

Management of acute-onset pancreatitis in dogs: a Narrative Review

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ABSTRACT

Acute-onset pancreatitis (AP) is common in dogs and presents diagnostic as well as management challenges. Until recently, the management of AP in dogs was based mainly on supportive and symptomatic care. Identification and management of a possible cause of the disease is important, but the majority of cases are considered to be idiopathic. Fluid therapy that is tailored to the patient's needs is crucial to provide adequate hydration while preventing overhydration. Antiemetics are required to control vomiting and fluid loss and aid in early nutritional support. Recognition and management of complications is also crucial. Furthermore, analgesics for abdominal pain are very important. More recently, pharmaceutical modification of the inflammatory cascade has gained interest and the first specific therapeutic agent for the treatment of AP, fuzapladib sodium, has been shown to have a reasonable expectation of effectiveness in a pilot study. This drug has been licensed for the treatment of clinical signs of AP in dogs in Japan and also has achieved FDA conditional approval in the US. Antibiotics should not be used indiscriminately but are indicated for patients with aspiration pneumonia, gastrointestinal bacterial translocation, or evidence of another bacterial infection. Proton pump inhibitors and plasma are not routinely prescribed in pancreatitis unless specifically indicated. Nonsteroidal anti-inflammatory drugs should be avoided. Corticosteroid therapy, once thought to be contraindicated, may have some beneficial effects, as shown in a single retrospective study. However, further studies are required before their routine use can be recommended. Finally, a surgical approach is rarely indicated.

Keywords: management, acute, narrative, review, pancreatitis

Introduction

Pancreatitis is common in dogs and can be either acute or chronic, with some cases showing evidence of both patterns of disease, which most likely represents acute on chronic disease.^{1,2} Acute pancreatitis is histologically associated with neutrophilic infiltration and, in severe cases, pancreatic necrosis. Acute pancreatitis is potentially reversible.¹ In contrast, chronic pancreatitis is associated with lymphocytic plasmacytic infiltration and irreversible changes with acinar atrophy and fibrosis.¹ One histopathologic study¹ reported

that almost two-thirds of pancreatitis cases are chronic. Clinically, the differentiation of acute and chronic pancreatitis is not possible, but chronic cases are commonly subclinical to mild and often remain undiagnosed. Acute pancreatitis is associated with an acute onset and worsening of clinical signs and, if severe, systemic complications and significant morbidity and mortality. The clinical differentiation between acute and chronic pancreatitis is difficult and requires histopathological confirmation. The designation acute-onset pancreatitis (AP), which refers to cases in which clinical signs appear suddenly, is the preferred designation.

Diagnosis of pancreatitis is challenging, but there is general agreement that optimal diagnosis is achieved by integrating clinical, imaging, and clinicopathologic findings. Measuring the concentration of pancreatic lipase in serum has been reported to represent the most sensitive and specific clinicopathologic parameter for the diagnosis of AP in the dog.³

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Until recently, the management of AP was mostly symptomatic and supportive, including identification and management of the cause of the disease, fluid therapy, recognition and management of complications, antiemetics, analgesics, nutritional support, and appetite stimulants.^{4,5} At the same time, antibiotics, anti-inflammatory agents, gastric acid suppressants, fresh frozen plasma, and pancreatic surgery are not widely considered to be standard management of AP in dogs or in people.^{4,5} These latter therapies have specific indications for their use. Recently, the first specific therapeutic agent, fuzapladib sodium, has become available for the treatment of AP in dogs.⁶ This narrative review was prepared by an international group of experts in the field on the basis of evidence, when available. However, the team of authors fully admits that this effort is incomplete, as few blinded and controlled studies on the treatment of AP in dogs are available. Where appropriate, we have also included findings from other species, while recognizing that there are species-specific differences that may preclude the direct transfer of data from other species to dogs.

