diagnosis of pancreatitis. *Veterinary Clinics of North America – Small Animal Practice* **33**, 1181-1195

Steiner, J. M. & Williams, D. A. (2003) Development and validation of a radioimmunoassay for the measurement of canine pancreatic lipase immunoreactivity in serum of dogs. *American Journal of Veterinary Research* **64**, 1237-1241

Steiner, J. M., Broussard, J., Mansfield, C. S., *et al*. (2001a) Serum canine pancreatic lipase immunoreactivity (cPLI) concentrations in dogs with spontaneous pancreatitis. *Journal of Veterinary Internal Medicine* **15**, 274 [Abstract]

Steiner, J. M., Finco, D. R., Gumminger, S. R., *et al*. (2001b) Serum canine pancreatic lipase immunoreactivity (cPLI) in dogs with experimentally induced chronic renal failure. *Journal of Veterinary Internal Medicine* **15**, 311 [Abstract]

Steiner, J. M., Berridge, B. R., Wojcieszyn, J., *et al*. (2002) Cellular immunolocalization of gastric and pancreatic lipase in various tissues obtained from dogs. *American Journal of Veterinary Research* **63**, 722-727

Steiner, J. M., Teague, S. R. & Williams, D. A. (2003) Development and analytic validation of an enzyme-linked immunosorbent assay for the measurement of canine pancreatic lipase immunoreactivity in serum. *Canadian Journal of Veterinary Research* **67**, 175-182

Steiner, J. M., Wilson, B. G. & Williams, D. A. (2004) Development and analytical validation of a radiommunoassay for the measurement of feline pancreatic lipase immunoreactivity in serum. *Canadian Journal of Veterinary Research* **68**, 309-314

Steiner, J. M., Rutz, G. M. & Williams, D. A. (2006) Serum lipase activities and pancreatic lipase immunoreactivity concentrations in dogs with exocrine pancreatic insufficiency. *American Journal of Veterinary Research* **67**, 84-87

Steiner, J. M., Newman, S., Xenoulis, P., *et al*. (2008) Sensitivity of serum markers for pancreatitis in dogs with macroscopic evidence of pancreatitis. *Veterinary Therapeutics* **9**, 263-273

Steiner, J. M., Teague, S. R., Lees, G. E., *et al*. (2009) Stability of canine pancreatic lipase immunoreactivity concentration in serum samples and effects of long-term administration of prednisone to dogs on serum canine pancreatic lipase immunoreactivity concentrations. *American Journal of Veterinary Research* **70**, 1001-1005

Stockhaus, C., Teske, E., Schellenberger, K., *et al*. (2013) Serial serum feline pancreatic lipase immunoreactivity concentrations and prognostic variables in 33 cats with pancreatitis. *Journal of the American Veterinary Medical Association* **243**, 1713-1718

Strombeck, D. R., Farver, T. & Kaneko, J. J. (1981) Serum amylase and lipase activities in the diagnosis of pancreatitis in dogs. *American Journal of Veterinary Research* **42**, 1966-1970

Suchodolski, J. S., Collard, J. C., Steiner, J. M., *et al*. (2001) Development and validation of an enzyme-linked immunosorbent assay for measurement of alpha-1-proteinase inhibitor/trypsin complexes in canine sera. *Journal of Veterinary Internal Medicine* **15**, 311 [Abstract]

Suter, P. F. & Lowe, R. (1972) Acute pancreatitis in the dog. A clinical study with emphasis on radiographic diagnosis. *Acta Radiologica – Supplementum* **319**, 195-208

Swift, N. C., Marks, S. L., MacLachlan, N. J., *et al*. (2000) Evaluation of serum feline trypsin-like immunoreactivity for the diagnosis of pancreatitis in cats. *Journal of the American Veterinary Medical Association* **217**, 37-42

Trivedi, S., Marks, S. L., Kass, P. H., *et al*. (2011) Sensitivity and specificity of canine pancreas-specific lipase (cPL) and other markers for pancreatitis in 70 dogs with and without histopathologic evidence of pancreatitis. *Journal of Veterinary Internal Medicine* **25**, 1241-1247

