

Management of acute pancreatitis in dogs: a critical appraisal with focus on feeding and analgesia

C. MANSFIELD AND T. BETHS

Faculty of Veterinary and Agricultural Sciences, The University of Melbourne, 250 Princes Highway, Werribee, Victoria 3030, Australia

Knowledge about acute pancreatitis has increased recently in both the medical and veterinary fields. Despite this expansion of knowledge, there are very few studies on treatment interventions in naturally occurring disease in dogs. As a result, treatment recommendations are largely extrapolated from experimental rodent models or general critical care principles. General treatment principles involve replacing fluid losses, maintaining hydrostatic pressure, controlling nausea and providing pain relief. Specific interventions recently advocated in human medicine include the use of neurokinin-1 antagonists for analgesia and early interventional feeding. The premise for early feeding is to improve the health of the intestinal tract, as unhealthy enterocytes are thought to perpetuate systemic inflammation. The evidence for early interventional feeding is not supported by robust clinical trials to date, but in humans there is evidence that it reduces hospitalisation time and in dogs it is well tolerated. This article summarises the major areas of management of acute pancreatitis in dogs and examines the level of evidence for each recommendation.

Journal of Small Animal Practice (2015) **56**, 27–39
DOI: 10.1111/jsap.12296

Accepted: 26 May 2014

INTRODUCTION

Pancreatitis develops when there is excessive activation of trypsin and other pancreatic proteases within the pancreas, which overwhelms local safeguards within the acinar cell (Lasson & Ohlsson 1984, Mansfield 2012). This initial activation may be due to oxidative stress or hypotension, and is experimentally worsened by low acinar pH and high intracytosolic calcium concentration (Rinderknecht 1986, Mithofer *et al.* 1995, Windsor & Hammodat 2000, Noble *et al.* 2008, Bhoomagoud *et al.* 2009). Trypsin and chymotrypsin then directly stimulate the migration of neutrophils to the pancreas with subsequent production of reactive oxygen species, nitric oxide, cytokines and activation of other pathways (complement, kallin–kallikrein and renin-angiotensin system) that further perpetuate inflammation in the pancreatic and peri-pancreatic area (Frossard 1999, Bhatia *et al.* 2000, Keck *et al.* 2005). Clinical signs of pancreatitis are dependent on the degree of local pancreatic inflammation (pain, vomiting and dehydration) and the degree of systemic complications (such as cardiac arrhythmias, disseminated intravascular coagulation and acute lung injury).

Acute pancreatitis (AP) is considered to be a reversible condition unless the initial triggers of disease persist, in which case chronic or recurrent inflammation develops (Holm *et al.* 2003, Stevens *et al.* 2004). AP is characterised histologically by neutrophilic inflammation or necrosis of the pancreatic or peri-pancreatic area with no fibrosis or exocrine atrophy present (Newman *et al.* 2006, Watson *et al.* 2007, Kalli *et al.* 2009). Clinically the differentiation between acute necrotising pancreatitis, AP without necrosis and chronic active AP (inflammation and fibrosis from a previous insult) is difficult. Therefore, veterinary clinical nomenclature usually relates to the severity and longevity of clinical signs rather than to the histological characteristics. The term mild AP should be used when there is no multisystem failure, whilst severe AP should refer to the presence of multisystem failure or development of complications that require a higher intensity of treatment. Typically, dogs that have severe AP also have pancreatic or peri-pancreatic necrosis (Mansfield *et al.* 2008).

The reported mortality rate for AP in dogs ranges from 27 to 58% (Strombeck 1990, Cook *et al.* 1993, Charles 2007). This rate may not reflect the mortality in general veterinary practice, as these reports originate from referral centres and euthanasia

for non-medical reasons (i.e. financial) may exert an influence. Even taking these factors into account, AP in dogs has a mortality rate higher than that reported in human studies of 5 to 15% (Al Mofleh 2008). The treatment for AP in dogs is largely extrapolated, either from first principles, experimental studies in species other than dogs, or from medical studies.

In this review, each of the major aspects of management of AP is addressed and assigned an overall level of evidence (LOE) for each treatment in both humans and dogs (Table 1). The LOE was classified as follows: level A is based on consistent randomised control trials and cohort studies in different populations of subjects; level B is based on consistent retrospective cohorts, experimental cohorts of the same species, case-control studies or extrapolated from level A studies; level C is based on case series, or extrapolation from level B studies; level D is expert opinion without explicit critical appraisal or extrapolated from bench-top research or physiological (first) principles (Elwood *et al.* 2010).