Conventional Supportive and Symptomatic Care

Identification and management of the cause

While most AP cases in dogs are considered to be idiopathic, several risk factors of AP have been identified, including dietary factors, drugs/toxins, endocrinopathies, lipid disorders, miscellaneous factors, and various breed predispositions or hereditary factors.⁷ Hereditary pancreatitis is an important form of pancreatitis in humans and may play a role in several dog breeds that are overrepresented. The Miniature Schnauzer is more commonly affected than any other breed.⁸⁻¹⁰ Recently, 3 mutations of the serine peptidase inhibitor Kazal type 1 gene have been reported to cosegregate with pancreatitis in the Miniature Schnauzer, but none of these mutations are considered functional.^{11,12} While hereditary factors may confer an increased risk of disease, little can be done to therapeutically address this risk. Hypertriglyceridemia, but not hypercholesterolemia, is an important risk factor for pancreatitis in both humans and dogs. Determining the cause of severe hypertriglyceridemia (ie, evaluation for endocrine disorders) and managing it are important.^{8,13,14} A low-fat diet (< 20 g of fat/1,000 kcal) should be chosen for nutritional support in these patients (more details can be found in the section on nutrition). Hypercalcemia is another risk factor, and determining the cause as well as management should be undertaken. Finally, while drug-induced pancreatitis is considered to be rare in dogs, it can occur. While any drug could be implicated in an individual dog, the drugs with the most evidence for association with pancreatitis include selected antiepileptic drugs (eg, phenobarbital and potassium bromide), chemotherapy drugs (ie, L-asparaginase), and some

others (eg, azathioprine).¹⁵⁻¹⁷ In humans, potentially any drug should be considered a risk factor for pancreatitis as an idiosyncratic reaction (ie, non-dose-dependent and nonpredictable) or as an intrinsic reaction in which presence of underlying inflammation increases tissue sensitivity to the potentially toxic effects of a drug.^{18,19} A careful drug history should be obtained, and if the dog is on any drug considered to be a potential cause of acute pancreatitis, alternative options should be considered.

Fluid therapy

Dogs with AP often present with dehydration and hypovolemia secondary to vomiting, diarrhea, and dysrexia.⁹ The pancreas is particularly susceptible to hypovolemia. In addition to the systemic effects of dehydration on overall circulating blood volume, the pancreas may experience a greater decrease in local blood flow due to increased capillary permeability, arterial vasospasm, and formation of microthrombi.²⁰ Poor pancreatic perfusion may lead to progression of an acute self-limiting pancreatitis to a more severe necrotizing pancreatitis. The role of fluid therapy cannot be overemphasized, and because there is no specific therapeutic agent for AP in people, many studies have looked at the effects of fluid type and rate of infusion on the clinical outcomes in human patients with AP. While pancreatitis guidelines in people recommend normal saline or lactated Ringer's solution,²¹ a recent meta-analysis²² in people found that fluid resuscitation using lactated Ringer's solution reduces the progression of AP from a mild to moderate or even severe pancreatitis. However, there was no difference in the development of systemic inflammatory response syndrome (SIRS) or multiorgan dysfunction syndrome (MODS) with either fluid type.²² Currently, there is no strong evidence to show that the use of colloids or fresh frozen plasma is beneficial in AP patients.²³ At the same time, the use of colloids has been associated with complications, such as the development of coagulopathies or acute kidney damage.²⁴ Aggressive early fluid resuscitation has been recommended for many years in both human and veterinary pancreatitis patients. However, a recent multicenter randomized clinical trial in humans investigating the effects of aggressive versus moderate fluid resuscitation found that aggressive fluid resuscitation increases the incidence of fluid overload without preventing the progression to moderate or severe pancreatitis.²⁵ On the basis of findings in people, dogs with AP should be supported with a goal-directed fluid resuscitation plan with efforts to avoid fluid overload. A patient's hydration status, maintenance requirement, and ongoing losses should be estimated when the fluid volume is being determined for the individual patient. This assessment should be repeated every few hours, especially during the early course of hospitalization. Lactated Ringer's solution during initial fluid resuscitation is suggested. Careful clinical and hemodynamic monitoring are essential to ensure that the patient returns to euvoolemia without being fluid overloaded, preventing the development of interstitial edema, third-spacing of fluids, and worsening of hypoalbuminemia. Electrolyte disturbances such as hypokalemia should be corrected by supplementation in IV fluids where

appropriate. Fluid therapy, depending on fluid type, is also useful at correcting acid-base abnormalities (eg, metabolic acidosis) without the need for sodium bicarbonate administration.

