Acute pancreatitis in dogs and cats: pathogenesis, clinical signs and clinicopathologic findings

Acute pancreatitis bij honden en katten: pathogenese, klinische symptomen en laboratoriumafwijkingen

I. Van den Bossche, D. Paepe, S. Daminet

Department of Small Animal Medicine and Clinical Biology
Faculty of Veterinary Medicine, Ghent University
Salisburylaan 133, B-9820, Merelbeke, Belgium

dominique.paepe@ugent.be

ABSTRACT

Acute pancreatitis is a (usually sterile) inflammation with acute onset and characterized by necrosis and edema; it does not permanently disrupt the pancreatic architecture and is completely reversible. It is thought that, despite the pancreatic defense mechanisms, premature activation of trypsin in the acinar cells starts a cascade of reactions that result in autodigestion. Most cases are idiopathic. Dogs are often presented with gastrointestinal signs, whereas lethargy and anorexia are the most commonly observed symptoms in cats. Diagnosing pancreatitis remains a challenge, but the recent development of the pancreatic lipase immunoreactivity test is promising.

SAMENVATTING

Acute pancreatitis is een plotse (meestal steriele) ontsteking die de structuur van de pancreas niet definitief aantast en die compleet reversibel is. Deze ontsteking wordt gekarakteriseerd door necrose en oedeem. Er wordt verondersteld dat, ondanks verdedigingsmechanismen, een vroegtijdige activering van trypsin in de acinaire cellen een cascade van reacties veroorzaakt met autodigestie tot gevolg. De meeste gevallen zijn idiopathisch. Honden worden vaak aangeboden met gastro-intestinale klachten, terwijl lethargie en anorexie de meest voorkomende symptomen zijn bij katten. Het diagnosticeren van pancreatitis blijft een uitdaging maar de recente ontwikkeling van de "pancreatic lipase immunoreactivity" test is veelbelovend.

INTRODUCTION

Acute pancreatitis is a common, sometimes life threatening disorder in companion animals. Clinical signs and laboratory abnormalities of patients with acute pancreatitis can resemble other diseases. Therefore, the diagnosis can be challenging for the practitioner. However, a rapid and correct diagnosis facilitates early therapy, which improves the chances of survival. This report is the first in a series of three that will present a review of acute pancreatitis in dogs and cats. Pathogenesis and underlying factors are described, followed by an overview of the most common clinical signs. Finally, the advantages and disadvantages of some possible diagnostic laboratory methods are summarized. The second article will discuss the medical imaging, treatment and prognosis of acute pancreatitis in small animals. Two clinical cases will be discussed in the final report.

FUNCTION OF THE NORMAL PANCREAS

The pancreas consists mainly of exocrine tissue (98%), with the endocrine islets of Langerhans composing the remaining 2% (Watson, 2004). The major function of the exocrine acinar cells is to produce, store and secrete a fluid rich in enzymes that helps in the initial digestion of proteins, lipids and polysaccharides (Williams, 2000). The pancreas produces lipase, α-amylase, phospholipase A2, elastases, carboxypeptidases, trypsin and chymotrypsin (Bunch, 2003; Watson, 2004; Mix and Jones, 2006).

PREVALENCE AND PATHOGENESIS OF ACUTE PANCREATITIS

Acute pancreatitis is defined as pancreatic necrosis, often with a neutrophilic infiltrate. Because there is no fibrosis or chronic inflammation that disrupts the normal architecture of the pancreas, as in the case of chronic pancreatitis, acute pancreatitis is a completely reversible process (Watson *et al*., 2007). It represents a spectrum of disease, ranging from mild to severe and from a single episode to recurrent episodes (Watson, 2004; Watson, 2007). The true prevalence of pancreatitis is probably underestimated because of the difficult ante-mortem diagnosis (Mix and Jones, 2006; Watson, 2007). In a post-mortem examination of 200

dogs (whose history and complaints were often not known) (Watson *et al*., 2007), 34% showed lesions compatible with chronic pancreatitis, and only 2.6% showed lesions of the acute form. This difference in prevalence can partially be explained by the fact that dogs who recover from acute pancreatitis might not show any histological evidence. De Cock *et al.* (2007) found a 15.7% prevalence of acute pancreatitis in cats, which is higher than in dogs, but still less common than the chronic form (prevalence of 60%). Of the cats with acute pancreatitis, only 9.6% also suffered from chronic pancreatitis, which is in contrast to the conclusion of Forman *et al*. (2004), who found this combination of lesions in 44% of their patients.

