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Acute pancreatitis in dogs: A review

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Abstract
Acute pancreatitis is the more clinically recognized form of inflammation in pancreas. Failure of zymogens activation causes inflammation and necrosis of the pancreatic tissue thereby resulting in leakage of pancreatic digestive enzymes into the peritoneal space or the intravascular space. Chances of disease occurrence varies with respect to age, breeds etc. Dogs with acute pancreatitis attain "praying position" or "position of relief" in response to cranial abdominal pain. In addition, there is vomiting, anorexia and depression. Blood examination shows peripheral blood neutrophilia with a degenerative left shift, anemia and thrombocytopenia. Azotemia, hyperbilirubinemia, hypocalcemia, hyperglycemia and eleveted levels of liver enzymes are usual findings. Disease is diagnosed by radiography, ultrasonography, Computed tomography and immunological tests. Fluid therapy, plasma, analgesics, antiemetics are generally recomended. Also, dogs are provided healthy diet.

Keywords: Dogs, Pancreatitis, Neutrophillia and inflammation

Introduction
The pancreas is a flat, thin organ located in an abdomen, caudal to the stomach and is composed of a left limb or lobe, which lies behind the greater curvature of the stomach and adjacent to the cranial aspect of the transverse colon; a right limb or lobe which lies just medial to the proximal duodenum and a body between these two limbs (Saunders, 1991; Evans, 1993) [59, 17]. It is composed of two major types of cells responsible for both endocrine and exocrine roles. The endocrine function is localized in distinct islet of langerhans that constitute less than 1% to 2% of the pancreas (Evans, 1993) [17] and produce hormones required to regulate glucose and to some extent lipid metabolism. The islets of langerhans constitute four different types of cells namely, the alpha cells which secrete glucagon, beta cells secrete insulin, gamma cells secrete somatostatin and delta cells secrete pancreatic polypeptidase. The exocrine part, constitutes about 98% is composed of acinar cells and ductular cells. The major function of the exocrine pancreas is production, storage, and secretion of digestive enzymes important for degradation of ingested proteins, fats, and polysaccharides which are subsequently released into the stomach and/or small intestine as food reaches these organs (Williams, 2000) [82]. The digestive enzymes produced by the pancreatic acinar cells, are stored until the pancreas is stimulated to secrete them into the duodenum.
The ductal system in dog consists of 2 ducts; the pancreatic duct, which lies adjacent to the common bile duct just before it enters the duodenum through the major duodenal papilla and the accessory pancreatic duct which enters the duodenum at the level of minor papilla (Evans, 1993) [17].

Pancreatitis And Its Pathophysiology
Pancreatitis was first described by Dr. Reginald Fitz in 1889. Pancreatitis is inflammation of the Pancreas and can be acute or chronic. Both acute and chronic forms of pancreatitis occur in dogs, with the acute form being more clinically recognized (Williams, 2000; Van Den Bossche, 2010) [84, 73]. Acute pancreatitis is usually sterile inflammation with acute onset and characterized by necrosis and edema; which doesn't permanently disrupt the pancreatic architecture and is completely reversible. Acute pancreatitis is thought to occur primarily because of inappropriate activation of zymogens to their active forms within the pancreas, thereby resulting in autodigestion, pancreatic inflammation and necrosis of the pancreatic tissue (Williams, 2000) [84].

Depending on the severity of inflammation, pancreatic edema may occur, resulting in leakage of pancreatic digestive enzymes into the peritoneal space or the intravascular space. In the initial stages the body is able to protect itself from damage due to the limited supply of alpha- macroglobulins and other protease inhibitors in systemic circulation by binding to the leaked digestive enzymes, thereby inactivating them and expediting their removal from the body. Once this limited supply is exhausted, there is widespread inflammation and activation of the coagulation, fibrinolytic and complement cascades due to the circulating digestive enzymes. Disseminated intravascular coagulation, shock, and multiorgan failure (Williams, 1996) [83] may also develop in the affected animals.