Recognition and management of complications

Acute-onset pancreatitis in dogs can range from mild self-limiting disease to severe disease with local and/or systemic complications. Local complications seen with AP in people and dogs include pancreatic necrosis, pancreatic fluid accumulations, pancreatitis-associated extrahepatic bile duct obstruction (EHBDO), regional thromboembolic disease, and gastrointestinal dysmotility, while systemic complications include aspiration pneumonitis/pneumonia, SIRS, MODS, disseminated intravascular coagulation (DIC), acute kidney injury, or cardiac injury.^{1,26–32}

Pancreatic fluid accumulations are infrequently reported in dogs with AP. When they do occur, diagnostic sampling of fluid accumulations is considered to be safe and should be performed to differentiate a sterile from a septic process.^{33,34} A recent study²⁷ of a small cohort of dogs with fluid accumulations and suspected pancreatic abscessation found aspiration of the fluid collection to be safe and fluid analysis to be helpful to determine case management regarding either medical or surgical intervention and the need for antibiotic therapy. This study also found few cases with pancreatic fluid accumulations that were septic, further questioning the indiscriminate use of antibiotics without an appropriate indication. Another local complication of pancreatitis is EHBDO, resulting from local pancreatic inflammation compressing the common bile duct. In 1 small study,²⁶ 80% of dogs with pancreatitis-associated bile duct obstruction survived and most of them (94%) were managed medically without the need for decompressive cholecystocentesis. Dogs needing percutaneous or surgical decompression of the gallbladder had a higher mortality rate than those that did not. Neither the degree of hyperbilirubinemia nor bile duct dilation on ultrasound predicted survival. Bile duct stent placement is also rarely required, and dogs undergoing stent placement often had a poor outcome. Some patients may benefit from a short course of anti-inflammatory corticosteroids to lessen inflammatory compression of the common bile duct, but there are no studies evaluating the benefit of corticosteroids in AP with EHBDO.

Patients with AP may develop gastric stasis and/or intestinal ileus secondary to pancreatic inflammation^{35,36} and also from concurrent use of opioids for pain management. Support of GI motility may be a prerequisite to return to voluntary food intake. Opioid-sparing techniques (more information can be found in the section on analgesia) should always be considered to help reduce the dose and duration of opioid use (eg, continuous rate infusions of lidocaine or ketamine). The use of prokinetic agents should be considered in patients with clinical evidence indicating poor gastrointestinal motility. Ultrasound can be helpful in detecting poor gastrointestinal motility.³⁶

Cisapride, erythromycin, and metoclopramide are commonly used prokinetic drugs in dogs.³⁶ Cisapride and erythromycin hasten gastric emptying time and increase esophageal sphincter tone and are helpful when gastric stasis, gastroesophageal reflux, or reflux esophagitis are present.³⁶ Metoclopramide, a dopamine antagonist, is helpful in promoting upper gastrointestinal motility, but its use may potentially be counterproductive since dopamine controls inflammation and pancreatic perfusion in AP.³⁷

Pneumonitis due to aspiration of sterile gastric contents is a common sequela in humans with AP, especially when vomiting, regurgitation, or marked sedation is present.³⁸ If a dog with AP develops fever, dyspnea, and tachypnea while in the hospital, a 3-view thoracic radiograph or point-of-care ultrasound should be performed to confirm the presence of pneumonitis. Antibiotics are not always indicated with aspiration pneumonitis, as it is often sterile. However, some dogs may develop aspiration pneumonia and require antibiotics, especially if they have been treated with gastric acid suppressants.^{38,39}

Transient hyperglycemia and diabetic ketoacidosis can occur in some dogs with AP due to insulin exhaustion and/or resistance and may require insulin administration.⁴⁰ With clinical improvement of AP, many dogs may revert to normoglycemia and will not require long-term insulin therapy.

Dogs with severe AP can present with severe systemic inflammation, resulting in SIRS and MODS, the management of which has previously been considered difficult and unrewarding.⁷ However, a novel therapeutic option (more information can be found in the section on anti-inflammatory therapy) may decrease pancreatic inflammation, acute respiratory disease syndrome (ARDS), or SIRS and has been shown to improve clinical activity scores in dogs with presumed AP.⁶ Dogs with severe AP can also be hypercoagulable and at an increased risk of developing DIC.³¹ It is important for the clinician to recognize signs of DIC and consider starting antithrombotic therapy. In a study⁴¹ of dogs at risk of developing DIC that were evaluated with a combination of 6 coagulation parameters (ie, prothrombin time, activated partial thromboplastin time, D-dimer concentration, decreased antithrombin activity, fibrinogen concentration, and platelet count), ≥ 3 abnormal coagulation parameters helped to identify overt DIC with high sensitivity and specificity. Antithrombotic therapy should be considered in hospitalized dogs with severe AP, particularly those with acute necrotizing pancreatitis, that have signs consistent with hypercoagulability. In 1 study,²⁸ 10 of 26 dogs with acute pancreatitis evaluated by CT angiography had portal vein thrombosis, which was associated with longer hospitalization and a greater risk of clinical relapse. Other frequent complications of AP include myocarditis and acute kidney injury.^{29,42} While myocarditis in dogs with severe pancreatitis cannot be specifically managed, cardiac arrhythmias should be managed as they occur.²⁹ Appropriate fluid management decreases the likelihood of acute kidney injury, one of the most common complications in people with severe acute pancreatitis, but once developed, it should be managed accordingly.

