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Topical Review

Acute Pancreatitis in Dogs: Advances in Understanding, Diagnostics, and Treatment

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A B S T R A C T

Acute pancreatitis in dogs is a potentially reversible condition, but in severe forms it can cause systemic and local complications. These complications are driven by the cytokine, complement, and kinin systems, with the roles of these systems along with other substances such as nitric oxide being increasingly studied. The intestinal tract and altered pancreatic microcirculation also contribute greatly to the perpetuation of disease. Diagnosis remains difficult, because the true diagnostic utility of the current tests available is problematic to establish. Further understanding of the pathophysiology of this disease has opened up new areas of research into optimal treatments. In particular, the role of enteral nutrition has been the focus of much attention, and current recommendations are to feed earlier in the disease than previously thought.

There is much confusion about the nomenclature surrounding pancreatitis and its various definitions in the veterinary literature. This is probably because pathological classifications are dependent on histological descriptions. Because the different types of pancreatitis overlap in their clinical presentation and biopsy specimens are rarely obtained ante-mortem in acute pancreatitis, a clinical bias in terminology currently exists in the veterinary literature. Some references distinguish between acute pancreatitis (AP) and acute pancreatic necrosis (APN) as being different entities.[1] What is most likely is that the response is to the same stimuli, but the progression and final outcome is different between the two.

AP is considered a completely reversible condition, unless the initial triggers of disease persist, and chronic or recurrent inflammation ensues as discussed in another section of this journal.[2,3] AP is also characterized by having no fibrosis or exocrine atrophy.[4-6] Clinically, the histological differentiation between APN, AP, and recurrent AP is seldom determined because pancreatic biopsy is not undertaken ante-mortem. Therefore, the medical nomenclature usually relates to the severity and longevity of clinical signs. Mild AP causes no multisystem failure and has an uncomplicated recovery, whereas severe AP causes multisystem failure or development of complications. The presence of infected necrosis and the extent of the necrosis are the two most important determinants of outcome in people.[7] Such a determinant has not been made in dogs, partly because of the difficulty in assessing the amount of necrosis.

Pathophysiology

The pathophysiology of AP in dogs is still to be conclusively determined, and our current understanding is extrapolated from human and experimental models. The earliest cellular event thought to occur is co-localization of pancreatic zymogens (inert pancreatic enzymes) and lysosomal proteases within the acinar cell due to an apical block as demonstrated in Figure 1.[8] Trypsin is then activated and leads to activation of the other pancreatic zymogens to active enzymes.[8] This is normally prevented from occurring by physical separation of zymogen granules and lysosomal granules.[9] Additionally, pancreatic secretory trypsin inhibitor (PSTI) within the acinar cells allows for immediate inhibition of trypsin should it be activated within the acinar cells, but is overwhelmed if more than 10% of the trypsin is activated.[8,10] As well as co-localization, initial activation of trypsin may be due to oxidative stress or hypotension, and in general is worsened by a low acinar pH and high intracytosolic calcium concentrations.[7,8,11-13]

Activated pancreatic enzymes are then released in the pancreatic tissue, and local inflammation ensues. Trypsin and chymotrypsin are capable of directly initiating neutrophil migration into the pancreas, with the subsequent production of reactive oxygen species and nitric oxide causing ongoing inflammation.[14] Neutrophils have also been implicated in causing a shift from apoptosis to necrosis in pancreatitis, along with substances such as endothelin-1 and phospholipase-A2 (PLA-2).[7,15]

A complex and interdependent "cytokine storm" then ensues, with multiple cytokines stimulating inflammation, as well as being produced by inflammatory cells.[16] Interleukin (IL)-8 is one of the major initiators of neutrophil migration early in the course of AP and also upregulates intercellular molecule adhesion 1 to promote adhesion of neutrophils to the endothelial wall.[17,18]

In addition to multiple cytokines being stimulated, there is an alteration in pancreatic circulation that exacerbates inflammation.[19] Necrotizing pancreatitis causes a progressive reduction in capillaries after acinar cell injury that cannot be reversed by fluid resuscitation alone in experimental models.[20] Other inflammatory pathways being investigated in experimental models include the kallikrein-kinin and complement system.[21-23] Another aspect under investigation of considerable interest because of the potential to intervene pharmacologically is the role of substance P, which has been shown to be expressed at high levels in a mouse model of AP.[24] Expression of substance P appeared to be particularly related to lung injury, and genetic deletion of neurokinin 1 receptors was protective against the systemic effects of pancreatitis.[24] It is also suggested that NO and substance P interact and synergistically amplify pain and inflammation.[25] Additionally, the intestine is thought to contribute to or exacerbate inflammation directly due to intestinal ischemia.[26]

Etiology and Risk Factors in Dogs

The list of potential etiologies that can cause pancreatitis in dogs is long and includes dietary factors, hyperlipoproteinemia, drugs, toxins, hypercalcemia, duct obstruction, duodenal/biliary reflux, pancre-