The exact mechanism by which acute pancreatitis develops is still incompletely understood. In normal conditions, a number of pancreatic defense mechanisms are available to prevent autodigestion. Proteolytic enzymes are synthesized and secreted in the form of catalytically inactive precursors called zymogens (for example trypsinogen) (Steiner, 2003a; Watson, 2004; Mix and Jones, 2006). In the acinar cell, damage by lysosomal proteases is prevented by the storage of zymogens in granules (Watson, 2004; Mix and Jones, 2006). The activation of zymogens occurs by cleavage of an activation peptide of the polypeptide chain, but this normally does not occur until they are secreted into the small intestine. The first zymogen activated is trypsinogen, which is cleaved by enteropeptidase synthesized by the enterocytes of the duodenal mucosa to form trypsin. Trypsin plays a central role in the activation cascade by cleaving the activation peptides from the other zymogens and itself (Watson, 2004; Mix and Jones, 2006). At least two mechanisms are available to prevent further damage in the event of inappropriate early intra-pancreatic activation of proteases. The first mechanism involves small amounts of trypsin that can hydrolyze itself (Watson, 2004). The other possibility is the temporary binding of trypsin to pancreatic secretory trypsin inhibitor (PSTI). This is a low-molecular-weight molecule that is present in the zymogens and that can inactivate approximately 10 percent of the total amount of trypsin (Watson, 2004; Mix and Jones, 2006). Plasma protease inhibitors play an important role as protection mechanisms against the possible fatal effects of protease release in the vascular space. Alpha-macroglobulins (α-M1 and α-M2) and α1-proteinase inhibitors (α-1-antitrypsin) inhibit neutrophil elastase and form complexes with proteases, which are then removed from the plasma by the reticulo-endothelial system. This removal is crucial, because the bound proteases retain their proteolytic activity (Steiner, 2003a).

It is thought that inappropriate premature activation of trypsin in the acinar cells initiates a cascade of early activation of zymogens, especially proelastase and prophospholipase, with autodigestion of the pancreas as a result (Bunch, 2003; Watson, 2004). Activation of intracellular enzymes results in cellular necrosis and subsequent sterile inflammation, which leads to peri-pancreatic fat necrosis. Activated enzymes can cause vascular injury and activation of coagulation and vasoactive amine, fibrinolytic and complement cascades. Enzyme release in the abdomen can result in local or generalized peritonitis (Bunch, 2003; Steiner, 2003a; Watson, 2004; Mix and Jones, 2006). The release of proteases in the systemic circulation can overwhelm the protection mechanism and result in systemic inflammatory response syndrome and multi-organ failure. The production of potent proteolytic enzyme*s*, oxidative substances such as H_2O_2, and pro-inflammatory cytokines plays an important role in the progression of pancreatitis and in the development of multiple organ failure (Ruaux, 2000; Brady and Otto, 2001).

PREDISPOSING FACTORS OF ACUTE PANCREATITIS

The triggering factors of acute pancreatitis in dogs and cats are usually unknown and most cases are considered idiopathic, although the practitioner should certainly be on the lookout for possible underlying factors (Simpson, 2001a; Washabau, *2*001; Watson, 2004; Zoran, 2006; Watson, 2007). Possible risk factors are shown in Table 1. Cholangiohepatitis and inflammatory bowel disease (IBD) are often coexisting disorders in cats suffering from acute pancreatitis (also called the triade disease or triaditis) (Weiss *et al*., 1996). In cats with cholangiohepatitis, the concurrent pancreatic lesions are usually mild, while the IBD tends to be severe (Weiss *et al*., 1996). The reason why cholangiohepatitis is often a concurrent disease in cats with pancreatitis, and not in dogs, can be explained by the different anatomic construction of the pancreatic and bile ducts in these two species. Hepatic lipidosis is another disease often diagnosed in cats with acute pancreatitis (Akol *et al*., 1993).

CLINICAL SIGNS OF ACUTE PANCREATITIS

The clinical signs of acute pancreatitis in dogs and cats are nonspecific and similar to those of numerous other gastrointestinal pathologies and metabolic disorders. Furthermore, they vary with the severity of the disease. Most typically, dogs present with anorexia (91%), acute vomiting (90% of which 10% hematemesis) and weakness (79%) (Hess *et al*., 1998). Small or large bowel diarrhea is described in 33% of the cases (Hess *et al*., 1998). The majority of cats are referred to a veterinarian because of lethargy (50%-100%), anorexia (63%-100%), dehydration (33%-92%) or tachypnoea (74%) (Hill and Van Winkle, 1993; Gerhardt *et al*., 2001; Ferreri *et al*., 2003). In contrast to dogs, gastrointestinal signs are rather sparse in cats (Hill and Van Winkle, 1993; Gerhardt *et al*., 2001; Ferreri *et al*., 2003). Possible clinical signs and physical examination findings are reported in Table 2.

In more severely affected dogs, collapse and shock can occur (Simpson and Lamb, 1995; Bunch, 2003;

Table 1. Risk factors for the development of acute pancreatitis in dogs and cats.