Antiemetics

Vomiting is the most common clinical sign of AP in dogs.⁴³ The control of vomiting improves quality of life, prevents further dehydration from fluid loss through vomiting, and allows for early return to enteral nutritional support that is considered crucial for outcome in patients with severe disease. Vomiting is thought to occur in dogs with pancreatitis due to both centrally and peripherally mediated mechanisms.^{44,45} Maropitant citrate is a selective neurokinin-1 (NK-1) receptor antagonist that acts on both central and peripheral emetic pathways.⁴⁶ It has been shown to be effective in controlling vomiting in dogs with pancreatitis.⁴⁷ Maropitant citrate blocks substance P from activating NK-1 receptor stimulation along the vomiting pathway. There is evidence in mice that maropitant may also contribute to analgesia by blocking NK-1 receptors on pain pathways.⁴⁸ However, clinical support for the analgesic properties of maropitant citrate in cases of AP is lacking.⁴⁹ Ondansetron is a 5-HT₃ receptor antagonist and is reported to have both antiemetic and antinausea properties in dogs.^{50,51} Since ondansetron and maropitant act on different receptors, an additive effect may be achieved when combining both medications. Metoclopramide only has minimal antiemetic properties and is not recommended as an antiemetic in dogs with AP.⁵²

Analgesia

Abdominal discomfort should be assumed to be present in any dog with a diagnosis of pancreatitis.⁵ The classic signs of abdominal discomfort, such as a crouched stance ("prayer posture") or overt pain on abdominal palpation, may not be noted in some dogs. Other signs may include restlessness, reluctance to move, trembling, or vocalization.⁵³ Some stoic dogs may exhibit very vague clinical signs. Pain is likely present when tachycardia, tachypnea, and an increased blood pressure are present.⁴³ It is helpful to incorporate a pain scoring system when evaluating the patient, evaluate the patient frequently during therapy, and adjust the pain management on the basis of individual response to therapy. Despite the commonality of abdominal pain in dogs with pancreatitis, there is limited consensus as to the best treatment approach in dogs with AP. Opioids are typically utilized as first-line agents, and NSAIDs are typically avoided due to concerns for their gastrointestinal adverse effects and the frequency of hypovolemia/dehydration and the associated risk of acute kidney damage.⁵

Full μ -opioids (eg, methadone, morphine, fentanyl) are preferred in the majority of cases due to their superior analgesic properties relative to partial μ -opioid agonists (eg, buprenorphine), which may be suitable for mild pain in some dogs.⁵⁴ Some authors propose that fentanyl has disproportionately more negative impacts on ileus relative to other opioids, but on the basis of personal experience, the authors of this review disagree with this statement and prefer the use of an opioid with a short half-life, such as fentanyl, which allows for more rapid dose escalation or de-escalation in response to the