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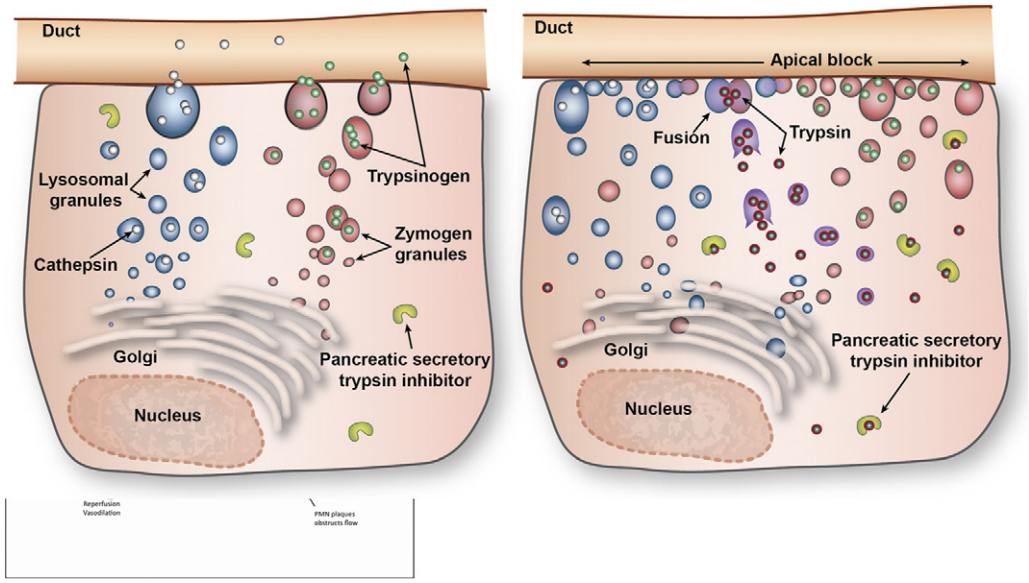

Fig. 1. Demonstration of the co-localization theory. In the normal cell on the left, the zymogen granules and lysosomes are manufactured within the Golgi apparatus, but processed and transported to the apex separately. In the abnormal cell on the right, there is an apical block, which allows zymogen granules to fuse with lysosomes. Cathepsin B, a lysosomal protease, is then able to activate trypsinogen to trypsin in the acinar cells. Pancreatitis develops when the local safeguard PSTI is overwhelmed by trypsin, and pancreatic enzymes are then activated within the acinar cell. Figure reproduced with permission from Journal of Veterinary Internal Medicine.

atic trauma, ischemia/reperfusion, and idiopathic causes.[1] Specific diseases such as babesiosis and leishmaniasis are also reported to cause pancreatitis in dogs, although for the latter it is unclear whether it is the disease or the treatment that is responsible.[27-29] Drugs that have been reported in the veterinary literature to cause pancreatitis include azathioprine, chlorthiazide, hydrochlorthiazide, zinc, potassium bromide, vinblastine, sulfonamides, cisplatin, organophosphates, L-asparaginase, and 5-aminosalicylate among others, although many of these are speculative and not proven.[30-34] The potential of glucocorticoids to directly cause pancreatitis in dogs is now largely dismissed, because corticosteroids have been shown to increase nonspecific lipase activity but not canine pancreatic lipase (cPL), without causing pancreatic inflammation.[35-37]

There is often evidence cited that low-protein, high-fat diets induce pancreatitis and high-fat diets in dogs cause a severe pancreatitis.[38,39] These studies did not assess whether there was pancreatic necrosis or inflammation, rather the volume of pancreatic secretion and the pancreatic enzymes within those secretions were assessed. Therefore, it is unproven at a cellular level despite a strong anecdotal association between the development of pancreatitis and feeding of high-fat, low-protein diets to dogs. Overweight dogs are certainly at greater risk of pancreatitis, and this may be associated with abnormal dietary intake and altered lipid status, or it can indicate a general predisposition to inflammation.[40,41] A chronic inflammatory state is associated with adipose tissue, and adipokines in people, and probably also occurs in dogs.[42,43] In one retrospective survey, dogs with recent ingestion of unusual food items and garbage ingestion showed an increased risk of developing pancreatitis, rather than dogs that appeared to have a higher intake of treats and snacks.[41] This study suggested, but could not prove, that inappropriate food rather than the fat/protein content of food per se may be the most important factor in the development of pancreatitis.

AP may also directly result from hypoxia and ductal hypertension via an effect on pancreatic microcirculation as previously discussed.[19] This is reflected in the high incidence of pancreatitis reported after abdominal surgery, especially adrenalectomy, although factors other than hypotension may contribute.[41,44] Despite the experimental association between premature trypsin activation and hypercalcemia,[11] common conditions such as lymphoma that cause hypercalcemia are not reported to cause pancreatitis in dogs. This may be that the increase in calcium usually seen in dogs is more gradual than that seen in people, where hypercalcemia-associated pancreatitis is most often seen in cardiopulmonary bypass.[45] It may also be that AP is subclinical and escapes diagnosis in those dogs.

Hereditary pancreatitis occurs in people, and although a variation in the *SPINK* gene has been recognized in Miniature Schnauzers, a causal relationship with pancreatitis has yet to be established.[46,47] Concurrent disease, particularly diabetes mellitus, hypothyroidism, and hyperadrenocorticism, are commonly reported in canine pancreatitis.[40,41,48] All 3 of these endocrinopathies are associated with changes in serum lipid concentrations, and the association between hyperlipidemia and pancreatitis cannot be discounted.[49] Equally, polyphagia associated with these conditions could indirectly lead to ingestion of inappropriate dietary items.

Mortality Rates in Dogs

The reported mortality rate for AP in dogs ranges from 27% to 58%.[1,48,50,51] This reported rate is questionable because the reports were from referral centers and therefore predisposing to more severe cases, or there was a lack of definitive gold standard diagnosis. Euthanasia for nonmedical reasons may also influence the true mortality of this condition. Even taking those factors into account, it is a higher mortality rate than the 5% to 15% reported in human studies.[15]

Clinical Signs

Dogs with AP generally present with a sudden onset of anorexia, depression, abdominal pain, and vomiting (Table 1).[52] The findings on clinical examination vary considerably with the severity and stage of AP and the associated degree of dehydration and shock. Severely affected dogs may have signs of dehydration and shock such as tachycardia, tachypnea, prolonged capillary refill time, hypothermia, and dry mucous membranes. Mildly affected dogs may have less dramatic signs.