Initially search engines such as PubMed and Web of Science were searched for the terms “canine OR dog” and “acute pancreatitis”. This initially identified 1782 articles. After excluding articles that were in duplicate, not available in English, written prior to 1965, discussed other diseases such as chronic pancreatitis or were related to another species, 158 remained. Of these, a total of 133 experimental studies on dogs (ex vivo or in vivo) of treatment modalities, 13 reviews, 2 individual case reports, 8 retrospective case series and 2 small prospective studies were found. As there is a dearth of well-structured studies in many areas of management of AP in dogs, medical and experimental studies in each area were separately reviewed.

Many of the recommendations given for treatment of severe and complicated AP require a high level of nursing support and

are intensive in nature, and as such dogs with severe AP may be better treated in a referral intensive care unit. It should also be kept in mind that these are recommendations only, but it is hoped that future prospective studies will enable a stronger LOE to be applied to this common disease.

INTRAVENOUS FLUID THERAPY

Vomiting and inappetence result in dehydration in dogs with AP, which generally requires intravenous (iv) fluid replacement. In addition to the systemic effects of dehydration or hypovolaemia, the pancreas is susceptible to altered blood flow (Gardner *et al.* 2008). Disturbed pancreatic microcirculation is usually multifactorial in origin and can occur as a result of increased vascular permeability resulting from inflammatory cytokines, and microthrombi formation resulting from hypercoagulability (Fig 1) (Gardner *et al.* 2008). There is a theoretical benefit in using alkalinising fluids, such as lactated Ringer's solution (LRS), to increase pH and therefore prevent further trypsin activation within the acinar cell (Bhoomagoud *et al.* 2009). Although a protective effect was not shown in experimental rodent studies (Kellum 2002), one randomised prospective study in humans did demonstrate that LRS given iv reduced signs of systemic inflammation more than saline (Wu *et al.* 2011). Further studies are required to determine whether there is a tangible advantage in using LRS as the first-choice crystalloid in dogs with AP (current LOE in dogs D).

There are multiple rodent experimental studies that show a beneficial effect of dextrans on crystalloid therapy in AP (Donaldson & Schenck 1979, Knol *et al.* 1983, Schmidt *et al.* 1993,

Table 1. Assessment of the overall level of evidence for major treatment strategies of acute pancreatitis (AP) in dogs

Treatment intervention	Treatment recommendations	Level of evidence
Intravenous fluid therapy	Lactated Ringers preferable crystalloid Dextrans beneficial if unable to maintain perfusion with crystalloids No benefit of fresh frozen plasma	B (humans) D (dogs) C (dogs) A (humans) C (dogs)
Anti-emetic therapy	Metoclopramide potentially detrimental Maropitant ideal first line treatment	D (dogs) B (dogs)
Antibiotics	Not required unless suspect bacterial translocation Amoxicillin-clavulanate or ticarcillin first drug of choice if needed	A (humans) D (dogs) C (dogs)
Gastric cytoprotection	Nasogastric suctioning contraindicated Omeprazole first-line drug of choice at 2 to 2.5 mg/kg orally daily in divided doses	A (humans) D (dogs) C (dogs)
Corticosteroids	Hydrocortisone could be considered in cases non-responsive to iv fluid resuscitation	B (humans) D (dogs)
Surgical intervention	No indication for surgical intervention with AP unless infection is documented	A (humans) B (dogs)
Pancreatic fluid collections	Fluid collections should be aspirated via ultrasound guidance only if associated with pain	A (humans) C (dogs)
Post-recovery treatment	Exocrine pancreatic supplementation and a low-fat diet should be given for 4 weeks Serum triglyceride and cholesterol concentrations should be measured 2 to 4 weeks postrecovery from AP. If hyperlipidaemic, a low-fat diet should be continued indefinitely, and if necessary lipid-lowering medications prescribed. If hyperlipidaemia is not present, then the regular diet can be cautiously reintroduced	D (dogs) D (dogs)