severity of discomfort and ileus. Ileus may be the result of inadequate analgesia (pain) or excessive analgesic dosing, and monitoring the response to dose alterations is required to make this determination.⁵ Morphine has been shown to worsen the severity of pancreatitis, increase bacterial translocation, and delay the pancreatic regenerative response to experimentally induced pancreatitis in mice.⁵⁵ Opioid analgesia has also been shown to affect gastrointestinal motility independent of disease severity, and increased opioid usage has been shown to be associated with prolonged hospitalization in humans.^{56,57} These combined factors have increased interest in opioid-sparing techniques in dogs with pancreatitis. Common opioid-sparing techniques used in veterinary medicine include the use of adjunctive analgesics or local blocks.⁵³ Adjunctive use of continuous rate infusions of ketamine and/or lidocaine are common in dogs with pancreatitis. Ketamine is an N-methyl-D-aspartate receptor antagonist and has been shown to reduce opioid requirements and may improve pain control in people and dogs.^{58–60} Potential adverse effects of ketamine at high doses include muscle spasm, increased salivation, and potentially tachycardia or hypertension, although these effects are rarely seen at the doses utilized for analgesia.⁶¹ Lidocaine is a voltage-gated sodium channel blocker that may have opioid-sparing effects when administered at a continuous rate infusion in dogs.⁶² Local block techniques that have been reported in dogs with pancreatitis include epidural analgesia and the transversus abdominis plane block.^{63,64} These techniques may provide analgesia while reducing or eliminating systemic opioid usage and warrant further investigation. Regardless of the protocol chosen, it is important to assess pain after administration of analgesia approximately every 2 to 4 hours to ensure that treatment has been effective. Naturally, the time frame for reevaluation is dependent on the duration of action of the analgesic(s) that have been selected and the severity of pain.

Oral analgesia remains a significant challenge in dogs with pancreatitis. Many of the orally administered agents anecdotally prescribed to manage pain have little evidence to support their use and the evidence that does exist largely supports their use in nonacute conditions. Gabapentin is an anticonvulsant medication with GABA-mimetic effects. Gabapentin has been shown to reduce the need for rescue analgesic agents in dogs undergoing a mastectomy, but it has also been shown to be nonbeneficial in other acute pain settings, including intervertebral disc disease and in dogs undergoing a forelimb amputation.^{65–67} Codeine is an oral opioid analgesic with a high first-pass effect that may be suitable for use in dogs with pancreatitis. A recent study⁶⁸ found that a combination product of acetaminophen with codeine was noninferior to an NSAID for postoperative analgesia; however, formulations with acetaminophen are currently not recommended in dogs with acute pancreatitis. Tramadol has been historically prescribed for analgesic management for pancreatitis outpatients, but a recent study⁶⁹ suggested that

dogs are unable to generate significant concentrations of the active metabolite O-desmethyl tramadol and its use has fallen out of favor. Oral butorphanol has been considered, but this drug has weak analgesic properties and poor oral bioavailability and thus is not routinely recommended.

Nutrition

The role of nutrition in pancreatitis has advanced significantly over the past several years. Traditionally, it was believed that dogs with pancreatitis should be held off food to prevent pancreatic secretions and minimize pancreatic inflammation and necrosis.⁷⁰ However, it has now been shown experimentally in rats and clinically in people that pancreatic secretions decrease early in acute pancreatitis, as damaged pancreatic acinar cells are unable to respond to normal physiologic stimuli.^{71–73} The rationale of holding off food in patients with pancreatitis is no longer a valid premise.^{71–73} Holding the patient off food has many negative impacts, including promoting enterocyte damage, gut barrier dysfunction, and changes in the gut microbiome.^{74,75} Early enteral nutrition has been shown to be safe and well tolerated in dogs with severe AP.⁷⁶ Early enteral nutrition has also been shown to improve voluntary return to food intake and reduce gastrointestinal complications in dogs with pancreatitis.⁷⁷ Contraindications for early enteral nutrition include uncontrolled vomiting or abdominal pain associated with feeding.

The authors recommend early enteral nutrition in dogs with pancreatitis. Oral food intake can be encouraged by providing adequate analgesia and antiemetics, using multiple food textures, and warming the food to increase acceptance. If animals are not eating within 3 days (including the prehospital period) assisted enteral nutrition should be pursued. Alternatively, a brief trial with an appetite stimulant, such as capromorelin or mirtazapine, could be attempted, although success with this approach is minimal.

Due to their minimally invasive nature, nasogastric or nasoesophageal tubes are typically used for inappetent dogs during hospitalization. These tubes can be placed under sedation, whereas other tubes such as esophagostomy tubes typically require placement under general anesthesia. Recently, it was proposed that nasogastric and nasoesophageal tubes can be used in the at-home environment without significant complications, but this has yet to become common practice.⁷⁸

Typical nutrient profiles used in dogs with pancreatitis include low to moderate fat and easily digestible (“gastrointestinal”) diets. These diets are fed frequently and in small volumes. Ketogenic diets and stone dissolution diets, which are often high in fat, should be avoided until their safety has been studied in more detail.^{79,80} Excess soluble fiber should be avoided, as it may worsen gastric emptying, particularly in dogs that are vomiting or regurgitating.⁸¹

For small feeding tubes, such as a nasoesophageal or nasogastric tubes, a liquid diet is required. Many liquid diets are low in caloric density. The authors are aware of one low-fat liquid diet designed specifically

for veterinary use that has a caloric density around 1 kcal/mL (Low Fat Liquid; Royal Canin SAS) and a fat-free liquid elemental diet designed for human use (Vivonex; Nestlé) that can also be used in dogs.

