Canine Pancreatitis:

Updates and Focus on Evidence-Based Medicine

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Background:
The concept of evidence-based medicine (EBM) arose in the 1990's as a methodology to apply best clinical practices to patients to optimize outcomes. It is defined as the conscientious, explicit, and judicious use of current best evidence from research for the care of an individual patient. This concept then migrated to the field of veterinary medicine about a decade later. However, many obstacles exist that prohibit the widespread adoption of EBM in our field: lack of high quality patient centered research, need for basic understanding of clinical epidemiology by veterinarians, absence of adequate searching techniques and accessibility to scientific databases, and inadequacy of EBM tools that can be applied to busy daily veterinary practice.

The goal of this presentation is to help us to better think critically about clinical decisions, and when able, seek guidance from best evidence from research to improve outcomes and quality of care.

Pancreatitis: causes and symptoms
The exocrine pancreas releases digestive enzymes for fats and proteins. Pancreatitis is an inflammatory condition of the pancreas that occurs secondary to inappropriate activation of exocrine pancreatic digestive enzymes within the parenchyma of the pancreas. Normally, these enzymes exist as inactive precursors called zymogens, and are activated by the enzyme enterokinase which is located in the small intestine. When this safety feature is disrupted, pancreatitis with autodigestion of the pancreas results.

Predisposing factors were thought to be related to the *SPINK1* gene, hypertriglyceridemia, disorders of lipid metabolism, and corticosteroid administration. However, these have not been found to be true when evaluated. Factors that are likely to cause pancreatitis are consumption of a high fat diet (including dietary indiscretion, table scraps, "grain-free" diets, and prescription renal and stone dissolution diets), and medications including anti-convulsants (Phenobarbital, KBr), azathioprine, and L-asparaginase.

Clinical presentation typically includes: history of dietary indiscretion/consumption of high fat diet, anorexia, vomiting, abdominal pain, diarrhea (occasionally with hematochezia), and weakness or lethargy.

Diagnostics:
Complete blood count findings are often variable and non-specific, but if severe thrombocytopenia is present, this may be a poor prognostic indicator for survival. The chemistry panel can help to evaluate

for other comorbidities, and may show a mild hypocalcemia with pancreatitis, the etiology of which is unknown. Elevations in BUN and/or creatinine may also be a poor prognostic indicator for survival.

Amylase activity is neither sensitive nor specific for pancreatitis and should not be used for diagnosis. Lipases can be released by many organs besides the pancreas, including the stomach and liver. Also total serum lipase activity may be increased with neoplasia, steroid administration, and renal, hepatic, and gastrointestinal disease. For this reason, it is prudent to be cautious with over-interpreting lipase assays not specific for pancreatic lipase for a diagnosis of pancreatitis, such as Antech's PrecisionPSL. An excellent discussion regarding the use of lipase assays in the diagnosis of pancreatitis can be found at Texas A&M Gastrointestinal Laboratories website at:
https://vetmed.tamu.edu/gilab/research/pancreatitis-information/

The most sensitive and specific pancreatitis test currently available is the measurement of serum levels of canine pancreatic lipase immunoreactivity, or Spec cPL. The normal reference range is <200 mcg/L, and a cutoff value for diagnosis of pancreatitis is 400 mcg/L. As a highly specific assay, a diagnosis of pancreatitis is unlikely if the value is in the reference range. However, elevations may occur secondary to diseases other than pancreatitis, particularly if within the gray zone levels of 201 – 400 mcg/L. Serial measurements may be used to monitor disease progression, and severe elevations of greater than 1000 mcg/L may be a poor prognostic indicator for survival.

Abdominal radiographs can be helpful to rule out other causes of gastrointestinal distress but are not a primary diagnostic tool for pancreatitis. Abdominal ultrasound is used very often in the clinical setting for diagnosing pancreatitis, however, a recent study showed wide-ranging sensitivity and specificity for a diagnosis of pancreatitis when the following characteristics were examined separately and together: pancreatic enlargement, abnormal pancreatic echogenicity, altered mesenteric echogenicity. The conclusion of that paper was that abdominal ultrasound findings should not be used in isolation for pancreatitis diagnosis, and is a poor indicator of disease severity.

Treatment:
Crystalloid fluid therapy is well accepted for the treatment of pancreatitis. It is acknowledged that pancreatic microcirculation may be disturbed by dehydration, hypovolemia, microthrombi and increased capillary permeability. These disturbances may lead to necrotizing pancreatitis, so correction of dehydration and hypovolemia is recommended. A fluid plan should be constructed around fluid deficit, on-going losses, estimated losses and monitoring and correction of electrolyte imbalances.

It is unclear if colloids should be part of therapy based on analysis of human critical care patients showing increased risks of renal dysfunction and mortality related to use of hydroxyethyl starch solutions in this population.

Anti-emetic therapy is prudent to increase comfort and decrease risks of aspiration, with maropitant, an NK1 receptor antagonist with peripheral and central anti-emetic properties, being frequently used. In addition, studies have shown benefits with maropitant in reduction of visceral pain when used as a pre-medication for spay surgery. Ondansetron is a 5-HT3 receptor antagonist that can be used concurrently with maropitant for additive effects in pancreatitis patients with refractory vomiting. Some references recommend avoiding the use of metoclopramide due to negative impacts on pancreatic perfusion, however, these hypotensive effects were found in rats and humans, so the relevance of this in canine patients is unclear.

Pain control is also warranted with opioids being frequently used in the hospital setting but care should be taken to avoid gastrointestinal ileus and nausea associated with their use.