Level A is based on consistent randomised control trials and cohort studies in different populations of subjects; level B is based on consistent retrospective cohorts, experimental cohorts of the same species, case-control studies or extrapolated from level A studies; level C is based on case series, or extrapolation from level B studies; level D is expert opinion without explicit critical appraisal, or extrapolated from bench-top research or physiological (first) principles. Adapted from Elwood *et al.* 2010. Further discrimination is given by indicating the species of study

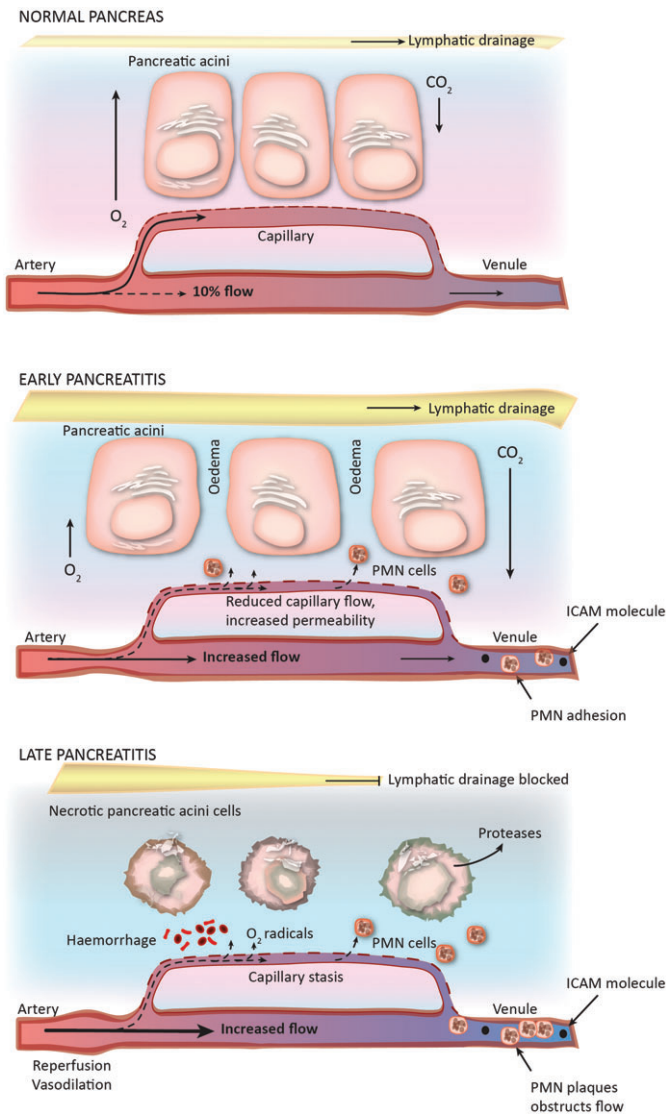


FIG 1. Diagrammatic representation of circulatory changes in pancreatic circulation with disease. ICAM Intracellular adhesion molecule, PMN Neutrophils. Reproduced with permission from Mansfield 2012

1996). Administration of dextrans has been associated with alteration in haemostasis (Mehler *et al.* 2004). That being said, additional therapy with dextrans, hetastarch or hypertonic saline (at a low bolus dose), may be beneficial in those dogs that have severe disease (current LOE in dogs: C).

Plasma

Purported benefits of plasma transfusion in treatment of AP include replacement of circulating α -macroglobulins, coagulation factors and anti-inflammatory factors (Weatherton & Streeter 2009). It is unlikely that any benefit of plasma is because of its colloid-like properties, as fresh frozen plasma (FFP) has only approximately 20 to 30% of the oncotic properties of synthetic colloids (Weatherton & Streeter 2009). Despite an experimental benefit of FFP in rats (Leese *et al.* 1988), there has been no proven benefit in humans (Leese *et al.* 1987, Leese *et al.*

1991) or in dogs (Weatherton & Streeter 2009), and it remains an expensive treatment for veterinary cases. The study in dogs (Weatherton & Streeter 2009) was a retrospective one and therefore had inherent bias, limiting the strength of recommendations that can be made for FFP. Despite this limitation, it is observed that administration of FFP should probably be reserved for those dogs with documented coagulation abnormalities. This lack of benefit of FFP has a LOE D in dogs, and A in humans.

