“Management of Acute Pancreatitis in Dogs”

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Management of Acute Pancreatitis

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Pancreatitis develops when there is excessive activation of trypsin and other pancreatic proteases within the pancreas, which overwhelms local safeguards within the acinar cell. This initial activation may be due to oxidative stress or hypotension, and experimentally is worsened by low acinar pH and high intracytosolic calcium concentration. \(^1\) Trypsin and chymotrypsin then directly stimulate neutrophil migration to the pancreas, with subsequent production of reactive oxygen species, nitric oxide, cytokines and activation of other pathways (complement, kallin-kallikrein, renin-angiotensin system) that further perpetuate inflammation in the pancreatic and peri-pancreatic area. \(^6\,\,7\,\,8\) Clinical signs of pancreatitis are dependent both on the degree of local pancreatic inflammation (variable severity of pain, vomiting, dehydration), and the degree of systemic complications (such as cardiac arrhythmias, disseminated intravascular coagulation or acute lung injury).

The reported mortality rate for acute pancreatitis (AP) in dogs ranges from 27% to 58%. \(^9\,\,10\,\,11\,\,12\) This reported rate may not reflect the mortality in general veterinary practice, as the reports originate from referral centres and euthanasia for non-medical reasons (i.e. financial) may also exert an influence. Even taking these factors into account, it is a higher mortality rate than the 5-15% reported in human studies. \(^13\) The treatment for AP in dogs is largely extrapolated, either from first principles, experimental studies in species other than dogs or medical studies.

**Intravenous fluid therapy**

Vomiting and inappetance result in dehydration in dogs with AP, which generally requires IV fluid replacement. In addition to the systemic effects of dehydration or hypovolaemia, the pancreas is very sensitive to altered blood flow. Disturbed pancreatic microcirculation is usually multi-factorial in origin and
can occur as a result of increased vascular permeability resulting from inflammatory cytokines, and
microthrombi formation resulting from hypercoagulability. There is a theoretical benefit in using
alkalinising fluids, such as lactated ringer’s solution (LRS), to increase pH and therefore prevent further
trypsin activation within the acinar cell. Further studies are required to determine if there is a tangible
advantage in using LRS as the first choice crystalloid in dogs with AP.

There are multiple rodent experimental studies that show a beneficial effect of dextran over crystalloid
therapy in AP. Dextran administration has been associated with alteration in haemostasis, and is used
cautiously in dogs. That being said, additional therapy with dextran, hetastarch or hypertonic saline (at a
low bolus dose) may be of benefit in those dogs that have severe disease and third space loss; and have not
shown substantial improvement in their venous pH, serum chloride concentration or severity of systemic
inflammation at 24 hours.

Plasma
Purported benefits of plasma transfusion in treatment of AP include replacement of circulating α-
macroglobulins, coagulation factors and anti-inflammatory factors. It is unlikely that any benefit seen with
plasma will be due to colloid like properties, as fresh frozen plasma (FFP) has only about 20-30% of the
oncotic properties of colloids. Despite an experimental benefit of FFP in rats, there has been no proven
benefit in people or in dogs, and it remains an expensive treatment for veterinary patients. In the light
of these findings, administration of FFP should probably be reserved for those dogs with documented
coagulation abnormalities.

Analgesia
Pain is a common clinical sign of AP, and is manifested in dogs typically with a crouched appearance and
guarding of the abdomen on palpation. Pain is likely to be mediated due to local effects- whereby the
inflamed and enlarged pancreas itself causes pain, or by subsequent amplification of visceral pain. There are
a number of amino acids (glutamate and aspartate) and neuropeptides (substance P, neurokinin A, calcitonin gene-related peptide) involved in a complex circuit of pain recognition and transmission.

Accurate identification and characterisation of this pain is essential to optimise management. Multidimensional scales published for use in dogs that consider aspects other than pain intensity include the Melbourne Pain Scale and the Glasgow Composite Pain Scale (GCPS). A short form of the GCPS is accessible to practitioners online (http://www.gla.ac.uk/schools/vet/research/painandwelfare/downloadacutepainquestionnaire/).