Risk factor	Dog	Cat
Breed	Terrier or non-sporting breed[1,2,3,4]	Domestic shorthair breeds and Siamese[5,6,7]
Gender	Controversial (no gender predilection, intact males, neutered dogs)[1,2,3,4]	Controversial (no gender predisposition, neutered males)[5,6,7]
Age	Middle-aged to older[1,2,8]	No age predisposition, in most cases cats older than 7 years, suppurative form more in younger animals (mean age 3.5 years)[5,7]
Ischemia	Hypovolemia, shock, hypotension, severe anemia, infarct, vasoactive amine-induced vasoconstriction, disseminated intra-vascular coagulation, temporary venous occlusion during surgery in the cranial abdomen[1,3,4]	Decreased blood flow and alterations in microvascular permeability[9,10]
Diet	High-fat diet, obesity, malnutrition[1,2,4,8,11,12]	Not reported
Hyperlipidemia	Inherent abnormal lipid metabolism (Miniature schnauzers)[4,9,11], accumulation of toxic fatty acids in the pancreas[1], ingestion of a large fatty meal[3], concurrent disease[2,4,13]	Not reported
Concurrent disease	Diabetes mellitus[13], hypercortisolism[13], hypothyroidism[2,4]	Cholangiohepatitis, inflammatory bowel disease, hepatic lipidosis[14,15]
Pancreatic duct obstruction	Biliary calculi (uncommon in dogs), sphincter spasm, tumor, trauma, surgical intervention, parasites, cholangitis, edema of the duct through the duodenal wall and maybe congenital anomalies[4]	Biliary duct obstruction[9,10] due to cholelithiasis, inspissated bile, trauma, neoplasia or stricture
Reflux of duodenal fluid	Abnormally high intraluminal pressure (vomiting, trauma of the duodenum)[3]	Not reported
Drugs	Thiazide diuretics, furosemide, azathioprine, L-asparaginase, sulfonamides, tetracyclines, procainamide, organophosphates, cholinergic agonists, oestrogens[4], potassiumbromide in combination with phenobarbital[16], steroids (only in association with intervertebral disc disease and surgery), propofol?[4]	Organophosphates, steroids?[9]
Infection	Viral, parasitic, mycoplasmal, bacterial?[3]	Feline infectious peritonitis, Toxoplasma gondii, Herpesvirus, Amphimerus pseudofelineus[10]
Trauma	Surgical manipulation, pancreatic biopsy and car accidents (abdominal trauma)[4,8,11,13]	Surgical manipulation, high rise syndrome[9,10]
Other causes	Uremic pancreatitis[1], prior gastrointestinal disease[2], hypercalcemia[4,11] and thrombus formation[2]	Uremia, hypercalcemia, lipodystrophia[9,10]

Adapted from: [1]Cook *et al*., 1993; [2]Hess *et al*., 1999; [3]Bunch, 2003; [4]Watson, 2004; [5]Hill and Van Winkle, 1993; [6]Kimmel *et al*., 2001; [7]Ferreri *et al*., 2003; [8]Mix and Jones, 2006; [9]Simpson, 2001b; [10]Washabau, 2001; [11]Simpson and Lamb, 1995; [12]Hess *et al*., 1998; [13]Watson, 2007; [14]Weiss *et al*., 1996; [15]Akol *et al*., 1993; [16]Gaskill and Gribb, 2000.

Watson, 2004; Mix and Jones, 2006; Watson, 2007). Possible complications due to systemic inflammatory response syndrome in these patients include hypotension, cardiac arrhythmias (usually ventricular), pancreatic abscesses or cysts, diabetes/diabetes ketoacidosis, intestinal obstruction and acute renal failure (Bunch, 2003; Mansfield *et al*., 2003; Watson, 2004; Mix and Jones, 2006). Damage to endothelial cells, mediated by proteolytic enzymes and oxidants, can lead to activation of the extrinsic coagulation pathway, resulting in disseminated intravascular coagulation (DIC) and thromboembolism (Ruaux, 2000). Interstitial edema can result from increased vascular permeability of the pulmonary vessels. This condition can cause ventilation-perfusion mismatches and, in the end, acute respiratory distress syndrome (ARDS) and organ hypoxia. Another factor that can contribute to ARDS is the activation of phospholipase A2 and elastase, which results in pulmonary surfactant degradation. Pleural effusion and pulmonary thromboembolism can also deteriorate the respiratory function (López *et al*., 1995; Ruaux, 2000; Mansfield *et al*., 2003). Absorption of endotoxin from the compromised adjacent areas of gut can contribute to sepsis and

Table 2. Prevalence of clinical signs and physical examination findings in dogs and cats with acute pancreatitis in percentages (%).