ANTI-EMETICS

Vomiting in dogs with pancreatitis is likely to be both centrally mediated owing to the presence of circulating emetic agents and peripherally mediated owing to ileus, peritonitis, and pancreatic distension (Elwood *et al.* 2010). Experimental rodent models have shown that dopamine infusion improves the outcome in AP and ameliorates the inflammatory severity of the disease (Karanjia *et al.* 1990). There is therefore a theoretical disadvantage in giving metoclopramide (a dopaminergic antagonist) to dogs with AP, although this is clinically unproven (LOE dogs D).

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 (Benchaoui 2007, De la Puente-Redondo *et al.* 2007a,b, Conder 2008, Sedlacek *et al.* 2008, Rau *et al.* 2010). Maropitant is also the only anti-emetic discussed in this review specifically labelled for that use in dogs in the UK. Substance P contributes to the development of visceral pain and increased capillary permeability (Frossard & Pastor 2002). 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 (Pastor & Frossard 2001). Although there is a danger of direct extrapolation, the NK1 receptor function is considered the same in dogs as in humans (Leffler 2009). 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 that this should be the preferred first-line anti-emetic (LOE B in dogs). Additional anti-emetic agents such as the serotonergic antagonists (e.g. ondansetron) can be added as necessary to improve nausea or emesis control, although they remain expensive.

Even dogs with AP that are not showing overt signs of nausea or vomiting should be treated with an anti-emetic, especially in the early stages to encourage voluntary eating. Clinical signs of nausea include repeated licking of lips and swallowing attempts or obvious aversion to food.

ANTIBIOTICS

Potential reasons for administration of antibiotics to dogs with AP include treatment of infected pancreatic necrosis or treatment of bacterial translocation (Wu & Conwell 2010b). Bacterial translocation has been documented in dogs with experimentally

induced pancreatitis (Kazantsev *et al.* 1994, Qin *et al.* 2002a), but has not been definitively documented in naturally occurring disease. If bacterial translocation were to occur, experiments suggest that the bacteria would originate from the small intestine (Fritz *et al.* 2010). Clinically, it is difficult to have definitive criteria for suspecting bacterial translocation as the severe (sterile) inflammation that accompanies AP often results in pyrexia and white cell changes that are indistinguishable from infection (Hess *et al.* 1998, Mansfield *et al.* 2008). In general, signs of poor gut mucosal health (melaena and haematochezia) combined with prolonged fasting and/or hypotension could increase suspicion of bacterial translocation, and then drugs such as amoxicillin–clavulanate that are broadly effective against gut pathogens should be given parenterally (LOE dogs C), unless a documented infection with a different antimicrobial susceptibility has been confirmed. The routine use of prophylactic antibiotics in dogs without signs of concern may lead to increased community resistance to antibiotics, and should be avoided if possible (LOE dogs D).

GASTRIC ACID SUPPRESSION AND NASOGASTRIC SUCTIONING

Reduction of gastric acidity medically or via physical suctioning of gastric contents is recommended by many in the treatment of canine AP (Stewart 1994, Williams 1994, Watson 2004, Kalli *et al.* 2009). It is proposed that reduction of gastric acid production could lead to decreased pancreatic exocrine stimulation and that AP predisposes to the development of gastric mucosal ulceration as a result of hypovolaemia and localised peritonitis (Williams 1994). One experimental study in rats showed that pantoprazole reduced inflammatory changes and leakage within acinar cells (Hackert *et al.* 2010), but there was no direct effect of proton pump inhibitors on pancreatic exocrine secretion *in vitro* (Cai *et al.* 2007). This would suggest that this group of drugs may directly reduce pancreatic inflammation in a way that is not associated with reduced pancreatic enzyme secretion.

Currently, there is no evidence that reducing gastric acidity improves outcome in dogs with AP. However, if there is clinical evidence of gastric ulceration (substantial haematemesis, melaena) or oesophagitis (repeated eructations, regurgitation), then gastric acid suppression is indicated. Oral doses of omeprazole, a proton pump inhibitor, have been shown to be the most effective at increasing gastric pH for the longest period of time in dogs compared with famotidine, pantoprazole, and ranitidine when given every 12 hours (Bersenas *et al.* 2005, Tolbert *et al.* 2011). Recent work would suggest that doses of oral omeprazole should be increased up to 2.5 mg/kg day, in divided doses (Tolbert *et al.* 2011; LOE B). The potential direct effect of proton pump inhibitors on pancreatic inflammation, combined with their greater efficacy, would suggest that they are first-line gastric cytoprotective choices in dogs with AP despite not being licensed specifically for use in dogs in the UK and being more expensive than H₂ antagonists (LOE C).