By determining a level of pain, an appropriate level of analgesia can be initiated (see Table One).

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<th>Anticipated levels of pain associated with acute pancreatitis</th>
<th>Potential analgesic combination</th>
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| **Mild to Moderate** | Quiet but responsive to surroundings  
Unsettled  
Looks around when abdomen is palpated | Buprenorphine with or without  
Lidocaine and/or Ketamine infusion |
| **Moderate to severe** | Decreased response to surroundings or stimuli  
Slow or reluctant to move  
Restless  
Stretching of abdomen, looking around at abdomen  
Flinches on abdominal palpation | Buprenorphine with Lidocaine and  
Ketamine infusion |
| **Severe to excruciating** | Non-responsive to stimuli  
Refuses to move or get up  
Screams, cries or snaps when tries to get up or abdomen palpated | Epidural Morphine with  
Lidocaine/Ketamine infusion |

Table One: An outline of the levels of pain that are potentially manifested in dogs with acute pancreatitis, as adapted from the Glasgow Composite Pain Scale. To any of those proposed analgesic combinations, Gabapentin could be added as part of the multimodal approach to pain treatment.

However, none of the analgesic agents recommended have been evaluated in dogs with spontaneous AP, let alone in experimental canine models. Hence, the level of evidence for these recommendations is poor. In addition, due to the potential severity of the pain associated with abdominal pain and AP in particular, a multimodal approach to pain treatment is advised. Due to the presence of hypovolaemia and dehydration in the majority of dogs with AP, NSAIDs are not recommended and will not be discussed further.
It is best to presume there is pain, and start with a high level of analgesia initially, then reducing down once pain has been well controlled.

Recommended dosages are:

- Buprenorphine 30-40 µg/kg q 4-6 hours, when ready to reduce dosage not frequency
- Ketamine CRI Start at approximately 20 µg/kg/minute. Reduce ketamine incrementally (stop when reach 5 µg/kg/minute)
- Lidocaine CRI start at approximately 40 µg/kg/minute. Reduce lidocaine incrementally (stop when reach 10 µg/kg/minute)
- Gabapentin 10 mg/kg PO q 12-24 hours
- Morphine 0.1 mg/kg epidural (experience required)

The analgesic effect of opioids is provided mostly through their action in the central nervous system on receptors such as the mu and delta receptors (spinal and supra spinal) and the kappa receptor (spinal). The full mu agonist opioid agents (e.g. morphine, methadone, hydromorphone, meperidine, fentanyl) are considered the most effective analgesics of the group and are usually used to treat moderate to severe pain while the partial mu agonist (e.g. buprenorphine) and the mu antagonist kappa agonist (e.g. butorphanol) are less effective and are used for milder pain level. Respiratory depression has been reported with the use of all these agents, however, at recommended analgesic doses and unless used concomitantly with other central nervous system depressants or in animals with respiratory disease, the respiratory depression described with these drugs is rarely clinically significant. Decreased gastric emptying time and intestinal propulsive activity have been demonstrated in dogs as well as increased sphincter tone (pylorus or biliary sphincter), predominantly with the full mu agonists and so these should be avoided when given systemically.

In a rat model of AP, it was suggested that NMDA receptors were involved not only in initiation but also in the maintenance of central sensitization during visceral inflammation. Ketamine is the most potent and specific NMDA antagonist in clinical use today and plays a role in the reduction of central sensitisation.
and may help reduce nociception from intraabdominal organs and visceral peritoneum\(^\text{30}\). Lidocaine is a local anaesthetic which reversibly blocks voltage-gated sodium channels and thereby prevents membrane depolarisation. It is usually administered locally to block nerve conduction. When administered as an infusion, lidocaine exerts analgesic effects that seem to be peripheral and central in origin.\(^\text{32,33}\) In addition, lidocaine also has anti-inflammatory properties through reducing the liberation of superoxide anions, a common pathway of inflammation.\(^\text{34,35}\) These benefits make it an attractive analgesic option in dogs with severe pain resulting from AP.