The exact mechanism by which acute pancreatitis develops is still incompletely understood. Normally, to prevent autodigestion various pancreatic defense mechanisms exist. 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) [67, 76, 52]. In the acinar cell, storage of zymogens in granules prevents their damage by lysosomal proteases (Watson, 2004; Mix and Jones, 2006) [76, 52]. Cleavage of a small amino terminal peptide called trypsin activation peptide (TAP) of the polypeptide chain, causes activation of zymogens, but this normally does not occur until they are secreted into the small intestine. Trypsinogen is the first zymogen to be activated, which is cleaved by brush border enzyme enteropeptidase (previously enterokinase) synthesized by the enterocytes of the duodenal mucosa to form trypsin (Watson, 2004; Mix and Jones, 2006) [76, 52]. Recently, chymotrypsin C, an another pancreatic enzyme, has also been implicated in activating or inactivating trypsinogen in the small intestine, depending on the calcium concentration of the environment (Szabo *et al.,* 2012) [71]. Calcium concentration being high within the pancreatic duct and small intestinal lumen but very low in the acinar cells, favour trypsin activation (LaRusch and Whitcomb, 2011) [39]. However activation of trypsin is also pH dependent: although trypsin requires a relatively high pH to function (i.e. the alkaline pH of the small intestine), its activation appears to be exquisitely pH sensitive. Trypsin plays predominant role in the activation cascade by cleaving the activation peptides from the other zymogens and itself (Watson, 2004; Mix and Jones, 2006) [76, 52]. Damage caused due to inappropriate early intra-pancreatic activation of proteases is prevented by two mechanisms. The first mechanism involves small amounts of trypsin that can hydrolyze itself (Watson, 2004) [76] or a low-molecular-weight molecule pancreatic secretory trypsin inhibitor (PSTI), present in the zymogens can inactivate approximately 10 percent of the total amount of trypsin by temporarily binding to it (Watson, 2004; Mix and Jones, 2006) [76, 52]. Another protection mechanism against the possible fatal effects of protease release in the vascular space is played by plasma protease inhibitors. 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, 2003) [65]. A cascade of early activation of zymogens, especially proelastase and prophospholipase is initiated by premature activation of trypsin in the acinar cells where the developing granules are normally kept strictly separated from lysosomes and might inadvertently get activated (Bunch, 2003;Watson, 2004) [9, 76]. Zymogen granules abnormally fuse with lysosomes which contain proteases, due to disturbance in cellular metabolism or an increase in the permeability of the lipoprotein membrane that, at low pH are capable of activating the zymogens (Schlines, 2007) [61]. Zymogen granules also contain trypsin inhibitors, which are not active at the low pH present in lysosomes. If the zymogen activation process proceeds vigorously, pancreatitis can result with autodigestion of the pancreas. Activation of intracellular enzymes results in cellular necrosis and subsequent sterile inflammation, which leads to peri-pancreatic fat necrosis (Bunch, 2003; Watson, 2004) [9, 76]. Neutrophil migration is initiated by Trypsin and chymotrypsin into the pancreas, with the subsequent production of reactive oxygen species and nitric oxide causing ongoing inflammation (Keck *et al.,* 2005) [37]. There is shift from apoptosis to necrosis in pancreatitis, implicated by neutrophils along with substances such as endothelin-1 and phospholipase-A2 (PLA-2) (Windsor, 2000; Al-Mofleh, 2008) [86,1]. In the early course of Acute Pancreatitis, Interleukin (IL)-8 is one of the major initiators of neutrophil migration and also upregulates intercellular molecule adhesion1 to promote adhesion of neutrophils to the endothelial wall (Bhatia, 2000; Frossard, 1999) [6, 21]. Alteration in pancreatic circulation besides, stimulation of multiple cytokines exacerbates inflammation (Cuthbertson, 2006; Makhija, 2002) [14, 47]. The serum and tissue anti-proteases are consumed by the activated trypsin and other protease enzymes resulting in the activation of the kinin, coagulation, fibrinolytic and complement cascades leading to systemic problems such as hemorrhage, shock, disseminated intravascular coagulation (DIC) and vascular collapse (Bunch, 2003; Ettinger *et al.,* 2005)[9, 16].