Multiple randomised clinical trials are available for assessing nasogastric suctioning in humans with mild to moderate AP;

none of which showed any benefit and many showed prolongation of pain and nausea (Levant *et al.* 1974, Naeije *et al.* 1978, Field *et al.* 1979, Fuller *et al.* 1981, Loiudice *et al.* 1984, Navarro *et al.* 1984, Sarr *et al.* 1986). 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 is not recommended in dogs with AP (LOE humans A; LOE dogs D).

CORTICOSTEROIDS

Corticosteroids may exert multiple positive benefits in AP by inhibiting the 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, pulmonary vascular permeability, and release of elastase and free radicals from adherent neutrophils (Sun *et al.* 2007). Experimental *in vitro* and *in vivo* models demonstrate that dexamethasone increases the expression of pancreatitis-associated protein (PAP) (Kandil *et al.* 2006). PAP is upregulated in pancreatic inflammation and is thought to have multiple protective effects (Iovanna *et al.* 1991, Zenilman 1996, Ortiz *et al.* 1998, Heller 1999). Corticosteroids have been removed from the list of drugs that are considered to cause pancreatitis in humans, and similarly, they are not believed to cause pancreatitis in dogs (Parent 1982, Fittschon & Bellamy 1984, Bang *et al.* 2008). Currently, a number of prospective trials are being carried out to evaluate the potential benefit of glucocorticoids in humans with severe AP, but their routine use is not recommended yet.

During acute illness, the hypothalamic–pituitary axis is stimulated, but in approximately 10 to 20% of critically ill and 60% of humans with septic shock, this pathway becomes impaired (Marik 2008). This altered adrenal function has been termed critical illness-related corticosteroid insufficiency (CIRCI), but it remains a subject of some debate. Mechanisms that lead to CIRCI are complex and poorly understood, but CIRCI occurs effectively when there is adrenal insufficiency along with tissue resistance to the effects of corticosteroid, owing to a prolonged and severe pro-inflammatory state (Marik 2008). CIRCI appears to occur most frequently in diseases that alter lecithin-cholesterol acyltransferase (LCAT). LCAT converts free cholesterol into cholesteryl ester and produces high-density lipoproteins. The role of LCAT in canine AP is unknown, but could theoretically contribute to the lipid perturbations commonly seen in severe AP.

CIRCI causes hypotension and a poor response to fluid or vasopressor therapy; it is in the subgroup of humans with poor response to resuscitative measures (fluid and vasopressor therapy) and those with acute lung injury, where cortisone replacement therapy appears to be the most effective (Marik 2008). Low-dose hydrocortisone tapering over 2 weeks is the currently recommended treatment for humans with septic shock and CIRCI, whilst methylprednisolone is recommended for those with acute lung injury.

These treatment recommendations have not been extended to humans with AP to date (Muller *et al.* 2006, Peng *et al.* 2009), and there is no published evidence that CIRCI occurs in dogs with AP. There may be a potential reason for using low-dose hydrocortisone in dogs with severe AP that have poor systolic pressures and minimal response to fluid resuscitation (LOE B humans, D dogs); however, it is believed that optimisation of other aspects of AP management should be completed before prospective analysis of corticosteroid therapy is carried out.

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 (Hess *et al.* 1998). Pain is likely to be mediated as a result of local effects whereby the inflamed and enlarged pancreas itself causes pain, or by subsequent amplification of visceral pain. From a simplistic point of view, the pain pathway is divided into a nociceptive ascending and an anti-nociceptive descending pathway. The former starts at the periphery, in this case the inflamed and enlarged pancreas, and sends information in the dorsal horn through a first set of nerve fibres with co-release of amino acids (glutamate and aspartate) and neuropeptides (substance P, neurokinin A and calcitonin gene-related peptide) (Lemke & Creighton 2010). At this level, intense and/or prolonged afferent input may result in the activation of the N-methyl-D-aspartate (NMDA) receptor involved in central sensitisation. From the dorsal horn, a second set of neurons carry the nociceptive (painful) information to the thalamus where a third group of neurons send the information to the cortex (Price & Nolan 2007). The descending anti-nociceptive pathway starts at the supraspinal level and projects to neurons in the dorsal horn of the spinal cord. This pathway modulates the nociceptive input through different neurotransmitters such as opioids, norepinephrine, α_2 -agonists and serotonin (Lemke & Creighton 2010).