Controversial treatments include the use of corticosteroids in pancreatitis. A recent study showed a dose of 1 mg/kg/day shortened hospitalization time, and patients had more rapid clinical improvement and decreased mortality. However, this was a non-blinded, non-randomized clinical trial with 45 patients treated with corticosteroids and 20 patients in an untreated control group. This outcome would have to be repeatable with better study design in order to be accepted and recommended as standard of care.

Antibiotics typically are not needed in cases of pancreatitis as it is a sterile inflammation within the pancreas. They do have a role if aspiration pneumonia is present. Some references recommend the use of antibiotics in pancreatitis if melena or hematochezia is present due to the concern for bacterial translocation from the intestines, however, this has not been validated by research.

Plasma transfusions have been used in the treatment of pancreatitis with the potential benefits of improving hypoalbuminemia, replenishing coagulation factors, and replacing circulating anti-proteases. However, a single retrospective study on the use of plasma transfusions in 77 dogs over a 10-year period did not show benefit, and the current recommendation is to reserve this therapy for pancreatitis patients with diagnosed coagulopathies.

The previous dogma for pancreatitis involved NPO in order to “rest the pancreas” and prevent further release of digestive enzymes leading to more damage. However, this perspective has shifted with findings of prolonged anorexia leading to increased gastrointestinal permeability with bacterial and endotoxin translocation. Early enteral nutrition has been shown to stimulate intestinal mucosal regeneration and blood flow, decrease inflammation and ileus, and lead to an improved return to voluntary food intake. This is now considered standard of care for hospitalized patients, with a naso-gastric tube providing an easy means to provide liquid nutrition early (within 48 hours) in cases of anorectic patients with pancreatitis. The amount to feed can be used by calculating the resting energy requirement (kilocalories per day) as:

RER = 70 x (body weight in kilograms)$^{0.75}$

Typically with prolonged anorexia, to avoid refeeding syndrome, we start with 1/3 of RER on day one of feeding, and move up to 2/3 RER the following day if tolerated. If the patient is doing well without large residual volumes in the stomach, nausea, vomiting, or regurgitation, we move to full RER on day 3.

In the non-acute setting, transition to a low-fat prescription diet is the best recommendation to avoid further episodes of pancreatitis. Good options include Royal Canin Gastrointestinal Low Fat (canned and dry), Purina EN Low Fat (canned and dry), and Hill's i/d Low Fat (canned, dry and stew). Keep in mind that both Purina EN and Hill's i/d come in non-low fat formulations, which may be too high in fat for some patients with pancreatitis, so take care to recommend the correct product. Royal Canin also manufactures prescription Gastrointestinal Canine dog treats, which is helpful, as many owners find giving treats to be an important aspect of the human-animal bond.

References:

Adamik KN, Yozova ID, Regenscheit N. Controversies in the use of hydroxyethyl starch solutions in small animal emergency and critical care. *J Vet Emerg Crit Care* 2015;25(1):20-47.

Cridge H, et al. Association between abdominal ultrasound findings, the specific canine pancreatic lipase assay, clinical severity indices, and clinical diagnosis in dogs with pancreatitis
J Vet Intern Med. 2020;34:636-643

Furrow E, et al. High prevalence of the c.74A>C SPINK1 variant in miniature and standard Schnauzers. *J Vet Intern Med.* 2012;26(6): 1295-9.

Graca R, Messick J, McCullough S, et al. Validation and diagnostic efficacy of a lipase assay using the substrate 1,2-o-dilauryl-rac-glycero-3-glutaric acid (6'-methyl-resorufin) ester for the diagnosis of acute pancreatitis in dogs. *Vet Clin Pathol* 2005;34:39–43.

Harris JP, et al. Retrospective evaluation of the impact of early enteral nutrition on clinical outcomes in dogs with pancreatitis: 34 cases (2010-2013). *J Vet Emerg Crit Care* 2017;27(4):425-433.

Lem KY, Fosgate GT, Norby B, et al. Associations between dietary factors and pancreatitis in dogs. *JAVMA* 2008;233:1425-1431.

Mansfield C, Beth T. Management of acute pancreatitis in dogs: a critical appraisal with focus on feeding and analgesia. *Journal of Small Animal Practice (2015)* 56, 27–39

Marquez M, et al. Comparison of NK-1 receptor antagonist (Maropitant) to Morphine as a pre-anesthetic agent for canine ovariohysterectomy. *PLoS One* 2015; 10(10):1-10

Ohta H, et al. Effects of immunosuppressive prednisolone therapy on pancreatic tissue and concentration of canine pancreatic lipase immunoreactivity in healthy dogs.
Can J Vet Res. 2018;82(4): 278-286.

Okanishi H, Nagata T, Nakane S, Watari T. Comparison of initial treatment with and without corticosteroids for suspected acute pancreatitis in dogs. *J Small Anim Pract* 2019;60(5):298-304.

Sato T, et al. Assessment of severity and C-reactive protein concentration and various biomarkers in dogs with pancreatitis *J Vet Med Sci* 2017;79(1):35-40

Steiner JM. Canine pancreatitis: diagnosis and treatment. In Ettinger SJ, et al, editors: Textbook of veterinary internal medicine, ed 8, St. Louis, 2017, Elsevier, pp 1683 -1688.

Vandeweerd JM, Kirschvink N, Clegg P, et al. Is evidence-based medicine so evident in veterinary research and practice? History, obstacles and perspectives.
The Veterinary Journal 2012;191(1): 28-34

Weatherton LK, Streeter EM. Evaluation of fresh frozen plasma administration in dogs with pancreatitis: 77 cases (1995-2005).
J Vet Emerg Crit Care 2009;19(6):617-622.

Xenoulis PG, et al. Serum triglyceride and cholesterol concentrations and lipoprotein profiles in dogs with naturally occurring pancreatitis and healthy control dogs
J Vet Intern Med. 2020;34:644-652