Signalment

Breed Predilection

Acute pancreatitis can affect any breed; however several breeds are over represented like schnauzer, Yorkshire terrier, spaniels, boxer, Shetland sheepdog and collies.

Age & Range

Typically affects middle-aged to older patients that may be overweight or have history of dietary indiscretion.

Predisposing causes

Risk factors associated with development of acute pancreatitis in dogs.

Risk factors are given in Table 1. (Adapted from: 1. Cook *et al*., 1993 [13]; 2. Hess *et al*., 1998 [27]; 3. Bunch, 2003 [9]; 4. Watson, 2004 [76]; 5. Hill and Van Winkle, 1993 [29]; 6. Ferreri *et al*., 2003 [18]; 7. Mix and Jones, 2006 [52]; 8. Simpson, 2001b [63]; 9. Washabau, 2001 [75]; 10. Simpson and Lamb, 1995 [63]; 11. Weiss *et al*., 1996 [81]; 12. Akol *et.al*., 1993[2] ; 13. Gaskill and Gribb, 2000 [23].

Causes

Causes of pancreatitis include

Intrinsic factors such as biliary disease, hypertriglyceridemia, gastric/duodenal disease, and primary pancreatic disease – tumor, cyst.

Extrinsic factors include diet (high fat), drugs/toxins, and surgical manipulation. Direct effects could include direct toxicity or hypersenstivity reaction. Indirect effects could

include ischemia, thrombosis, and increased viscosity of pancreatic fluid. Many drugs can potentially cause pancreatitis, but a few are more commonly associated with the disease. These drugs include seizure medications, such as potassium bromide; chemotherapy drugs such as vinblastine, cisplatin, L-asparaginase and azathioprine; and antibiotics, such as tetracycline and the sulfonamides, steroids (only in association with intervertebral disc disease and surgery), propofol, thiazide diuretics, procainamide, organophosphates, cholinergic agonists Trimethoprim, sulfamethoxazole has been thought to cause an immune mediated pancreatitis in dogs (Schlines, 2007, Dalefield *et al.*, 1999; Trepanier *et al.,* 2003) [61, 15, 72].

Clinical picture

Dogs with Acute pancreatitis generally present with a sudden onset of anorexia, depression, vomiting (which can be either self limiting ceasing within 12-24 hours or life threatening depending upon the severity of the disease), abdominal pain, sometimes fever and diarrhea (Hess *et al.,* 1998) [27]. Affected dogs attain "praying position" or "position of relief" in response to cranial abdominal pain (Bunch, 2003) [9]. There are signs of dehydration and shock such as tachycardia, tachypnea, prolonged capillary refill time, hypothermia, and dry mucous membranes. Acute renal failure may develop secondary to hypovolemia and ischemia resulting from vomiting as well as potential development of intravascular coagulopathy and direct inflammation (Zhang *et al.,* 2008)[87]. Aggregation of activated neutrophils in the glomeruli is caused due to activation of nuclear factor kappa B (Satoh *et al.,* 2003) [58]. Acute lung injury also may develop in dogs, the pathogenesis of which is linked to platelet activating factor, although PLA-2, tumor necrosis factor alpha (TNF-α), and IL-1 may also play a role (Lopez *et al.,* 1995, Gomez-Cambronero *et al.,* 2002) [45, 25]. Other systemic complications include disseminated intravascular coagulation and cardiac arrhythmias, mediated by the many systemic inflammatory cascades. Diabetic ketoacidosis is a commonly reported comorbidity in canine with Acute pancreatitis (Lem *et al.,* 2008) [44], causing trypsin activation and acinar cell necrosis, rather than the exocrine inflammation destroying the acinar cells (Bhoomgoud *et al.,* 2009) [7]. Late-onset complications such as chronic relapsing pancreatitis and the subsequent development of exocrine pancreatic insufficiency or diabetes mellitus have been described in dogs (Watson, 2003; Watson *et al.,* 2010) [77, 78].