Even if animals do not display typical signs of pain, it is sensible to assume that there exists a degree of pain in all dogs with AP. Accurate identification and characterisation of this pain is

essential to optimise its management. Behavioural and physiological characteristics associated with pain in dogs and cats have been described (Mathews 2000, Price & Nolan 2007) and different pain scoring systems have been developed to help the veterinarian with pain assessment. A guide to identify pain has been developed by the WSAVA Global Pain Council (<http://www.wsava.org/sites/default/files/Guidelines%20for%20the%20Recognition%2C%20Assessment%20and%20Treatment%20of%20Pain.pdf>). The most commonly used pain scoring systems are descriptive and rely on a highly subjective interpretation of behavioural signs (Dobromylskyj *et al.* 2000). To improve the quality of the pain assessment, composite scoring systems such as the dynamic and interactive visual analogue scale (DIVAS) have been developed (Lascelles *et al.* 1997). The DIVAS scoring system consists of three scaled components: observation of the animal from a distance; measurement of the animal's response to interaction; and response to wound (or in the case of AP, abdominal) palpation. The addition of these three components gives a number that defines the level of (dis)comfort in the animal. Unfortunately, even this pain-scoring scale looks at only one aspect of the pain experience: the intensity.

Multidimensional scales published for use in dogs that consider aspects other than pain intensity include the Melbourne Pain Scale (Firth & Haldane 1999) and the Glasgow Composite Pain Scale (GCPS) (Holton *et al.* 2001). Amongst these, only the GCPS has been designed using psychometric principles (established process of item selection, questionnaire construction and testing for validity, reliability and sensitivity). However, the original GCPS was too long to be of use in a busy clinical practice, and so a shorter form has since been assessed and validated (Morton *et al.* 2005, Murrell *et al.* 2008). The short form of the GCPS is accessible to practitioners online (<http://www.gla.ac.uk/schools/vet/research/painandwelfare/downloadacutepainquestionnaire/>); it provides veterinarians with a practical tool that might be of clinical relevance to manage AP.

Even using this abridged GCPS, it is possible for factors to influence the correct assessment of pain recognition. It is recommended that these factors be taken into account when assessing pain in dogs with AP (Table 2), and a few key points to facilitate

Table 2. Confounding factors that may interfere with pain assessment of animals, and key points which may facilitate with accurate assessment

Factors that may affect pain assessment	Key points to facilitate pain assessment
Altered environment (e.g. in hospital, the presence or not of the owner, the presence of other animal of the same species or not)	Good knowledge of species-specific behaviour Knowledge and comparison of the behaviour before with after the trauma or illness
Species differences (e.g. "Normal" comportment for given species, varied reaction to pain between species)	Response to analgesic treatment is the best marker for accurate diagnosis of pain Behaviour is easily altered by age, illness or drugs
Within-species variation [e.g. Individual dogs react differently (Labrador <i>versus</i> Greyhound)]	Assess interaction with owner or handler Assess response to abdominal palpation or manipulation The assessor must be experienced in pain assessment
Drugs might alter behaviour (e.g. sedative agents do not always provide analgesia although case appears comfortable; analgesic drugs might provide sedation)	If possible, the same person should assess the animal at least on a daily basis during hospitalisation Animal should reassess frequently and a good knowledge of the length of action of particular analgesic agent or procedure must be well known

pain recognition are provided. By determining a level of pain, an appropriate level of analgesia can be initiated (Table 3). However, none of the analgesic agents recommended have been evaluated in dogs with spontaneous AP or in experimental canine models. Hence, the LOE for these recommendations is poor (level D), and the recommendations are based on the authors' professional opinion. Owing to the potential severity of the pain associated with AP, a multimodal approach to pain treatment is advised. This methodology involves the use of analgesic agents influencing the pain process through different mechanisms, allowing for better pain control, lower drug dosages and less potential side effects (Dobromylskyj *et al.* 2000).