Clinical signs	Dogs[1]	Cats[2,3,4,5]
Anorexia	91	63 - 100
Acute vomiting	90 (with 10% hematemesis)	35 - 52
Weakness / Lethargia	79	50 - 100
Polyuria/polydipsia	50	20
Diarrhea	33 (with 16% melena and 4% hematoschezie)	11 - 15
Neurological symptoms	20	15
Weight loss	11	33
Tachypnoea	No prevalence reported	74
Dyspnoea	No prevalence reported	20
Physical examination findings		
Dehydration	97	33 - 92
Painful abdominal palpation	58	9 - 25
Fever	32	7
Icterus	26	16 - 64
Cardiac murmur	20	No prevalence reported
Blood coagulation abnormalities	11	No prevalence reported
Hypothermia	7	68

Adapted from: [1]Hess *et al*., 1998; [2]Hill and Van Winkle, 1993; [3]Gerhardt *et al*., 2001; [4]Kimmel *et al.,* 2001; [5]Ferreri *et al*., 2003.

multi-organ failure (Watson, 2004). Extrahepatic biliary obstruction (EHBO) can develop secondary to peri-pancreatic inflammation and edema, because one of the pancreatic ducts ends next to the bile duct in the major duodenal papilla. Acute pancreatitis seems to be one of the most common causes of EHBO in dogs (Herman *et al*., 2005; Mayhew *et al.*, 2006).

Thirty-eight percent of cats have acute cardiovascular shock at presentation (Hill and Van Winkle, 1993). Complications are largely the same as those in dogs (Washabau, 2001). However, in contrast to dogs, acute pancreatitis was not found to be a risk factor in two studies on cats with EHBO (Bacon and White, 2003; Buote *et al*., 2006). In a retrospective study, necropsy was performed on 40 cats with acute pancreatitis: 20% of them had thrombosis, although it was not specified whether this was venous or arterial, and the localization of the thrombosis was not mentioned. Lung lesions were present in 30% of the cats: pulmonary edema, a sign of ARDS, was the most common pathology, although it could have developed secondary to fluid administration. Other complications included pleural effusion (12%), abdominal effusion (7.4%), a combination of pleural and abdominal effusion (22%), and pericardial effusion (5%) (Hill and Van Winkle, 1993).

CLINICOPATHOLOGIC FINDINGS

Because acute pancreatitis can be a severe and potentially life threatening disease, an accurate and timely diagnosis is essential. An ideal diagnostic marker should be inexpensive, easily available and non-invasive. Other essential characteristics are that the marker should have a high specificity (low number of false positive results) in combination with a high sensitivity (low number of false negative results). Because an ideal test does not yet exist, diagnosing acute pancreatitis remains a challenge. Biopsy and histological examination of pancreatic tissue remains the gold standard, and in absence of this test the diagnosis can only be tentative. Nevertheless, careful evaluation of the entire clinical picture can help in confirming the suspicion and excluding other differential diagnoses such as intestinal foreign bodies, gastroenteritis, peritonitis and pyometra, all of which can cause an acute abdomen. A comparison of different diagnostic tests can be found in Table 3.

Complete blood count

Hematologic findings are nonspecific in dogs and cats with acute pancreatitis. Leucocytosis is a more common finding in dogs (62%) than in cats (30%), while leucopenia is more typically found in cats (15% versus 3.3%) (Hill and Van Winkle, 1993; Hess *et al*., 1998; Watson, 2004). However, according to Gerhardt *et al*. (2001), leucocytosis is present in 62% of cats with acute pancreatitis. In more severe cases of acute pancreatitis in dogs and cats, a degenerative left shift or toxic white blood cells can be present (Hill and Van Winkle, 1993; Simpson and Lamb, 1995; Hess *et al*., 1998). Fifty-five percent of cats show normochromic, normocytic regenerative anemia (Hill and Van Winkle, 1993), while only 28.6% of affected dogs have decreased red blood cell concentrations (Hess *et al*., 1998). Hemoconcentration resulting from dehydration (Mansfield and Jones, 2001; Bunch, 2003; Watson, 2004) is also possible. Thrombocytopenia can follow the development of DIC (Hess *et al*., 1998; Simpson and Lamb, 1995; Bunch, 2003; Watson, 2004). It is recommended to test coagulation profiles in all dogs

Table 3. Specificity and sensitivity of different tests for diagnosing acute pancreatitis.

Diagnostic test	Dog		Cat	
	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)
Serum amylase	57[2]	62 - 69[1,2]	No diagnostic value	
Serum lipase	55[2]	39 - 73[1,2]	No diagnostic value	
cTLI	65[2]	33 - 36[3,6]		
fTLI			82[5]	28 - 33 (if upper ref fTLI > 100 µg/l)[4,5] 48 (if upper ref fTLI > 88 µg/l)[5] 62 (if upper ref fTLI > 82 µg/l)[5] 86 (if upper ref fTLI > 49 µg/l)[5]
cPLI	80[3]	61 - 80[3,6]		
fPLI			91[4]	67[4]
Serum TAP	76 - 90[2,7]	53 - 54[2]	Not determined	
UTCR	Not determined	26[2]	No diagnostic value	

cTLI = canine trypsin like immunoreactivity; fTLI = feline trypsin like immunoreactivity; cPLI = canine pancreatic lipase immunoreactivity; fPLI = feline pancreatic lipase immunoreactivity; TAP = trypsinogen activation peptide; UTCR = urinary TAP-to- creatinine ratio
Adapted from: [1]*Hess et al*., 1998; [2]Mansfield and Jones, 2000b; [3]Steiner *et al*., 2001a; [4]Forman *et al*., 2004; [5]Gerhardt *et al*., 2001; [6]Steiner *et al*., 2007; [7]Mansfield *et al*., 2003

and cats suspected of acute pancreatitis, and obligatory if they have thrombocytopenia (Hill and Van Winkle, 1993; Hess *et al*., 1998).