Histological Scoring Of Pancreatitis

A follow-up study by Newman *et al.* (2006) [53] suggested a histological grading system for canine pancreatitis in which a number of histological features were graded on each histological section between 0 and 3 where grade 0=none of the section affected; grade 1 was up to 10% of the section affected; grade 2 was 10–40% of the section affected and grade 3 was over 40% of the section affected. The histological features graded were: neutrophilic inflammation; lymphocytic inflammation; pancreatic necrosis; fat necrosis; oedema; fibrosis; atrophy and nodules. This grading system has subsequently been used by others in canine studies (Watson *et al*. 2011; Bostrom *et al*., 2013) [79, 8] but has yet to be extensively validated by independent pathologists.

Mortality Rates

The reported mortality rate for AP in dogs ranges from 27% to 58% (Charles, 2007; Cook.*et al*., 1993; Ruaux, 1998) [11, 13, 57].

Diagnosis

Haematological findings

Complete blood cell count should be conducted on all the patients. Peripheral blood neutrophilia with a degenerative left shift and leucocytosis is common; anemia and thrombocytopenia are the early indications of disseminated intravascular coagulation. An elevated packed cell volume may be observed secondary to hemoconcentration (Steiner, 2003; Hess *et al.,* 1998) [65, 27].

Serum Biochemistry

Azotemia: Azotemia is often present in dogs with acute pancreatitis which may be pre-renal or renal in origin (Hill *et al.,* 1993; Hess *et al*.,1998; Gerhardt *et al*., 2001; Bunch, 2003) [29, 24, 9]. Prerenal azotemia develops as a result of dehydration and renal azotemia may occur secondary to hypovolemia or shock or may be associated with multiorgan dysfunction. If fluid therapy doesn't resolve it, then there is possibility of renal failure (Williams, 2000) [82].

Hyperbilirubinemia: Hyperbilirubinemia (two-fold to five-fold increase), present in 30-53% of dogs noticed in cases of cholestasis (Hill *et al.,* 1993; Hess *et al*., 1998; Gerhardt *et al*., 2001; Washabau, 2001) [29, 27, 24, 75] which develops secondary either to pancreatic inflammation or to fibrosis, which obstructs (partially or completely) the common bile duct (Bunch, 2003; Watson, 2004; Mix *et al.,*2006) [9, 76, 52].

Elevated Hepatic enzymes: Hepatic ischemia, local inflammatory mediators and toxic pancreatic mediators in the portal circulation lead to hepatocellular injury with increased liver enzymes in dogs (ALT, ALKP and AST) (Hill *et al.,* 1993; Hess *et al.,* 1998) [29, 27]. Alkaline phosphatase (ALKP) may be two to 15 times normal and alanine aminotransferase (ALT) may be two to five times normal. Cholestasis can also result in increased AST, ALT and alkaline phosphatase (AP) (Watson, 2004) [76].

Hyperglycemia and hypoglycemia: Hyperglycemia develops due to glucagon release in excess of insulin from an inflamed pancreas, in combination with stress-related increases of cortisol and catecholamines (Hill *et al.,* 1993; Bunch, 2003; Watson, 2004) [29, 9, 76]. 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) [76]. More severe cases of acute pancreatitis are usually characterized by hypoglycemia (39%) (Hess *et al*., 2000)[28].

Hypocalcaemia: Mild to moderate hypocalcaemia has also been reported in dogs with pancreatitis. Hypocalcaemia is thought to occur as a result of deposition of calcium (such as soaps in peri-pancreatic fat) within the pancrease, which occurs secondary to pancreatic inflammation, an acute shift of calcium in soft tissues, and hormonal imbalances (e.g. thyrocalcitonine and abnormal parathyroid responsiveness) are possible factors (Bunch, 2003; Watson, 2004; Mix *et al.,* 2006) [9, 76, 52]. However hypocalcaemia is rarely severe enough to result in clinical signs related to low serum calcium (Williams, 1996) [83].