Analgesic agents can be classified as opioids (full and partial μ -agonist); non-steroidal anti-inflammatory drugs (NSAIDs), NMDA antagonists (e.g. ketamine), local anaesthetic agents, α_2 -adrenoceptor agonists and adjuvant drugs (e.g. tramadol and gabapentin). Recommended routes of administration and dosages are detailed in Table 4. Because of the presence of hypovolaemia and dehydration in the majority of dogs with AP, NSAIDs and α_2 -adrenoceptor agonists are not recommended and will not be discussed further.

The analgesic effect of opioids is provided mostly through their action in the central nervous system on the μ and δ receptors (spinal and supra spinal) and the κ receptor (spinal) (Lemke & Creighton 2010). The full μ -agonist opioid agents (e.g. morphine, methadone, hydromorphone, meperidine and fentanyl) are considered the most effective analgesics of the group and are usually used to treat moderate to severe pain, while the partial μ -agonist (e.g. buprenorphine) and the μ -antagonist κ -agonist (e.g. butorphanol) are less effective and are used for milder pain level (Lemke & Creighton 2010). Respiratory depression has been reported with the use of all these agents, particularly the μ -agonists. However, at recommended analgesic doses and unless used concomitantly with other central nervous system depressants or in animals with respiratory disease, the respira-

tory depression described with these drugs is rarely clinically significant (Kerr 2007). 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 μ -agonists, and is the biggest complication associated with this group of analgesic agents in dogs with AP. Morphine should be avoided with conditions of the gall bladder and biliary tract. Pethidine, fentanyl or butorphanol do not increase the pressure in the bile duct to the same extent as seen with morphine and can therefore be used (Kerr 2007). Fentanyl, a synthetic opioid 100 times as potent as morphine, can be administered iv and transdermally (fentanyl patches). Unfortunately, fentanyl's systemic absorption from transdermal patches is erratic and will vary with body temperature, peripheral circulation and hydration (Lemke & Creighton 2010). Even with good hydration and normothermia, the onset time is slow with a 12- to 24-hour lag time before effective plasma concentrations are reached which can last for 3 to 5 days. Fentanyl has a profound negative effect on gastrointestinal motility, and so is seldom used in the management of AP.

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 sensitisation during visceral inflammation (Zhang *et al.* 2004). Ketamine is the most potent and specific NMDA antagonist in clinical use today (Berti *et al.* 2009) and plays a role in the reduction of central sensitisation (Gaynor 2008), and may help reduce nociception from intra-abdominal organs and visceral peritoneum (Berti *et al.* 2009). Ketamine has an opioid-sparing effect allowing a decrease in morphine consumption (Gaynor 2008). Ketamine can be administered as a continuous rate infusion (CRI), with or without a loading dose, adjunctively to traditional analgesia. The dose for ketamine infusion being so low, it is very uncommon for animals to develop behavioural or cardiovascular effects (Gaynor 2008). Although there is no study looking at the effect of long-term ketamine infusion on dogs, a

Table 3. An outline of the levels of pain that are potentially manifested in dogs with acute pancreatitis, as adapted from the Glasgow Composite Pain Scale and recommended analgesia

Anticipated levels of pain associated with acute pancreatitis		Potential analgesic combination	Level of evidence
Mild	Quiet but responsive to surroundings; unsettled; looks around when abdomen is palpated	Buprenorphine or methadone (or other full μ -agonist) at high-end of dosage and frequency, reducing down once pain well controlled	D (dogs)
Moderate	Decreased response to surroundings or stimuli; slow or reluctant to move; restless; stretching of abdomen, looking around at abdomen; flinches on abdominal palpation	Buprenorphine or methadone (or other full μ -agonist) at high-end of dosage and frequency, PLUS Lidocaine and Ketamine infusion. Once pain well controlled, reduce ketamine infusion first until 5 $\mu\text{g}/\text{kg}/\text{minute}$ then stop, then reduce lidocaine until 25 $\mu\text{g}/\text{kg}/\text{minute}$ then stop, then reduce dosage and frequency of opioid.	D (dogs)
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 or fentanyl infusion PLUS lidocaine/ketamine infusion. Once pain well controlled, change epidural to opioid as above, then reduce ketamine infusion first until 5 $\mu\text{g}/\text{kg}/\text{minute}$, stop and then reduce lidocaine until 25 $\mu\text{g}/\text{kg}/\text{minute}$, then stop, and then reduce dosage and frequency of opioid.	D (dogs)
Unexpected exacerbation of pain		Assess for pancreatic fluid collection and aspirate via ultrasound guidance	C (dogs)
Adjunctive management	Added with any level of pain	Gabapentin	D (dogs)
	Added if opioids associated with decreased gastrointestinal motility	Methylnaltrexone	D (dogs)
			C (humans)