Serum biochemistry

Azotemia is often present in dogs (59%) and cats (33%) with acute pancreatitis, and is usually pre-renal in origin (Hill and Van Winkle, 1993; Hess *et al.,* 1998; Gerhardt *et al*., 2001; Bunch, 2003). Several factors can play a role: volume contraction from vomiting, lack of fluid intake and extravasation of fluid into a third space from vascular injury (Bunch, 2003).

Hepatic ischemia, local inflammatory mediators and toxic pancreatic mediators in the portal circulation lead to hepatocellular injury with increased liver enzymes in both dogs and cats (alanine ALT and aspartate AST aminotransferase) (Hill and Van Winkle, 1993; Hess *et al.,* 1998). Hyperbilirubinemia (twofold to fivefold increase), present in 30 - 53% of dogs and 38 - 64% of cats, can be noticed in cases of cholestasis (Hill and Van Winkle, 1993; Hess *et al*., 1998; Gerhardt *et al*., 2001; Washabau, 2001). This cholestasis develops secondary either to pancreatic inflammation or to fibrosis, which obstructs (partially or completely) the common bile duct (Bunch, 2003; Watson, 2004; Mix and Jones, 2006). Cholestasis can also result in increased AST, ALT and alkaline phosphatise (AP) (Watson, 2004).

Sixty-five percent of dogs and cats with acute pancreatitis have hyperglycemia, which can develop due to glucagon release in excess of insulin from an inflamed pancreas, in combination with stress-related increases of cortisol and catecholamines (Hill and Van Winkle, 1993; Bunch, 2003; Watson, 2004). Concurrent diabetes mellitus or keto-acidosis or the development of diabetes after acute episodes of pancreatitis is another possible explanation for the detected hyperglycemia (Watson, 2004). Diabetes mellitus is more common in dogs with pancreatitis (13.9%) than in cats with pancreatitis (1%) (Cook *et al*., 1993; Ferreri *et al*., 2003). Pancreatitis is the most common concurrent disorder in dogs with diabetes keto-acidosis (41%) (Hume *et al*., 2006; De Causmacker *et al*., 2009). More severe cases of acute pancreatitis are usually characterized by hypoglycemia (39%) (Hess *et al*., 1998). This latter abnormality can occur secondary to reduced calorie intake, severe sepsis and concurrent liver disease (Watson, 2004).

Almost half of dogs and two-thirds of cats have high serum hypercholesterolemia (Hill and Van Winkle, 1993; Hess *et al*., 1998). Hypertriglyceridemia is another common but nonspecific finding (Bunch, 2003). Hyperlipemia can be either a cause or, more likely, a result of the disease (Watson, 2004). In addition, hyperlipemia can be associated with other diseases, such as endocrinopathies and hepatic lipidosis, that can concurrently affect both dogs and cats with pancreatitis (Hill and Van Winkle, 1993; Mansfield and Jones, 2001).

Mild to moderate hypocalcemia is rare in dogs with pancreatitis (3-5%) (Simpson and Lamb, 1995; Hess *et al*., 1998; Hess *et al*., 1999), but a frequent finding in cats (45 - 61%), although in only 9% of cats is calcium markedly depressed (Ca < 1.75 mmol/l; reference 2-2.75 mmol/l) (Hill and Van Winkle, 1993; Kimmel *et al*., 2001). Although hypocalcemia rarely causes clinical signs such as neurologic or cardiac abnormalities, it is associated with a worse clinical outcome. Fifty-three percent of cats that did not survive in the study of Kimmel *et al.* (2001) had a plasma ionized calcium concentration below or equal to 1 mmol/l (reference 1.10-1.28 mmol/l). The mechanism of hypocalcemia is not yet known, though it is assumed that depositions of calcium (such as soaps in peri-pancreatic fat), an acute shift of calcium into soft tissues, and hormonal imbalances (e.g. thyrocalcitonine and abnormal parathyroid responsiveness) are possible factors (Bunch, 2003; Watson, 2004; Mix and Jones, 2006).

Vomiting and reduced food intake can lead to hypo-

natremia, hypochloremia and hypokalemia (Watson, 2004). In dogs, hypochloremia is the most frequent electrolyte abnormality (81.3%), while hypokalemia is more common in cats (56%) (Hill and Van Winkle, 1993; Hess *et al*., 1998). Hypophosphatemia is an infrequent finding in cats (14%), but can be important to monitor, because uncorrected hypophosphatemia can result in hemolytic anemia, neuromuscular disorders and intestinal ileus (Hill and Van Winkle, 1993; Nelson, 2003).