Anti-Inflammatory Therapy

It has now been established that the progression of pancreatitis is directly related to inflammation, and anti-inflammatory agents may have beneficial effects in dogs with AP.³² In humans, there is some evidence that NSAIDs may have a beneficial effect on pancreatic damage in patients with AP, but these potential benefits have not been verified by double-blinded, controlled clinical trials and have not been studied in dogs.⁸² Almost all NSAIDs have been implicated in potentially causing pancreatitis in humans.⁸³ In dogs, NSAIDs can cause gastric ulcers and lead to acute renal toxicity in patients that are dehydrated and hypovolemic.⁸⁴ Thus, NSAIDs should not be routinely administered to canine patients with pancreatitis.

Metamizole (dipyrone) is a nonclassical NSAID that has been shown to have analgesic effects in humans with pancreatitis and has not been implicated in causing pancreatitis.⁸⁵ However, metamizole is not licensed in many countries and may even be illegal in some countries, including in the US, the UK, and Japan.

Recently, corticosteroids have been suggested to have beneficial effects in the treatment of canine pancreatitis and anecdotal observations suggest that some dogs improve after the administration of corticosteroids.⁸⁶ A single retrospective study⁸⁶ noted beneficial effects in dogs with pancreatitis; notably, earlier improvement of clinical signs and reductions in C-reactive protein concentrations when compared to a historical control group. Beneficial effects of corticosteroids may include their anti-inflammatory properties as well as the management of potential adrenal insufficiency. Adrenal insufficiency, while poorly documented, is a differential diagnosis for a dog with refractory hypotension, as cortisol is needed to maintain normal vascular responsiveness.⁸⁷ However, corticosteroids have a wide variety of effects, some of which may be detrimental to dogs with pancreatitis, and further controlled studies are needed before recommending corticosteroids in the first-line management of AP.

Fuzapladib sodium is a leukocyte function-associated antigen type-1 inhibitor that prevents the extravasation of neutrophils from the capillary beds (**Figure 1**). It has been shown to have a reasonable expectation of effectiveness in a pilot study in dogs with AP.⁶ Fuzapladib sodium was licensed for use in dogs with AP in Japan under the tradename Brenda or Brenda Z. More recently, fuzapladib sodium has received FDA conditional approval for the treatment of clinical signs of AP in the USA under the tradename PANOQUELL-CA1. In acute pancreatitis, activated neutrophils are extravasated into both pancreatic and extrapancreatic tissues, releasing cytokines, radical oxygen species, and proteases.^{88,89} Leukocyte function-associated antigen type-1 activation is crucial in neutrophil extravasation and can thus lead