Hypercholesterolemia: is also commonly identified in dogs with Acute pancreatitis (Mix *et al.,* 2006) [52].

Hyperlipemia: Hyperlipemia can be either a cause or, more likely as a result of the disease (Watson, 2004) [76]. 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 *et al.*, 1993; Mansfield *et al.,* 2001) [29, 48].

Hypoalbuminemia: Hypoalbuminaemia may be a consequence of systemic inflammation. Albumin may also be lost from leaky blood vessels into the extracellular space and into 'third spaces' (*e.g.,* peritoneal cavity, pleural cavity) as a result of pancreatitis-induced vasculitis.

Hyperproteinemia: occurs secondary to dehydration (Bunch, 2003, Mix *et al*., 2006) [9, 52].

Electrolyte abnormalities: Vomiting and reduced food intake can lead to hyponatremia, 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 *et al.,* 1993; Hess *et al*., 1998) [27, 29].

Hyperamylasemia and hyperlipasemia: Traditionally Serum amylase and lipase were used for diagnosing acute pancreatitis in companion animals but because of both pancreatic and extrapancreatic sources, they have poor specificity. Reported sensitivities of these enzymes for a diagnosis of pancreatitis are 50% to 70% (Mix *et al.,* 2006) [52].

Diagnostic imaging

The most commonly used imaging techniques for assessing the pancreas in veterinary patients are abdominal radiography and ultrasonography (Mix *et al.,* 2006) [52].

Radiography

Radiographic findings in dogs with pancreatitis are subjective and include loss of detail in the cranial abdomen, displacement of the stomach to the left, and displacement of the duodenum to the right or ventrally, widened pyloric-duodenal angle. The colon may be displaced caudally in some patients (Steiner, 2003; Mahafey *et al.,* 1998; Holm *et al.,* 2003) [70, 46, 30]. In a retrospective study of fatal cases of canine pancreatitis, only 24% of dogs had radiographic abnormalities attributable to pancreatitis (Hess *et al.,* 1998) [27]. Therefore, abdominal radiography has a low sensitivity in diagnosing pancreatitis (Raux, 2003) [56]. Abdominal radiography is still a very important part of the diagnostic workup for a dog with acute onset of vomiting or abdominal pain. This is mainly because of the ability to rule in or rule out intestinal obstruction or other changes such as free gas within the abdomen or a distended, fluid-filled uterus. Abdominal radiography is widely available, safe, noninvasive, and relatively inexpensive. Images may be evaluated immediately, which is important in critically ill patients.

Ultrasonography

Ultrasonography is more sensitive than radiography in diagnosing pancreatitis. Sensitivity and specificity of abdominal ultrasonography has been shown to be highly operator-dependent and sensitivity has been reported to be up to 68% in dogs (Hess, 1998) [27]. Changes in pancreatic echogenicity and development of focal lesions (Nyland, 1983; Lamb, 1995) [54, 38] due to pancreatic edema, necrosis, or hemorrhage secondary to pancreatitis can be detected. Acute necrotizing pancreatitis is frequently associated with an enlarged, hypoechoic pancreas and peripancreatic necrosis (manifested as hyperechogenicity surrounding the pancreas) and fluid accumulation around the pancreas (Mix *et al.,* 2006) [52]. Complications of pancreatitis, such as pancreatic abscesses or pseudocysts, may also be identified via ultrasonography. Extrahepatic biliary obstruction should be ruled out during an abdominal ultrasound (Schlines, 2007) [61].