Acute renal failure may develop secondary to the hypovolemia and ischemia resulting from vomiting as well as potential development of intravascular coagulopathy and direct inflammation.[53] It has been postulated that nuclear factor kappa B activation may also cause ag-

Table 1
Summary of clinical findings of 70 dogs with fatal acute pancreatitis. Adapted from Hess et al (1999)[52]

Historical Finding	Number of Cases	Percentage
Anorexia	64	91
Vomiting	63	90
Weakness	55	79
Diarrhea	23	33
Polyuria/Polydipsia	35	50
Neurological abnormalities	14	20
Melena	11	16
Weight loss	8	11
Hematemesis	7	10
Hematochezia	3	4

gregation of activated neutrophils in the glomeruli.[54] Additionally, endotoxin released during intestinal ischemia may promote renal vasoconstriction.[55] Acute lung injury also may develop in dogs with AP.[56] The pathogenesis of this is most closely linked to platelet activating factor, although PLA-2, tumor necrosis factor alpha (TNF-α), and IL-1β may also play a role.[57] Other systemic complications include disseminated intravascular coagulation and cardiac arrhythmias, all mediated by the many systemic inflammatory cascades initiated by acute pancreatitis.

Diabetic ketoacidosis is a commonly reported comorbidity in canine AP.[41,58] It is possible that the acidosis present in diabetic ketoacidosis may cause trypsin activation and then acinar cell necrosis, rather than the exocrine inflammation destroying the acinar cells.[12] Late-onset complications such as chronic relapsing pancreatitis and the subsequent development of exocrine pancreatic insufficiency or diabetes mellitus have been described in dogs.[59,60] Recently in people, subclinical exocrine insufficiency has been demonstrated after a bout of AP, and this may also occur in dogs.[61]

Acute fluid collections are defined in the human medical literature as fluid accumulations within the pancreatic parenchyma that develop in the first 6 weeks after a bout of acute pancreatitis.[62] On the other hand, a pseudocyst develops at least 6 weeks after an episode and does not contain an epithelial lining, and its contents are composed of amylase-rich pancreatic secretion, generally occurring in milder cases of acute pancreatitis.[62] Despite the terms "pancreatic abscess" or "pseudocyst" commonly being used in the veterinary literature, on review of this literature, development of fluid in the canine pancreas is invariably acute in onset and sterile in nature.[63-69] This suggests that instead they should be termed "acute fluid collections."

Another local complication that occurs in acute pancreatitis is the development of extrahepatic bile duct obstruction.[70] This may occur from physical obstruction of the bile duct due to the close proximity to the pancreas (Fig 2), or be functional secondary to localized peritonitis. This condition typically manifests as jaundice 3 to 7 days after the onset of acute pancreatitis. Dogs may be systemically well despite the jaundice, or at times this is associated with a deterioration in clinical status. In most dogs, the jaundice and bile duct obstruction resolve with time.[71] This may be due to reduction in the size of the pancreas. However, because the pancreas takes weeks to return to normal size, the resumption of oral intake and subsequent gall bladder contraction is more likely to speed up the process.

Diagnosis

Routine Clinical Pathology

Most laboratory abnormalities present in dogs with pancreatitis result from hypovolemia or inflammation and are therefore not specific for pancreatitis.[71,72] This is particularly clinically relevant because most of the differential diagnoses for pancreatitis, such as uremia or gastrointestinal inflammation, will also result in similar laboratory changes.[71] In brief, these changes include leukocytosis, azotemia, and increased liver enzymes. Decreased calcium has also been documented in dogs with acute pancreatitis, and has been suggested to be associated with a poorer prognosis.[51,73,74]

Lipase and Amylase

Serum lipase and amylase activities have been shown to increase in experimental and naturally occurring canine pancreatitis.[72,73,75] However, neither enzyme activity is specific to the pancreas because they also originate from gastrointestinal mucosa and are excreted by the kidneys.[76] Serum lipase activity has been shown to be markedly increased in some dogs with acute enteritis, gastro-enteritis, liver disease, and renal failure.[77-79] Lipase activity can also be elevated up to 5-fold by the administration of dexamethasone in dogs with no pancreatic inflammation.[76] Conversely, dogs with exocrine pancreatic insufficiency have been shown to have measurable serum lipase activities.[80,81] Serum lipase and amylase activities can also be normal in dogs that do have pancreatitis. In one retrospective review by Hess et al, $<$ 50% of dogs with acute fatal pancreatitis had increased lipase activities, whereas 30.8% had an elevated amylase activity.[52] Other estimates place the value more conservatively at 15% to 20% of cases with pancreatitis having normal serum lipase and amylase activities.[77,82] This means that not only is there a huge overlap of clinical and laboratory findings seen in dogs with pancreatitis and with other diseases, but also there is no guarantee that a dog with pancreatitis will have increased lipase or amylase activities.

Canine Trypsin-like Immunoreactivity (TLI)

Serum TLI concentration is an accurate and specific indicator of pancreatic function and is thought to be entirely pancreatic in origin.[83] It has been shown in experimental models of pancreatitis that there is an early increase in the serum TLI concentration, followed by a rapid decrease.[84] However, in clinical cases, the TLI concentration may have decreased by the time of sampling and can be affected in azotemia and so is seldom useful.[77,85] These reasons, along with an often lengthy delay in receiving results, make its usefulness for the diagnosis of AP limited.