Hyperproteinemia can be observed with dehydration (Bunch, 2003; Mix and Jones, 2006), while albumin can be low because of leakage due to vascular damage (Bunch, 2003).

Metabolic acidosis is also a possible finding in both dogs and cats (Hill and Van Winkle, 1993; Simpson and Lamb, 1995; Hess *et al*., 1998).

Although blood work alone is insufficient for diagnosing acute pancreatitis, it might be an important step in differentiating other diseases, in assessing the general condition of the patient and in defining the consequences and complications of pancreatitis.

More specific blood tests

Because of the shortcomings of the complete blood work, more specific laboratory tests were developed. Two types can be distinguished: enzymatic and immunoassays. Detection of released enzymes in blood can be performed by measuring a color or density change when the enzyme catalyzes a reaction in vitro. Therefore enzymatic assays only measure active enzymes, and not inactive precursors (zymogens in the case of pancreatitis). Furthermore, they are not species (or organ) specific, which is another disadvantage (Watson, 2004). The main reason that they were the preferred test in practice for a long time is their inexpensiveness and availability in comparison to immunoassays. These latter tests detect antigens on the surface of the molecule and therefore are independent of the active site. They are species and organ specific and can detect inactive precursors (Watson, 2004). Unfortunately, they are technically demanding, and therefore expensive and usually only available in a few laboratories (Ruaux, 2003). For this reason, they are not yet used in routine diagnostics. The specificities and sensitivities of different tests are described in Table 3.

Serum amylase and lipase are digestive enzymes that were 'traditionally' used for diagnosing acute pancreatitis in companion animals. They originate both from pancreatic and extra-pancreatic sources and therefore they are not pancreas specific. Several factors contribute to the rather low specificity of serum amylase and lipase activity in dogs. Decreased renal function, use of dexamethasone and prednisone, and hepatobiliary and gastrointestinal diseases like lymphoma can all lead to elevated enzyme concentrations in the absence of pancreatic disease (Simpson and Lamb, 1995; Bunch, 2003; Ruaux, 2003; Steiner, 2003a; Watson, 2004). The sensitivity of lipase is higher than that of amylase (Mansfield and Jones, 2000b), although in a study of 70 fatal cases, amylase was found to have a thirty percent higher sensitivity (Hess *et al*., 1998). The reason for this was not clear. Inflammation of the pancreas can lead to a dramatic change in the production of proteins (especially proteases), but this synthesis can be rapidly decreased within hours. Also, in severe cases of pancreatitis, normal levels can be the result of enzyme depletion or loss of tissue (Watson, 2004). It is for this reason that low or normal serum amylase and lipase concentrations may decrease, but this decrease does not exclude the likelihood of acute pancreatitis. Mansfield *et al*. (2003) believe that strongly elevated lipase concentrations indicate more severe cases of pancreatitis, although Ruaux (2003) disagrees with this finding.

In cats with acute pancreatitis, measurement of serum lipase and amylase activities has no diagnostic value, because the levels of both enzymes are often within normal limits or even below baseline values (Kitchell *et al.,* 1986; Parent *et al*., 1995; Simpson, 2001a; Simpson, 2001b; Washabau, 2001). Especially amylase is of no use because cats only produce small amounts of amylase in comparison to dogs (Kitchell *et al.,* 1986). As in dogs, kidney dysfunction and extrapancreatic sources (e.g. inflammatory bowel disease) can lead to increased amylase and/or lipase concentrations (Mansfield and Jones, 2001).

Because of the limitations described above, neither amylase nor lipase can be recommended as a diagnostic test for pancreatitis in dogs or cats (Parent *et al*., 1995). To improve the diagnostic accuracy, a pancreas specific isoenzyme of canine amylase has been developed, but this isoenzyme is not yet commercially available (Bunch, 2003).

Serum canine trypsin-like immunoreactivity (cTLI) is a well known test for diagnosing exocrine pancreatic insufficiency in dogs, but it can also be used for acute pancreatitis. Early in the disease, a rapid increase in cTLI can be detected (Bunch, 2003; Ruaux, 2003). Elevations have a high level of specificity, although decreased renal function can influence this result (Simpson and Lamb, 1995; Ruaux, 2003; Watson, 2004). The sensitivity is rather low, because the period during which cTLI is increased can be short due either to a rapid down regulation of trypsinogen synthesis (especially in severe cases, such as hemorrhagic necrosis of pancreatic tissue) or to cleavage by endopeptidases (Ruaux, 2003). cTLI is a poor predictor of outcome for acute pancreatitis (Mansfield *et al.,* 2003). Another limitation is that it does take several days to run this test (Simpson and Lamb, 1995; Mix and Jones, 2006).