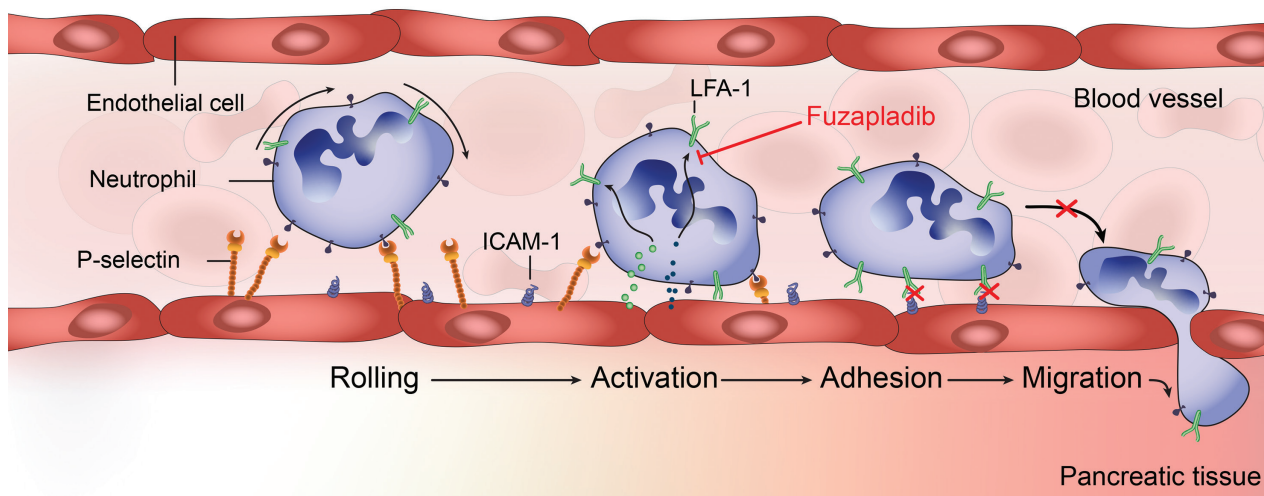


Figure 1—Neutrophil extravasation into the pancreas and other tissues occurs through the rolling, activation, adhesion, and migration of neutrophils. During inflammation, endothelial P-selectin activates the rolling phase by capturing neutrophils from the bloodstream. The rolling phase enables immunoglobulin-like cell adhesion molecule 1 (ICAM-1) expressed on the endothelial cells to bind with activated leukocyte-function associated antigen-1 (LFA-1) on the surface of neutrophils. This will cause neutrophils to adhere and migrate into the pancreas and other tissues, such as the lungs. Fuzapladib sodium prevents extravasation of neutrophils from the capillary bed by inhibiting LFA-1. (Reprinted with permission from Cridge H, Lim SY, Algül H, et al. New insights into the etiology, risk factors, and pathogenesis of pancreatitis in dogs: potential impacts on clinical practice. *J Vet Intern Med.* 2022;36[3]:847–864. doi:10.1111/jvim.16437.)

to excessive tissue damage.⁸⁹ For example, human patients infected with COVID-19 sometimes develop ARDS, which is due to massive extravasation of neutrophils into the lungs that may lead to death.⁹⁰ Similarly, dogs and humans that die during the early stages of pancreatitis often die of ARDS.³⁰ Blocking extravasation of neutrophils is a pathway undergoing considerable research for preventing the development of ARDS.⁹⁰ Fuzapladib sodium prevents extravasation of neutrophils by blocking activation of neutrophils through the inside-out signal. The inside-out signal physiologically leads to adherence of leukocyte function-associated antigen type-1 to immunoglobulin-like cell adhesion molecule 1 on the capillary surface, leading to neutrophil flattening with subsequent migration into the tissues surrounding the capillaries.⁸⁹

In a recent blinded placebo-controlled clinical pilot field effectiveness trial in the US, fuzapladib sodium given at a dose of 0.4 mg/kg IV for 3 consecutive days led to a significantly greater clinical improvement over the 3-day treatment period than treatment with an indistinguishable placebo, as assessed by the modified clinical activity index (**Figure 2**).⁶ The study also showed that fuzapladib sodium was safe.⁶ Given the mechanism of action of fuzapladib sodium, it would be expected that the drug would have its biggest impact in dogs that will develop severe forms of pancreatitis. However, reliable prediction of severity is not possible early in the disease process despite the fact that multiple clinical scoring systems have been developed for use in dogs.^{91–94} Further clinical studies with fuzapladib sodium are ongoing and expected to be concluded within a few years of this publication.

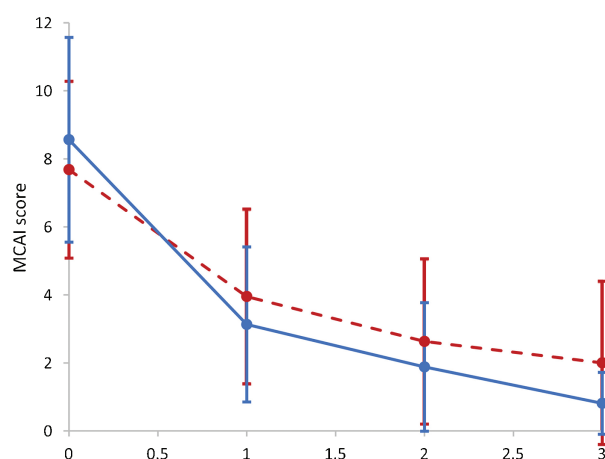


Figure 2—Mean total clinical activity index (MCAI) scores ($\pm$ SD) over time in 35 client-owned dogs with AP after a 3-day IV treatment with 0.4 mg/kg fuzapladib sodium ($n = 16$, blue line) or a placebo ($n = 19$, red line). The maximum total MCAI score possible was 19. (Reprinted with permission from Steiner JM, Laines C, Noshiro Y, et al. Fuzapladib in a randomized controlled multicenter masked study in dogs with presumptive acute onset pancreatitis. *J Vet Intern Med.* 2023;37[6]:2084–2092. doi:10.1111/jvim.16897.)