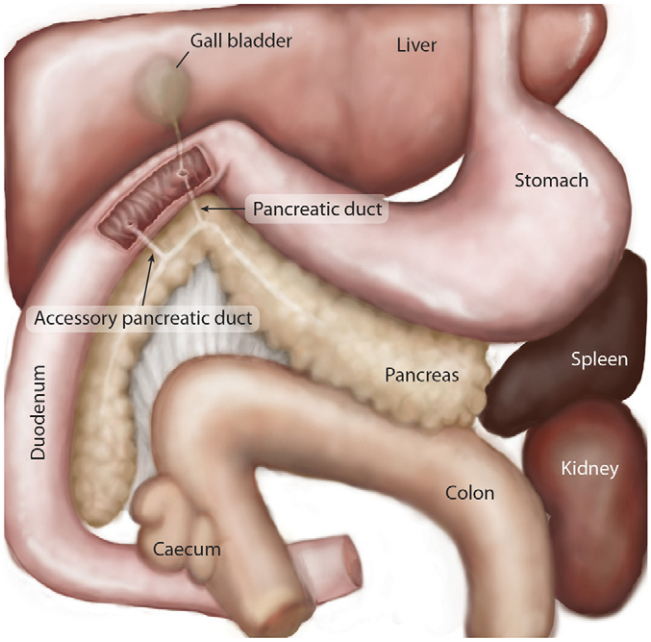

Fig. 2. Anatomical depiction of the canine pancreas, and its close proximity to a variety of abdominal organs. In particular, the close location to the gall bladder is particularly of interest in the development of extrahepatic bile duct obstruction.

Diagnostic Imaging

Radiology

The radiological abnormalities in acute pancreatitis are not sensitive for detecting pancreatitis.[51] Signs that may be apparent include decreased contrast and lack of detail in the cranial abdomen due to the surrounding peritonitis. As can be appreciated, this is often difficult to detect and is not specific for pancreatitis. Other changes include a widened pyloric-duodenal angle, with a shift of the descending duodenum to the abdominal wall.[71] Changes have only been reported in 22% of dogs with severe pancreatitis in one study,[52] whereas in another earlier study, 76% of radiographs were considered abnormal.[51]

Despite these limitations, 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.

Ultrasound

Abdominal ultrasonography is increasingly performed in general practice and aids substantially in the diagnosis of acute pancreatitis in dogs. Changes in pancreatic echogenicity and development of focal lesions can be detected.[86-88] Acute necrotizing pancreatitis is frequently associated with an enlarged, hypoechoic pancreas and peripancreatic necrosis (manifested as hyperechogenicity surrounding the pancreas) and is relatively easy to identify (Fig 3).[89] Ingesta and gas in the gastrointestinal tract may interfere with visibility, and generally the right lobe adjacent to the duodenum is identified first.[89]

Despite the common use of ultrasound for the diagnosis of AP, it is extremely difficult to elucidate a sensitivity or specificity for this diagnostic modality based on published reports. The diagnostic utility of ultrasound is highly operator dependent and also requires equipment that is of high standard. In 3 retrospective reviews there was a quoted sensitivity of about 68%, but operator skill and equipment were not described in detail.[52,77,90] It is also likely that this modality is much better at detecting acute necrotizing pancreatitis than detecting chronic pancreatitis because of the peri-pancreatic necrosis that results in an obvious hyperechoic area surrounding the pancreas. Specificity of this modality is virtually impossible to determine, because histology would need to be performed to establish this, and so would only be performed in severe cases at post-mortem, or mild cases at exploratory laparotomy. Certainly, ultrasound cannot distinguish between inflammation, necrosis, or neoplasia.

Fig. 3. Ultrasound image typical of acute pancreatitis in the dog. There are usually hyperechoic areas corresponding to necrotic peri-pancreatic fat (saponified fat) surrounding an enlarged pancreas with pockets of hypoechoic areas throughout the parenchyma.

Diagnostic Advances

Canine Pancreatic Lipase Immunoreactivity (cPLI)

Canine pancreatic lipase is a recently established laboratory test (first as a radioimmunoassay [cPLI], and then an enzyme immunoassay [cPL]) that has been well validated and is now widely used.[91,92] The premise of this test is that it measures the serum concentration of only pancreatic lipase, and therefore should only be increased in pancreatic inflammation.[93] 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. This new commercially available assay shows a good correlation to the original radioimmunoassay, as well as high reproducibility, although the absolute reference intervals for the 2 assays are different. Using Spec-cPL, results $\leq$ 200 μg/L are expected in healthy dogs, and results $>$ 400 μg/L are considered consistent with a diagnosis of pancreatitis.[94] An in-clinic rapid semiquantitative assay (SNAP-cPL, Idexx, Maine, USA) has also been developed and shows good alignment and reproducibility with Spec-cPL.[95]

An early study of cPL reported a sensitivity of 88%, much higher than for lipase activity in the same 11 dogs.[96] In a later study, 22 dogs with gross evidence of pancreatic disease on post-mortem were assessed.[90] Both cPLI and Spec-cPL had an overall sensitivity of 63.6%, compared with 40.9% and 31.8% for amylase and total lipase, respectively. The sensitivity of cPLI and Spec-cPL increased with increasing severity of pancreatic inflammation.

Another study recently assessed 70 dogs presented consecutively for post-mortem at a tertiary referral center.[97] Sixty-three of those were found to have pancreatic inflammation on histology (56 mild, 7 moderate), whereas 7 had no histological evidence of pancreatic inflammation. The estimated sensitivity of canine pancreatic lipase was 21% for mild disease and 71% for moderate disease. This was a lower sensitivity than for total lipase (54% and 71%, respectively) in the same cohort of dogs. Although only 7 dogs were classified as having normal pancreatic histology, there was a specificity of 86% for Spec-cPL as compared with 43% for total lipase reported.