Feline trypsin-like immunoreactivity (fTLI) is considered a better marker than amylase and lipase for feline acute pancreatitis. Indeed, Parent *et al.* (1995) concluded that fTLI was significantly increased in all 12 cats with acute pancreatitis, but not in sick or

healthy control cats, while no difference was noted in the concentration of amylase or lipase between these three groups of cats. However, these conclusions were challenged by two studies that showed lower sensitivities based on different upper reference values used (Table 3) (Gerhardt *et al*., 2001; Forman *et al*., 2004). According to Swift *et al*. (2000), fTLI was poorly correlated with the histological diagnosis: only one out of five cats with histological evidence of acute pancreatitis had a fTLI value above the reference range.

The development of an enzyme-linked immunosorbant assay and a radioimmunoassay for measuring serum canine pancreatic lipase immunoreactivity (cPLI) is an important step in diagnosing acute pancreatitis in dogs (Steiner and Williams, 2000; Steiner *et al*., 2001c). It can be considered the single best blood test because of its high specificity and sensitivity (Steiner *et al.,* 2001a). The high specificity results from the fact that canine pancreatic lipase is only expressed by pancreatic acinar cells, without cross-immunoreactivity with other lipases or related proteins expressed by other tissues (Steiner *et al*., 2000). Furthermore, renal failure and administration of steroids do not seem to contribute to elevated levels of cPLI (Steiner *et al*., 2001b; Watson, 2004). In a comparative study on 23 dogs with macroscopic evidence of pancreatitis, cPLI had the highest sensitivity (60.9%), followed by cTLI, trypsin/α1-proteinase inhibitor, serum amylase activity and serum lipase activity (Steiner *et al*., 2007).

Following the development of cPLI, a variant for the cat became available in 2002 (Wilson *et al*., 2002). Feline pancreatic lipase immunoreactivity (fPLI) has a high specificity, in combination with a high sensitivity in more severe cases of pancreatitis (Forman *et al*., 2004). Compared to fTLI, fPLI is more sensitive in diagnosing acute pancreatitis, because the duration and magnitude of increase of fPLI was greater in cats with experimental pancreatitis (10 days compared to 3 days, and 50x compared to 25x baseline value) (Williams *et al*., 2003).

The principle limitation of both cPLI and fPLI is the fact that waiting several days for results in critically ill patients is not always an option (Ruaux, 2003; Steiner, 2003a; Steiner, 2003b; Watson, 2004; Mix and Jones, 2006).

Because acute pancreatitis is an inflammatory process, acute-phase response proteins such as C-reactive protein (CRP) are released by the liver (Ruaux, 2003; Nakamura *et al*., 2008). In human medicine, the measurement of this protein constitutes an effective tool for assessing the severity of the disease, with more severe cases showing higher levels of CRP (Mix and Jones, 2006). Nakamura *et al.* (2008) investigated CRP levels in various diseases in 928 dogs. Acute pancreatitis is one of the diseases with the highest CRP levels. However, because CRP can be released secondary to any type of inflammation, infection, tissue damage or trauma, the specificity is too low to play a role in diagnosing acute pancreatitis (Spillman *et al.,* 2002; Mix and Jones, 2006). Measurement of CRP concentrations can however aid in assessing the severity of the disease. In a retrospective cohort study in 61 dogs with ultrasonographically or histologically confirmed acute pancreatitis, there was no correlation between this variable and outcome (Mansfield *et al*., 2008). However, within a 2-day period after onset of clinical signs, serum CRP concentrations in survivors and non-survivors differed significantly, and were related to severity. Therefore, sequential assessment of serum CRP concentration may be an effective and objective method for monitoring response to treatment (Mansfield *et al.*, 2008).

In cats, other acute phase proteins play a role in the pathogenesis of acute pancreatitis. A study of 10 cats detected a first peak of α1-acid glycoprotein (AGP) 24 hours after induction of pancreatitis, while the greatest increase of serum amyloid A occurred 24 hours later. Further research is warranted to confirm the possible use of these molecules in the early detection of feline pancreatitis (Fetz *et al*., 2005). In two studies, increase of α1-proteinase inhibitor was not significant and it was only present in 20% of cats with spontaneous disease (Fetz *et al*., 2004; Fetz *et al*., 2005).

During the activation of trypsinogen to trypsin, a small molecule called trypsinogen activation peptide (TAP) is released. A significant TAP increase can be seen in serum and urine during the first hours after the development of pancreatitis, especially in the more severe, necrotizing forms. For less severe forms, the usefulness is thus limited (Ruaux, 2003). Because the onset of the disease is not known in veterinary patients, it is possible that the concentration of TAP is already decreasing at the time of measurement (Ruaux, 2003), which could explain the rather low sensitivity. It is considerably more sensitive and specific in assessing the severity than cTLI (Mansfield *et al*., 2003), but its lability and limited availability limit its usefulness (Williams, 2000).

TAP is detectable in the plasma and urine of cats suspected of pancreatitis. Although serum TAP has a higher sensitivity than fTLI in the study by Allen *et al*. (2006), its measurement does not show any advantage over determination of fTLI because of the lower specificity, high cost and limited availability.