Computed tomography

CT is the most widely used diagnostic test in assessing pancreatitis in humans and is considered to be the most effective method of detecting inflammatory disease of the pancreas (Haaga *et al.,* 1977) [26]. However, limited information is available regarding the value of CT in veterinary patients. Peripancreatic changes, including the presence of peripancreatic fluid and thickening of tissue in the pancreatic regions, may also be noted. A major concern with the use of CT in diagnosing pancreatitis in dogs is the requirement of anesthesia to obtain images. Even in sedated or moribund patients, motion artifact interferes with accurate CT of the pancreas (Mix *et al.,* 2005) [51]. The suitability of an individual patient for anesthesia must be assessed before pursuing abdominal CT. The availability of CT is limited and may be financially prohibitive for some owners.

Biopsy

Biopsy of the pancreas remains the gold standard in diagnosing canine acute pancreatitis (Steiner, 2003) [65]. It is highly specific, but the sensitivity of pancreatic biopsy is poor because pancreatitis may be localized to small regions within the pancreas. Pancreatic biopsy may be performed via surgically (laparoscopy or laparotomy) or ultrasound guided fine needle aspiration (Schlines, 2007) [61]. Visual inspection of the pancreas may confirm suspected pancreatitis. However, a normal gross appearance of the pancreas does not exclude the possibility of microscopic pancreatic inflammation and clinically significant pancreatitis (Steiner, 2003) [70]. Laparoscopic evaluation of the pancreas is less invasive than laparotomy. Ultrasound-guided fine-needle aspiration of the pancreas may be performed without anesthesia and may reveal inflammation, necrosis, or sepsis of the pancreas (Center, 2004) [10]. Because of the regional nature of pancreatitis, normal results of fine-needle aspiration cannot exclude a diagnosis of pancreatitis. Therefore, fine needle aspiration of the pancreas is a relatively specific, but not sensitive, diagnostic test for pancreatitis.

Diagnostic Markers

Trypsinogen activation peptide

During the inappropriate activation of trypsinogen to trypsin, TAP is released into the Pancrease where it may diffuse into the intravascular or peritoneal space. Trypsin activation peptide (TAP) may be measured in the serum or urine of patients clinically suspected of having pancreatitis. A significant increase can be seen 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) [56]. 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) [56], which could explain the rather low sensitivity. It is considerably more sensitive and specific in assessing the severity than canine trypsin like immunoreactivity (cTLI) (Mansfield *et al*., 2003), but its lability and limited availability limit its usefulness (Williams, 2000) [82].

Serum canine trypsin like immunoreactivity (cTLI)

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) [9, 56]. Elevations have a high level of specificity, although decreased renal function can influence this result (Simpson *et al.,* 1995; Ruaux, 2003; Watson, 2004) [63, 56, 76]. 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 endopeptidase. CTLI is a poor predictor of outcome for acute pancreatitis (Mansfield *et al*., 2003) [50]. Another limitation is that it does take several days to run this test (Simpson *et al*., 1995; Mix *et,al*., 2006) [63, 52], sensitivity of serum TLI concentration for the detection of pancreatitis is limited to 30% to 60%, making serum cTLI concentration a suboptimal diagnostic test for canine pancreatitis(Steiner *et al*.,2001, Newman *et al*.,2004, Mansfield *et al*.,2000) [68, 53, 48].

Serum canine pancreatic lipase immunoreactivity (cPLI)