The specificity of Spec-cPL in dogs has also been assessed recently. In one study, 64 dogs (20 with gross evidence of pancreatitis on post-mortem, and 44 other dogs that were euthanized and submitted for post-mortem analysis) were assessed.[98] The pancreas from each dog was sectioned and inflammation scored, as previously described.[4] Forty dogs were classified as having no pancreatic disease because of an absence of clinical signs and no inflammation on histology. Thirty-eight of those 40 dogs had a Spec-cPL value $\leq$ 200 μg/L, and 39 had values $<$ 400 μg/L. This resulted in a specificity using the lower cutoff value of 95% (95% confidence interval 83.1-99.4), and using the higher cutoff value a specificity of 97.5% (95% confidence interval 86.8-99.9). This study assessed a number of healthy dogs, and there were no dogs with acute renal failure. Another recently published article assessed the specificity of Spec-cPL in dogs that died or were euthanized for a variety of reasons in a tertiary referral center.[99] In this study, the investigators attempted to stratify the dogs with pancreatic inflammation based on the severity of disease in order to only assign a diagnosis of positive pancreatitis to dogs that had a minimum amount of histological pancreatitis present. Specificity of 80% for Spec-cPL ($\leq$ 200 μg/L) was reported.

The 4 studies that assessed sensitivity of Spec-cPL (and cPLI) with pancreatic histology as the gold standard were combined for analysis.[90,96,97,99] Using the diagnostic cutoff of $>$ 400 μg/L, a sensitivity of 43.8% (43/98) overall was determined, although it must be emphasized that many of these dogs had minimal or very mild pancreatic inflammation, and so may not be the cohort tested in clinical practice.

Conversely, Spec-cPL appears to be highly specific for histological pancreatic inflammation.

These studies are useful guides, but the clinical relevance of the test is not fully evaluated in such studies, because dogs that have histological pancreatitis may be presented for another problem such as septic peritonitis. This is demonstrated in an as yet unpublished study, assessing SNAP-cPL in dogs with acute abdominal disease (abdominal pain, vomiting, diarrhea, abdominal distension) presenting to a veterinary emergency center.[100] This study showed a poor correlation between a positive test and a primary presentation of AP in dogs presenting with acute abdomen ($\kappa = 0.33$). A negative or low test had a good correlation to dogs having disease other than acute pancreatitis. This is similar to findings from a multicenter study that used Bayesian statistics to overcome the need for pancreatic histology as a gold standard. In that study, it was determined that dogs with Spec-cPL $\leq$ 200 μg/L and/or a negative SNAP-cPL were unlikely to have clinical AP.[101] Therefore, a positive Spec-cPL or SNAP-cPL should be considered in conjunction with other clinical signs and diagnostic imaging to ensure acute pancreatitis is the main cause of the clinical presentation. However, a negative result means acute pancreatitis is unlikely to be the cause of the dogs' presenting signs.

Serum Pancreatic Elastase-1

Pancreatic elastase (PE-1) came to the attention of researchers in the late 1960s, when elastase was shown to be involved in the pathogenesis of hemorrhagic pancreatitis in experimental models. This was later confirmed to occur at the same time or immediately after trypsin activation.[102] Studies have shown that when macrophages are exposed to pancreatic elastase they upregulate the expression of TNF-α, and so this supports the role of elastase in the systemic response to pancreatic inflammation.[103] Additionally, elastase has proteolytic effects, hydrolyzes scleroprotein elastin, is fibrinolytic, and increases the oxidative activity of neutrophils.

There is some support for serum PE-1 concentration as a diagnostic marker for pancreatitis in dogs.[104,105] A recent study determined that PE-1 had an overall sensitivity of 61% and specificity of 92%, comparable with published sensitivities for other pancreatic markers such as lipase and pancreatic lipase.[106] If only dogs with severe AP were evaluated, this sensitivity increased. There is a strong suggestion that serum elastase is not affected by renal clearance, but this has not been properly evaluated in dogs to date.[107]

Histopathology

Histological grading schemes have been developed for diagnosing pancreatitis in dogs, and to assist in assessing the sensitivity and specificity of diagnostic tests.[4,6,99] These have not been correlated to clinical severity, and therefore the clinical significance of those grading systems is not fully understood. It has been established that pancreatic histological changes can be unevenly distributed throughout the pancreas, necessitating frequent sectioning along the organ to be able to fully assess pancreatic inflammation.[108] Pancreatic biopsies are seldom obtained in dogs with acute disease and are probably most suitable for evaluation of chronic disease.

Assessing Severity

In people, early detection of severe as compared with mild AP is considered particularly important because this enables rapid transfer to intensive care units and improves the outcome.[15] There has also been an explosion in measuring various blood markers, such as IL-6, IL-8, IL-18, PLA-2, C-reactive protein (CRP), PMN-elastase, matrix metallopeptidase 9, serum amyloid A, trypsinogen-2, trypsinogen activation peptide, and procalcitonin. Of these, IL-6 seems to have the most clinical relevance in human gastroenterology.[109,110] TNF-α has been investigated in dogs with presumed pancreatitis, but was not shown to correlate with severity.[111]

CRP is an acute phase protein that changes rapidly in the circulation when there is inflammation, or tissue damage, and is the blood marker most commonly used in human medicine. CRP has been measured in dogs and has been shown to be increased in a number of inflammatory conditions, including AP.[112,113] Although CRP is increased in dogs with AP, there is a large variation in results between dogs, so a change in CRP from day to day may be more beneficial in dogs to predict outcome than a single result to predict severity.[114]

The biggest recent study assessing severity in people had more than 18,000 patients in over 200 centers and used classification and regression tree analysis to predict in-hospital mortality.[115] They determined that azotemia, impaired mental status, the presence of systemic inflammatory response syndrome, age $>$ 60 years and the presence of pleural effusion were most associated with prognosis. The mortality rate was significantly greater with a higher number of abnormalities present. This is a similar concept to a severity score developed in dogs using clinical and laboratory data that could easily be obtained in general practice within 24 hours of admission.[114] The poor prognostic indicators in that study were the presence of cardiac abnormalities, respiratory abnormalities, altered oncotic/hydrostatic pressures, or anorexia for 3 or more days. This scoring system is still to be evaluated in a large cohort of dogs.