Controversial Therapies

Antibiotics

While there are infectious causes of pancreatitis in dogs, they are rare. Most infectious causes of pancreatitis are part of systemic infections, such as with *Leishmania*, *Babesia*, or *Heterobilharzia americana*, rather than local bacterial infection.^{95–99}

However, pancreatitis can lead to a breakdown of the intestinal barrier function with bacterial translocation from the intestinal lumen.¹⁰⁰ In humans, roughly 50% of patients who die from AP die from a bacterial infection secondary to bacterial translocation.¹⁰¹ This usually happens very late in the disease process, often after several weeks of hospitalization, and initial antibiotic therapy is discouraged.^{4,102–105} While no studies have been conducted on the efficacy of early antibiotic intervention in dogs, very few cases of infectious complications due to bacteria have been reported. Routine and nondiscriminate antibiotic therapy is not recommended unless there is a high suspicion or documentation of a bacterial infection.^{27,106} Some dogs with AP will develop a bacterial infection that requires antibiotic therapy, such as dogs with aspiration pneumonia, gastrointestinal bacterial translocation, or localized bacterial peritonitis. In such cases, the selection of a specific antibiotic should be based on culture and sensitivity testing or consensus guidelines.

Gastric acid suppressants

Gastric acid suppressants are frequently used in the management of AP in dogs because of the perceived risk of upper gastrointestinal bleeding. However, the incidence of upper gastrointestinal bleeding in dogs with AP is unknown but thought to be low. Currently, the routine use of gastric acid suppressants is not recommended in dogs with AP.¹⁰⁷ In people, the indiscriminate use of acid suppressants may actually be detrimental, as they lead to a dramatic increase of bacterial colonization of the gastric lumen, which in turn may lead to aspiration pneumonia instead of pneumonitis following aspiration.³⁹ However, if a patient has clinical evidence of upper gastrointestinal bleeding (ie, hematemesis, melena) or esophagitis (ie, regurgitation, hard swallowing), gastric acid suppressants may be indicated. In dogs, proton-pump inhibitors (such as omeprazole or esomeprazole orally or pantoprazole parenterally) given twice daily are more potent in increasing gastric pH compared to administration of oral histamine type-2 receptor antagonists (such as famotidine) given either once or twice daily.¹⁰⁸ Famotidine continuous rate infusions may be effective and have a rapid onset of action in dogs with suspected active gastrointestinal bleeding.¹⁰⁹

Protease inhibitors

The pathogenesis of AP has not been fully elucidated, and trypsinogen-related pathways have been proposed that stipulate that protease inhibitors would bind prematurely activated trypsin, thus preventing a massive extrapancreatic activation cascade of proteases.¹¹⁰ However, several studies suggest that these protease inhibitors would only be useful if given at the time of induction of pancreatitis in experimental models but not once pancreatitis has been established.^{111,112} None of the current international treatment recommendations for humans with severe AP include the use of protease inhibitors, except in Japan where these agents may be used occasionally.

Conclusion and Future Direction

Acute-onset pancreatitis is a common disease in dogs and is associated with significant morbidity and even mortality. While the treatment of AP in the past has been primarily symptomatic and supportive, a new specific therapeutic agent, fuzapladib sodium, is now available in Japan and the US. Other supportive standards of care include fluid therapy, early identification and management of complications, antiemetics, analgesia, and early nutritional support. The use of corticosteroids, NSAIDs, antibiotics, and protease inhibitors remains controversial and is not currently considered first-line standard of care for most cases. More multicenter randomized clinical trials on the management of AP in dogs are needed but challenging due to the large variability of clinical presentations and rapid progression in many patients. More specifically, studies are needed to determine the ideal fat content and potentially other nutritional factors of diets fed to dogs with AP. Prospective studies evaluating the clinical utility of corticosteroids are also needed. Finally, the clinical efficacy of fuzapladib in dogs with AP needs to be confirmed in additional studies.

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