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 *et al.,* 2000; Steiner *et al*., 2001c) [67, 69] and developed by Texas A & M researchers. It can be considered the single best blood test because of its high specificity and sensitivity (Steiner *et al*., 2001a) [66]. 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 such as the stomach and salivary glands, as pancreatic lipase is antigenically unique compared with lipase produced in other parts of the body and cannot be measured with this test. (Steiner *et al*., 2000) [67]. Furthermore, renal failure and administration of steroids do not seem to contribute to elevated levels of cPLI (Steiner *et al*., 2001b; Watson, 2004) [68, 76]. The reference range for serum cPLI is reportedly 2.2–102 µg/L. Using a cut-off value of 200µg/L, the test was 82% sensitive and 100% specific (Richard). The major drawback of this test is that results are generally not available for several days because of the limited availability of the test. This delay in results is problematic, particularly in critically ill patients. The current commercially available test for specific canine pancreatic lipase (Spec-cPL) is a sandwich enzyme linked immunosorbent assay, using a recombinant peptide as the antigen and monoclonal antibody. Using Spec-cPL, results ≤ 200 µg/L are expected in healthy dogs, and results >400µg/L are considered consistent with a diagnosis of pancreatitis (Huth *et al.,* 2010) [35]. An in-clinic rapid semiquantitative assay (SNAP-cPL, Idexx, Maine, USA) has also been developed and shows good alignment and reproducibility with Spec-cPL (Beall *et al.,* 2011) [3]. Spec-cPL has a sensitivity of 63.6%. The sensitivity of cPLI and Spec-cPL increased with increasing severity of pancreatic inflammation.

C Reactive protein

Because acute pancreatitis is an inflammatory process, acute-phase response proteins such as C-reactive protein (CRP) are released by the liver. 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 *et al.,* 2006) [52]. 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) [64]. Measurement of CRP concentrations can however aid in assessing the severity of the disease (Holm *et al.,* 2004) [31]. A study in dogs with pancreatitis has shown elevated levels of CRP in dogs with pancreatic necrosis compared with dogs with edematous pancreatitis (Spillman, 2002) [64]. A more practical application of this test, rather than the diagnosis of pancreatitis, may be as a tool to monitor the progression or resolution of pancreatitis or as a prognostic indicator.

Urinalysis

Urinary TAP is considered even less accurate than serum TAP in diagnosing severe pancreatitis, because it is not significantly different between healthy dogs, dogs with pancreatitis and dogs with non-pancreatic disease (Mansfield *et al*., 2000a; Mansfield *et al*., 2003) [48, 50]. However, in the study by (Mansfield *et al.,* 2000a) [48] dogs that died of severe pancreatitis did have higher urinary TAP than dogs with milder forms.

Treatment

Intravenous fluid therapy

Vomiting and inappetance result in dehydration in dogs with AP, which generally requires IV fluid replacement. In addition to the systemic effects of dehydration or hypovolaemia, the pancreas is very sensitive to altered blood flow. Disturbed pancreatic microcirculation is usually multi-factorial in origin and can occur as a result of increased vascular permeability resulting from inflammatory cytokines, and microthrombi formation resulting from hypercoagulability (Gardner *et al.,* 2008) [22]. There is a theoretical benefit in using alkalinising fluids, such as lactated ringer's solution (LRS), to increase pH and therefore prevent further trypsin activation within the acinar cell (Bhoomagoud *et al.,* 2009) [7]. There is no current recommended preference for either the use of LRS or saline solution as the initial crystalloid of choice. There are multiple rodent experimental studies that show a beneficial effect of dextrans over crystalloid therapy in Acute pancreatitis (Hotz *et al.,* 1996, Huch *et al.,* 1995) [33, 34].

Plasma

Purpoted benefits of Plasma transfusion (6-12ml/kg) in treatment of AP include replacement of circulating α-macroglobulins, coagulation factors and anti-inflammatory factors (Weatherton *et al.,* 2009) [80]. Administration of plasma was shown to be superior to both crystalloid and colloid administration in a rat experimental model of pancreatitis (Leese *et al.,* 1998) [42]. Fresh frozen plasma (FFP) contains the anti-proteases that may help neutralize enzymes. FFP also has anti inflammatory proteins such as albumin which could be beneficial. Fresh frozen plasma (FFP) has only about 20-30% of the oncotic properties of colloids (Weatherton *et al.,* 2009) [80]. Despite an experimental benefit of FFP in rats (Leese *et al.,* 1988) [42], there has been no proven benefit in people (Leese *et al.* 1991, Leese *et al.* 1987) [40, 41] or in dogs (Weatherton *et al.,* 2009) [80] and it remains an expensive treatment for veterinary patients. In the light of these findings, administration of FFP should probably be reserved for those dogs with documented

coagulation abnormalities.