Treatment

There are a number of areas surrounding treatment of acute pancreatitis that have not been fully evaluated and may have the potential to improve outcome in affected dogs.

Intravenous Fluid Therapy

One of the major factors that progresses mild pancreatitis to severe pancreatitis is disturbed pancreatic microcirculation.[20] This disturbance is usually multifactorial in origin and can occur because of increased vascular permeability resulting from inflammatory cytokines and microthrombi formation resulting from hypercoagulability.[19] The increased capillary permeability leads to edematous changes in the acinar cells and further migration of inflammatory cells. In necrotizing pancreatitis, there is a progressive reduction in capillaries after acinar cell injury, which cannot be reversed by fluid resuscitation.[20]

One study in people has shown that early fluid resuscitation in AP (as opposed to at 24 and 72 hours after onset of pain) leads to a better clinical outcome, most marked in milder forms of the disease.[116] It has also been shown that using Lactated Ringer's solution (LRS) produces better outcomes than using normal saline solution.[117] In the veterinary literature, there is no current recommended preference for either the use of LRS or saline solution as the initial crystalloid of choice. It is possible that the acidosis produced with saline solution administration may directly contribute to the systemic inflammatory state by stimulation of cytokine production, especially nuclear factor kappa B. An algorithm based on the human studies for fluid therapy in dogs with AP is shown in Figure 4.

Crystalloid therapy alone, however, may not be adequate or well tolerated in dogs with severe AP. An experimental study that induced AP in dogs identified that the dogs resuscitated with LRS alone required approximately 5 L more fluid during resuscitation to maintain systemic pressures, and this resulted in pulmonary hypertension and pulmonary edema.[118] There are multiple experimental rodent studies that show that dextrans exert a beneficial effect in AP.[119,120] The benefit appears to be independent of the molecular weight, concentration

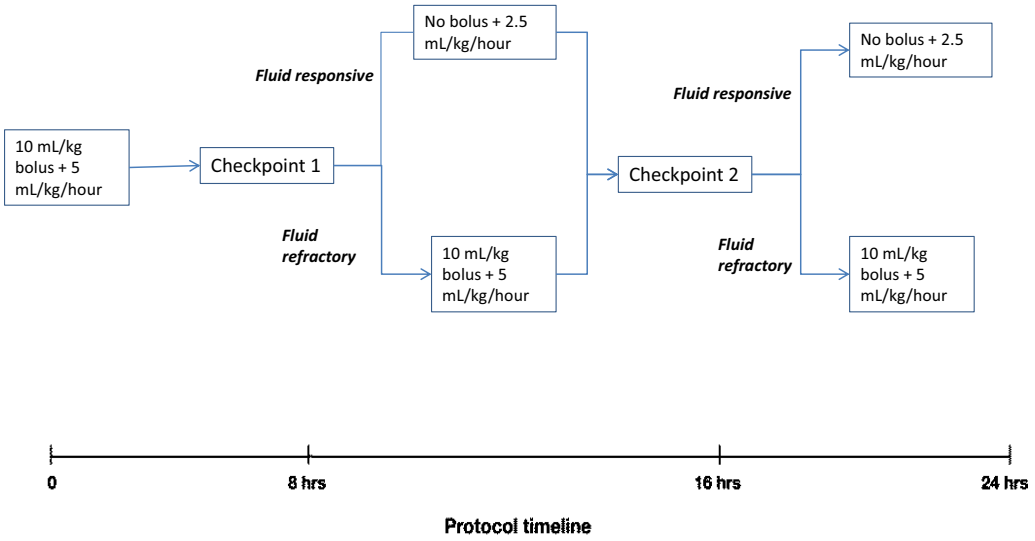

Fig. 4. Algorithm for fluid therapy as adapted from Wu et al.[117] Throughout the administration of fluid, careful attention to heart and respiratory rates should be paid to ensure there is not a volume (fluid) overload. If systolic blood pressure and peripheral output are not improved at each checkpoint, then the dog should be classified as fluid "refractory."

(6% or 10%), or combination with hypertonic saline solution, but has not been evaluated in dogs to date.

Plasma

The use of plasma in dogs with AP is widely reported in review articles and textbooks, although the use in this condition has been declining over the past 5 years.[121,122] Administration of plasma was shown to be superior to both crystalloid and colloid administration in a rat experimental model of pancreatitis.[123] Purported benefits include correction of hypoalbuminemia, replacement of circulating α-macroglobulins, replacement of coagulation factors, and amelioration of systemic inflammation.

There are no prospective controlled studies that prove the benefit (or lack thereof) of plasma transfusion in dogs with naturally occurring AP. One retrospective veterinary study analyzed data from a 10-year period and identified 77 dogs with pancreatitis that were admitted for treatment during that time.[124] There was a significant difference in mortality between the dogs that received plasma (7/20) compared with those that did not (6/57). However, because of its retrospective nature and the lack of stratification of disease severity or standardization of other treatments, there is significant bias in this conclusion. The dogs that received plasma by inference would be more severely affected, and so inherently were more likely to die because of their disease. However, the lack of benefit seen in this study does reflect much of the human literature on this same subject, and plasma is not currently recommended as treatment in people with AP, because it does not prevent early mortality.[125,126] That being said, correction of hypoalbuminemia when at a clinically significant level with colloids or potentially plasma should always be undertaken.