**Nutrition**

The role of nutrition in treatment of AP has gained a lot of attention recently in both human and veterinary medicine, and heralded a change of direction in management. The nutritional challenges of AP include that it is a catabolic disease with significant nitrogen losses; ileus often complicates feeding; and pancreatic necrosis can increase nutritional requirements.\(^\text{36}\) 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, with amino acids the major respiratory fuel that is required by the enterocytes.\(^\text{37}\)

Total parenteral nutrition (TPN) was historically recommended in the human and veterinary fields in severe cases of AP, however TPN has been shown to confer a negative prognosis. Most consensus statements in human gastroenterology support the notion of early enteral feeding in severe AP, although few clinical studies effectively compare enteral nutrition to full pancreatic rest. Multiple studies in people have shown that nasogastric feeding is safe and well tolerated, and a cheaper and easier alternative to insertion of a nasojejunal feeding tube.\(^\text{36-40}\) In a prospective pilot study in dogs with severe AP, oesophageal feeding was well tolerated and safe.\(^\text{41}\) Large scale multi-centre randomised studies are required to fully evaluate the benefits of enteral nutrition in dogs.
I currently recommend that dogs with mild-moderate AP be fasted until able to eat voluntarily, or they have reached 5-7 days of anorexia (including the pre-hospital period). In severe cases, interventional tube feeding (through a naso-oesophageal or oesophageal feeding tube) should be instituted as soon as possible. There is no current recommendation for the type of food to be administered in this acute setting. Although a study has shown no difference in dietary fat content on pancreatic secretion in healthy dogs, it seems logical to limit fat content as much as possible. Small amounts of vomiting should not stop feeding, however the volume and frequency of feeds could be reduced. It is not known what percentage of resting energy requirement (RER) is necessary, but extrapolation from people would suggest that full RER is generally not reached, and is not essential.

**Anti-emetics**

Vomiting in dogs with pancreatitis is likely to be both centrally mediated due to the presence of circulating emetic agents, and peripherally mediated due to ileus, peritonitis, and pancreatic distension. Experimental models have shown that dopamine infusion improves the outcome in AP, and ameliorates the inflammatory severity of the disease. There is therefore a theoretical disadvantage in giving metoclopramide (a dopaminergic antagonist) to dogs with AP, although this is clinically unproven.

Maropitant (Cerenia, Pfizer) blocks the Neurokinin 1 (NK1)-receptor, and substance P production; and is an effective anti-emetic agent that blocks centrally and peripherally mediated emesis. Substance P contributes to the development of visceral pain and increased capillary permeability. When the NK1 receptor is blocked experimentally, there is no difference in the amount of pancreatic inflammation produced, but distantly-mediated lung injury is reduced in rodents. Although there is a danger of direct extrapolation, the NK1-receptor function is considered the same in dogs as in people. Therefore, there may be additional benefits such as reduction of visceral pain and lung injury with the use of maropitant. Although there is no evidence of these adjunctive benefits of maropitant in dogs with AP to date, the authors consider
this should be the preferred first line anti-emetic, with ondansetron (0.5 mg/kg IV once then every 12-24 hours or as infusion over 6 hours) added as necessary to improve nausea or emesis control.

**Gastric acid suppression and nasogastric suctioning**

Currently, there is no evidence that reducing gastric acidity improves outcome in dogs with AP. However, if there is evidence of gastric ulceration (substantial haematemesis, melena) or oesophagitis, then gastric acid suppression is indicated. Oral omeprazole, a proton pump inhibitor, has been shown to be the most effective at increasing gastric pH for the longest period of time in dogs compared to famotidine, pantoprazole, and ranitidine.55,56 Dogs are often dosed with oral omeprazole at 0.7-1mg/kg daily, but recent work would suggest that doses should be increased up to 2.5 mg/kg day, in divided doses.56

In people with mild to moderate AP, there have been multiple randomised clinical trials assessing nasogastric suctioning; none of which showed any benefit and many that showed prolongation of pain and nausea.57-63 The physical presence of a nasogastric tube across the gastro-oesophageal sphincter may also predispose to the development of severe oesophagitis. As such, the use of indwelling nasogastric tubes, or repeated nasogastric suctioning, cannot be recommended in dogs with AP.