Plasma protease inhibitors form an important defense mechanism against developing acute pancreatitis. Theoretically, detection of trypsin/α1-proteinase inhibitor complexes in the circulation would be very specific because in the absence of pancreatitis only free trypsinogen can be found in the plasma (Ruaux, 2003; Steiner, 2003a). Unfortunately, the elevation is not always significant due to its transient nature (Ruaux, 2003). In cases of elevation of these molecules, the increase correlates with the severity of disease (Williams, 2000). During pancreatitis, α-macroglobulines are removed from the plasma, so their concentration should decrease. Unfortunately, measurement

of these molecules is not clinically useful (Steiner, 2003a) and it is poorly correlated with the severity of disease (Ruaux and Atwell, 1999).

Currently, the diagnostic usefulness of canine pancreatic elastase and various cytokines (TNF-α, IL-6, IL-8) is being investigated, but more clinical studies will be required before conclusions can be drawn (Spillman *et al.,* 2002; Mansfield, 2004). In one study, total TNF protein levels did not differ between groups of dogs with varying degrees of pancreatitis (Spillman *et al.,* 2002).

Acute pancreatitis can cause pleural effusion and ascites. Cytologic and biochemical analysis usually characterize the abdominal fluid as a non-septic exudate, often with high lipase activity (Simpson and Lamb, 1995; Bunch, 2003). This finding is not specific, because abdominal or intestinal trauma may also yield the same result (Bunch, 2003). However, according to the study by Guija De Arespacochaga *et al.* (2006), the concentration of lipase in abdominal fluid almost always doubled the serum activity of lipase in cases of pancreatitis. This finding can aid in diagnosing acute pancreatitis.

It should be noted that none of the assays described above are 100% specific or sensitive, and elevation of one or more enzyme(s) should always be correlated to clinical signs and history. Unfortunately, normal enzyme levels do not rule out a diagnosis of acute pancreatitis (Watson, 2004; Mix and Jones, 2006). In dogs, cPLI is the most reliable test at this moment, because of its high specificity and sensitivity. Recently, this test became commercially available in Belgium. Canine TLI can be considered a reasonable alternative, although the low sensitivity can be a problem. Measurement of serum amylase and serum lipase has little diagnostic value and should better be avoided. In cats, serum amylase and serum lipase have no diagnostic use. Fortunately, alternatives have recently become available. Feline PLI has both high specificity and high sensitivity, especially in severe cases. Feline TLI is less sensitive, but still a worthy alternative.

Urinalysis

Routine analysis of a urine sample obtained before fluids are administered can help in differentiating prerenal and renal azotemia and in assessing the degree of renal damage (Simpson and Lamb, 1995; Bunch, 2003; Watson, 2004). Damage to the glomeruli by pancreatic enzymes can cause transient proteinuria (Simpson and Lamb, 1995). Urinary TAP is considered even less accurate than serum TAP in diagnosing severe pancreatitis, because it was not significantly different between healthy dogs, dogs with pancreatitis and dogs with non-pancreatic disease (Mansfield and Jones, 2000a; Mansfield *et al*., 2003). However, in the study by Mansfield and Jones (2000a), dogs that died of severe pancreatitis did have higher urinary TAP than dogs with milder forms. Another possibility is the calculation of the urinary TAP-to-creatinine ratio (UTCR), which is considered a good prognostic indicator in dogs with increased values. However, it is not recommended as a sole diagnostic tool because of the low sensitivity (26.1%) (Mansfield and Jones, 2000b). In contrast to dogs, the UTCR has no use in cats, because no significant difference was detected between healthy cats and cats with pancreatitis (Allen *et al.,* 2006).

CONCLUSION

Acute pancreatitis is caused by premature activation of pancreatic enzymes within the acinar cells and is completely reversible. Most cases are idiopathic, but an underlying cause can be present. It is probably an underestimated disease in both dogs and cats, because of unspecific clinical symptoms and the absence of specific and sensitive tests. Routine complete blood count, serum biochemistry and urinalysis are a good first choice for excluding possible differential diagnoses, for evaluating the complications of acute pancreatitis and for assessing the general condition of the patient. For the definitive diagnosis, other laboratory tests must be used, of which pancreatic lipase immunoreactivity is currently the most reliable test. Both canine and feline PLI have a high sensitivity and specificity, and they both have recently become commercially available in Belgium. Measurement of canine or feline TLI is slightly less expensive than PLI and is an alternative in areas where PLI is not yet available. However, its low sensitivity is a significant disadvantage. Under no condition should measurement of serum lipase and amylase in dogs or cats be considered a possible alternative. In dogs, measurement of CRP or UTCR is well correlated with severity of disease and can aid in predicting the prognosis, but both tests are not yet widely available. By combining the clinical signs, physical examination findings and laboratory test results, most cases can be readily diagnosed, which aids in rapidly initiating a correct therapy.

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