Anti-emetics

Anti-emetics are a commonly used group of drugs in the management of AP in dogs. Vomiting in dogs with pancreatitis is likely to be both centrally mediated because of the presence of circulating emetic agents, and peripherally mediated because of ileus, peritonitis, and pancreatic distension.[127]

There are no studies published on the efficacy of individual anti-emetic drugs in canine pancreatitis. Experimental models have shown that dopamine infusion improves the outcome in AP and ameliorates the inflammatory severity of the disease.[128] There is therefore a theoretic disadvantage in giving metoclopramide (a dopaminergic antagonist) to dogs with AP, although this is unproven.

Maropitant, which blocks the NK1-receptor, is an effective anti-emetic agent that blocks centrally and peripherally mediated emesis.[129,130] As well as being effective in controlling emesis, there is another theoretical benefit to NK1-receptor antagonism, via blocked production of substance P. Substance P is a mediator that is produced by nerve endings throughout the body, and mediates capillary permeability as well as being involved in the pathogenesis of pain.[131] When the NK1 receptor was blocked in a genetic mouse model, there was no difference in the amount of pancreatic inflammation produced, but distantly mediated lung injury was reduced.[132]

Gastric acid suppression

The rationale for gastric acid suppression in management of AP is that a higher gastric pH will lead to decreased pancreatic exocrine stimulation, and that AP predisposes to the development of gastric mucosal ulceration because of hypovolemia and local peritonitis. There have been no studies that report on the efficacy of gastric acid suppression in dogs with AP.

In people with mild to moderate disease, there have been randomized clinical trials assessing nasogastric suctioning. None of these have shown any benefit of this treatment in reducing pain or hospitalization duration.[133,134] In fact, some of these have actually shown prolongation of pain and nausea.

If gastric acid suppression is required because of a concern regarding gastric mucosal health, it may be theoretically preferable to administer proton pump inhibitors (PPIs). PPIs may have direct beneficial effects by blocking the vacuolar ATPase pump on pancreatic acinar cells.[135] One experimental study in rats showed that pantoprazole reduced inflammatory changes and leakage of acinar cells.[136] I

Corticosteroids

Historical reluctance to use corticosteroids in dogs, and to a lesser extent in people, resulted from the presumption that corticosteroids could lead to pancreatitis. Although theoretically any drug can cause pancreatitis in any individual dog, corticosteroids are no longer con-

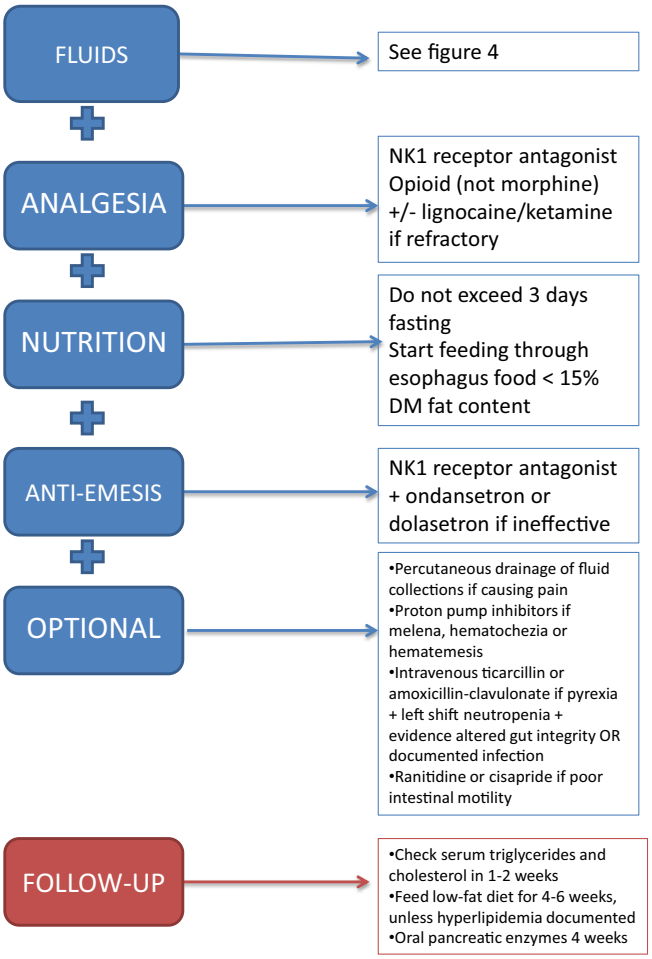

Fig. 5. Treatment considerations for acute pancreatitis in dogs, based on extrapolation from human and experimental data.

sidered high risk. Along with this, corticosteroids are the one group of drugs that are known to counteract virtually all pathways of inflammation. Corticosteroids inhibit release of proinflammatory mediators, decrease sequestration of neutrophils in the pulmonary vasculature, reduce adhesion of primed neutrophils to the endothelial surface of pulmonary vasculature, reduce release of elastase and free radicals from adherent neutrophils, and reduce pulmonary vascular permeability.[137] A specific role of corticosteroids in enhancing apoptosis, and increasing production of pancreatitis-associated protein, which confers a protective effect against pancreatic inflammation, has also been proposed.[138]

In addition, dogs with AP may have relative adrenal insufficiency, which is now termed as critical illness-related corticosteroid insufficiency (CIRCI).[139] CIRCI occurs when there is adrenal insufficiency along with tissue resistance to the effects of corticosteroids because of a prolonged and severe proinflammatory state. In particular, it causes hypotension and a poor response to fluid or vasopressor therapy in a subgroup of people. Low-dose hydrocortisone is the current recommended treatment for people with septic shock and CIRCI, whereas methylprednisolone is recommended for those with acute lung injury.[139] These recommendations have not been extended to people with acute pancreatitis to date, but are being evaluated. This is an area that warrants evaluation in dogs.