**Treatment of local complications**

Acute fluid collections are defined in the human medical literature as fluid accumulations within the pancreatic parenchyma that develop within 6 weeks following AP.64 A pseudocyst on the other hand develops at least 6 weeks after AP, does not contain an epithelial lining and its contents are composed of amylase-rich pancreatic secretion, generally occurring in milder cases.64 The term acute fluid collection is the most suitable term for the local pancreatic complications that occur in dogs, although insippated pancreatic tissue that develops 2-3 weeks following AP may be termed a phlegmon.9
Current medical recommendations are to not surgically debride sterile fluid collections, and if infection is documented then there should be treatment with antimicrobials for as long as possible prior to surgical debridement. Surgery to treat pancreatic acute fluid collections in dogs invariably results in a high mortality rate (>50%), regardless of the technique used. There have been reported spontaneous resolutions of acute fluid collections in the veterinary literature, and good responses to percutaneous drainage, suggesting these are preferable methods for managing this particular complication when pain is present.

**Corticosteroids**

Corticosteroids may exert multiple benefits in AP by inhibiting release of pro-inflammatory mediators, decreasing sequestration of neutrophils in the pulmonary vasculature; as well as reducing adhesion of primed neutrophils to the endothelial surface of pulmonary vasculature, release of elastase and free radicals from adherent neutrophils and pulmonary vascular permeability. Corticosteroids have been removed from the list of drugs that are considered to cause pancreatitis in people, and similarly they are not believed to cause pancreatitis in dogs. Currently there are a number of prospective trials being undertaken to evaluate the potential benefit of glucocorticoids in people with severe AP.

During acute illness the hypothalamic-pituitary axis is stimulated, but in about 10-20% of critically ill people and 60% of people with septic shock, this pathway becomes impaired. This altered adrenal function has been termed critical illness-related corticosteroid insufficiency (CIRCI). Mechanisms that lead to CIRCI are complex and poorly understood, but effectively CIRCI occurs when there is an adrenal insufficiency along with tissue resistance to the effects of corticosteroid, due to a prolonged and severe pro inflammatory state.

CIRCI causes hypotension and a poor response to fluid or vasopressor therapy. It is in the sub-group of people with poor response to resuscitative measures (fluid and vasopressor therapy) and those with acute
lung injury, where cortisone replacement appears to be the most effective. There is no documented evidence that CIRCI occurs in dogs with AP. Although there may be a potential role for using low-dose hydrocortisone in dogs with severe AP that have poor systolic pressures and minimal response to fluid resuscitation, optimisation of the other aspects of management of canine AP should be completed before stringent analysis of corticosteroid therapy is undertaken.

**Follow up**

Some general recommendations for treatment after discharge include:

- Remove/avoid triggers if known
- Discharge with 3 weeks pancreatic enzyme supplements and analgesia (I prefer gabapentin to tramadol)
- Feed a low-fat, well balanced diet until the follow-up revisit.
- Check fasting serum triglycerides and cholesterol 1-2 weeks later
  - If not hyperlipidaemic, then transition back to normal diet over about 4-6 weeks
  - If the dog is hyperlipidaemic, a low-fat diet will need to be fed for longer and underlying causes for the hyperlipidaemia such as hypothyroidism and/or hyperadrenocorticism should be evaluated for. Specific treatment such as omega-3 supplementation may be needed (gradually added to diet).
References

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54. Leffler A. Characterization of species-related differences in the pharmacology of tachykinin NK receptors 1, 2 and 3. *Biochemical pharmacology* 2009;77:1522.