Analgesia

Pain is a common clinical sign of acute pancreatitis, and is manifested in dogs typically with a crouched appearance (Hess *et al.,* 1998) [27]. Pain is likely to be mediated due to local effects- whereby the inflamed and enlarged pancreas itself causes pain, or by subsequent amplification of visceral pain. A number of amino acids (glutamate and aspartate) and neuropeptides (substance P, neurokinin A, calcitonin gene-related peptide) are involved in a complex circuit of pain recognition and transmission (Mansfield, 2003) [50]. Multidimensional scales published for use in dogs that consider aspects other than pain intensity include the Melbourne Pain Scale (Firth *et al.,*1999) [19] and the Glasgow Composite Pain Scale (GCPS) (Holton *et al.,* 2001) [32] as in Table 2.

Nutrition

If the enterocytes doesn't get the luminal nutrients and aminoacids then gastrointestinal tract is thought to be the main contributor of systemic inflammatory state during acute pancreatitis, which is a catabolic disease causing significant nitrogen loses increases nutritional requirements particularly due to pancreatic necrosis (Flint *et al.,* 2003) [20].

Anti emetics

In dogs affected with AP, vomiting is both centrally and peripherally mediated. Maropitant, an effective anti emetic agent blocks both centrally and peripherally mediated emesis by blocking Neurokinin1 (NK1) receptor and substance P production (Karanjia, 1990; Conder, 2008; Rau *et al.,* 2010; Benchaoui, 2007; Sedlacek *et al.,*2008; Victor 2007;) [36, 12, 4, 62, 74, 55].

Gastric acid reduction

Proton pump inhibitors are the preferable agents to increase the gastric Ph for gastric mucosal health by preventing the development of gastric mucosal ulcerations, also increased gastric Ph decreases exocrine pancreatic stimulation (Leffler, 2009; Bersens *et al.,* 2005) [43, 5].

Table 1: Risk factors of acute pancreatitis in dogs

Hyperlipidemia	Inherent abnormal lipid metabolism (Miniature schnauzers) 4, 9, 11, accumulation of toxic fatty acids in the pancreas1, ingestion of a large fatty meal3, concurrent disease 2, 4, 13
Concurrent diseases	Diabetes mellitus 13, hypercortisolism 13, Hypothyroidism 2, 4
Infection /infestation	Viral, parasitic, mycoplasmal, bacterial, protozoa (*Toxoplasma gondi, Babesia canis*),hepatic flukes.
Other causes	Uremic pancreatitis1, prior gastrointestinal disease 2, hypercalcaemia 4,11 and thrombus formation 2

Table 2: Catagories of Pain intensity.

Mild to Moderate	Quiet but responsive to surroundings Unsettled Looks around when abdomen is palpated	Buprenorphine with or without Lidocaine and/or Ketamine infusion.
Moderate to Severe	Decreased response to surroundings or stimuli Slow or reluctant to move Restless Stretching of abdomen, looking around at abdomen Flinches on abdominal palpation	Buprenorphine with Lidocaine and Ketamine infusion.
Severe to excruciating	Non responsive to stimuli refuses to move or getup screams, cries or snaps when tries to get up or when abdomen palpated.	Epidural morphine with lidocaine/ketamine infusion.

Conclusion

Because of the unspecific clinical symptoms, AP is an underestimated disease in canines resulting in severe morbidity or death in patients. The combined interpretation of history, clinical signs, various biochemical, serological tests and imaging techniques can be effective for confirmation of the disease. For evaluating the complications of AP and assessing the general condition of the patient, complete blood count, serum biochemistry and urinalysis are preferred and for definitive diagnosis other laboratory tests must be used, because of the high sensitivity and specificity, pancreatic lipase immunoreactivity (PLI) is currently the most reliable test in both canine and feline. Thus by the collective interpretation of various tests, most of the cases can be readily diagnosed for initiating a rapid corrective therapy.

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