Judicious use of corticosteroids is increasingly considered in dogs with severe AP that may not be responding adequately to conventional treatment.

Nutritional management

AP is a catabolic disease with significant nitrogen losses strongly associated with mortality.[140] The gastrointestinal tract itself is now also thought to be a major contributor to the systemic inflammatory state during AP, particularly if it is not supplied with luminal nutrients.[26]

Historically, in human (and veterinary) gastroenterology, the idea was to "rest" the pancreas and therefore provide no exocrine stimulation during bouts of AP. Early studies had shown that despite pancreatic secretion being less when nutrients were delivered to the jejunum than to the duodenum in both people and dogs, it still occurred to some extent.[141,142]

Interest in enteral feeding for AP began to increase in the medical field over the past 15 years because of the expense and complications associated with total parenteral nutrition (TPN).[143,144] Studies assessing nutritional modalities in AP, including some in dogs, show an array of benefits in enteral feeding compared with TPN, albeit delivered into the jejunum.[145-147] However, meta-analysis that supports the use of early enteral nutrition in severe AP does this in the face of knowledge that TPN is probably harmful. In this way, the studies are only comparing a treatment of unknown efficacy with one with harmful side effects.

Because of technical difficulties associated with nasojejunal (NJ) feeding, human studies have assessed delivery into the stomach (nasogastric). Nasogastric feeding was shown to be as well tolerated as NJ feeding, and there was no increase in pain upon feeding.[148,149] This has been investigated in a recent prospective pilot study in dogs that demonstrated esophageal tube feeding was well tolerated in dogs with AP.[150] This study compared enteral feeding to TPN and was unable to show a statistically significant difference in outcome or other parameters. However, the enteral feeding group had significantly fewer episodes of vomiting and/or regurgitation.

Even if the notion that enteral nutrition is well tolerated and perhaps beneficial is supported, it is still unclear as to what diet to feed. Intuitively, dogs with pancreatitis are generally fed a low-fat diet. In one study of healthy dogs, there was no significant difference in measurable pancreatic adaptation in dogs fed variable fat content.[151] This also brings into question whether feeding of a low-fat diet is essential in the management of AP in the dog and should be evaluated in future studies. Certainly, when dogs are grossly lipemic, feeding a low-fat diet is well advised. The addition of probiotics or omega-3 fatty acids has also not been fully investigated in dogs with AP. However, because there is no proven benefit in human medicine, this is an area that is not necessarily a high priority. Glutamine supplementation of food has been gaining increasing attention recently. This is based on the fact that glutamine is the preferred respiratory fuel for rapidly growing cells like enterocytes and lymphocytes, so potentially has a role to play both in gut health and lymphocyte function.[152] The pancreas is also considered to have the highest turnover of glutamine in the body.[152] In one study in people, enteral nutrition supplemented with glutamine, arginine, tributyrin, and omega-3 made no difference in measures of inflammation.[153] Clinical outcome was not assessed, however, and it is possible that the arginine in that study was detrimental because it has been shown to damage the pancreatic acini.[154]

Treatment of complications

Surgery to treat pancreatic acute fluid collections in dogs has invariably resulted in a high mortality rate (> 50%) regardless of the technique used.[63-65,67] Spontaneous resolutions of acute fluid collections in the veterinary literature have been reported, as well as good responses to percutaneous drainage, suggesting noninvasive methods are preferable for managing this particular complication.[68,69] Although there have been suggestions that feeding during pancreatitis may increase the risk of acute fluid collections (because of enzyme

stimulation), this is not borne out of any of the canine reports or human studies.

Various surgical techniques have been described to treat extrahepatic bile duct obstruction.[155,156] These are invariably associated with a high mortality rate. Percutaneous drainage of the gall bladder has been described and is a relatively safe procedure.[70] The risks associated with this are mainly peritonitis, but if the bile is sterile, then this is fairly self-limiting and manageable. There is a lack of established strict criteria for when drainage of the gall bladder is necessary, and in most circumstances it is questionable if it is required at all.

It is commonly accepted in the veterinary[70,157,158] and human literature[61,159] that analgesia is a vital component of managing AP. Recently, the use of patient controlled analgesia in human gastroenterology has improved outcomes and reduced hospitalization times.[159,160] For dogs with AP opioids should be used as first line treatment. Buprenorphine does not cause contraction of the sphincter, and therefore theoretically could be preferable as first line therapy.[161] If opioid analgesia is considered insufficient, then other multimodal delivery of analgesia can be used. It is important if the pain in an individual animal appears to be increasing that a complication such as acute fluid collection is ruled out and treated as necessary (as discussed). An alternative analgesic agent to consider is ketamine, given as a continuous rate infusion. This modality is attractive due to the lack of detrimental effect on gastrointestinal motility.[162] Other alternative modalities include epidural analgesia (morphine with or without gabapentin), inter-pleural blocks and lignocaine continuous rate infusion.[163,164] None of these have been evaluated in canine AP, and modification of the analgesia plan should be performed on an individual basis.

A summary of the current extrapolated treatment recommendations is depicted in Figure 5.

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