Tvarijonaviciute, A., García-Martínez, J. D., Caldin, M., *et al*. (2014) Serum paraoxonase 1 (PON1) activity in acute pancreatitis of dogs. *Journal of Small Animal Practice* **56**, 67-71

Watson, P. (2012) Chronic pancreatitis in dogs. *Topics in Companion Animal Medicine* **27**, 133-139

Watson, P. J., Archer, J., Roulois, A. J., *et al*. (2010) Observational study of 14 cases of chronic pancreatitis in dogs. *Veterinary Record* **167**, 968-976

Watson, P. J., Roulois, A. J., Scase, T., *et al*. (2007) Prevalence and breed distribution of chronic pancreatitis at post-mortem examination in first-opinion dogs. *Journal of Small Animal Practice* **28**, 609-618

Weatherton, L. K. & Streeter, E. M. (2009) Evaluation of fresh frozen plasma administration in dogs with pancreatitis: 77 cases (1995-2005). *Journal of Veterinary Emergency and Critical Care* **19**, 617-622

Webb, C. B. & Trott, C. (2008) Laparoscopic diagnosis of pancreatic disease in dogs and cats. *Journal of Veterinary Internal Medicine* **22**, 1263-1266

Weiss, D. J., Gagne, J. M. & Armstrong, P. J. (1996) Relationship between inflammatory hepatic disease and inflammatory bowel disease, pancreatitis, and nephritis in cats. *Journal of the American Veterinary Medical Association* **209**, 1114-1116

Westermarck, E. & Rimaila-Pärnänen, E. (1983) Serum phospholipase A2 in canine acute pancreatitis. *Acta Veterinaria Scandinavica* **24**, 477-487

Wiberg, M.E., Saari, S.A., & Westermarck, E. (1999) Exocrine pancreatic atrophy in German Shepherd dogs and Rough-coated Collies: an end result of lymphocytic pancreatitis. *Veterinary Pathology* **36**, 530-541.

Williams, D. A. (1996) The pancreas. In: Small Animal Gastroenterology. 3rd edn. Eds D. R. Strombeck, W. G. Guilford, S. A. Center, D. A. Williams and D. J. Meyer. Philadelphia, PA, USA: W.B. Saunders. pp 381-410

Williams, J.M., Panciera, D.L., Larson, M.M., *et al*. (2013) Ultrasonographic findings of the pancreas in cats with elevated serum pancreatic lipase immunoreactivity. *Journal of Veterinary Internal Medicine* **27**, 913-918

Xenoulis, P. G. & Steiner, J. M. (2012) Canine and feline pancreatic lipase immunoreactivity. *Veterinary Clinical Pathology* **41**, 312-324

Xenoulis, P. G. & Steiner, J.M. (2013) Necrosis and inflammation: canine (pancreas). In: Canine and Feline Gastroenterology. Eds R. J. Washabau and M. J. Day. St. Louis, MI, USA: Elsevier . pp 812-821

Xenoulis, P. G., Suchodolski, J. S. & Steiner, J. M. (2008) Chronic pancreatitis in dogs and cats. *Compendium on Continuing Education for the Practicing Veterinarian* **30**, 166-180

Xenoulis, P. G., Finco, D. R., Suchodolski, J. S., *et al*. (2009) Serum fPLI and Spec fPL concentrations in cats with experimentally induced chronic renal failure. *Journal of Veterinary Internal Medicine* **23**, 758 [Abstract]

Zavros, N. S., Rallis, T. S., Koutinas, A. F., *et al*. (2008) Clinical and laboratory investigation of experimental acute pancreatitis in the cat. *European Journal of Inflammation* **6**, 105-114

Zimmermann, E., Hittmair, K. M., Suchodolski, J. S., *et al*. (2013) Serum feline-specific pancreatic lipase immunoreactivity concentrations and abdominal ultrasonographic findings in cats with trauma resulting from high-rise syndrome. *Journal of the American Veterinary Medical Association* **242**, 1238-1243