LOE Level of evidence
The LOE is determined as described in Table 1

Table 4. Suggested doses for analgesic agents for dogs with acute pancreatitis

Drug	Dose	Duration of action	Comment
Full μ-agonist			
Morphine	0.1 to 0.5 mg/kg, im, sc 0.1 mg/kg/hour	4 to 6 hours CRI	Caution: histamine with iv injection
Hydromorphone	0.1 mg/kg epidural	12 to 24 hours	
Methadone	0.05 to 0.15 mg/kg iv, im, sc	2 to 6 hours	
Fentanyl	Dog: 0.1 to 1 mg/kg iv, im, sc 2 μ g/kg iv bolus	2 to 4 hours 0.3 hours	
	0.2 to 0.8 μ g/kg/minute	CRI	
	0.003 to 0.005 mg/kg/hour	Patches	Inconsistent efficacy
Remifentanyl	0.2 to 0.8 μ g/kg/minute	CRI	
Ketamine			
Ketamine	5 to 20 μ g/kg/minute	CRI	In addition to other analgesic agents
Local Anaesthetic			
Lidocaine	25 to 50 μ g/kg/minute	CRI	
	1 to 2 mg/kg epidural	2 to 4 hours	Caution muscle paralysis
Bupivacaine	1 to 2 mg/kg epidural	4 to 6 hours	Caution muscle paralysis
Partial μ-agonist			
Buprenorphine	10 to 40 μ g/kg, iv, im	6 to 8 hours	Generally start at a higher dose and frequency, then taper down if possible

iv Intravenous, CRI Continuous rate infusion, im Intramuscular, sc Subcutaneous

study of dogs undergoing forelimb amputation showed no side effects when ketamine was used intra-operatively at 10 μ g/kg/minute followed with ketamine postoperatively at a 2 μ g/kg/minute rate for up to 20 hours, apart from dysphoria in two dogs (Wagner *et al.* 2002).

Lidocaine is a local anaesthetic that 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 appear to be peripheral and central in origin (Devor *et al.* 1992, Jaffe & Rowe 1995). In humans, lidocaine has been shown to improve bowel function, decrease postoperative pain and reduce opioid consumption following major abdominal surgery (Lamont 2008, Vigneault *et al.* 2011). In addition, lidocaine also has anti-inflammatory properties by reducing the liberation of superoxide anions, a common pathway of inflammation (Hollmann *et al.* 2001, Cassuto *et al.* 2006). These benefits make it an attractive analgesic option in dogs with severe pain resulting from AP.

Tramadol is a synthetic codeine analogue that is a weak μ -agonist and a serotonin and noradrenaline reuptake inhibitor, by which it contributes to the reduction in nociceptive transmission within the spinal cord. Tramadol is available in oral and parenteral form, and has been shown to have an analgesic efficacy comparable with that of morphine when administered prior to ovariohysterectomy (Mastrocinque & Fantoni 2003). Common side effects associated with the agent are sedation, inappetence and dysphoria, and titration of the dose to minimise those effects is advised. Dosing guidelines are based on human extrapolation, and the recommended dose in dogs is 3 to 5 mg/kg twice or thrice a day, while one study (KuKanich & Papich 2004) reported in the dog that a dose of 5 mg/kg four to five times a day was necessary to reach analgesic plasma concentrations. At this time, there are no published pharmacokinetic data in dogs for dosage guidelines for the slow release formulation.

In human medicine, gabapentin is an anticonvulsant that has been shown to provide effective analgesia for neuropathic pain and postoperative abdominal surgeries. The anti-nociception obtained with gabapentin and its successor, pregabalin, results from inhibiting the release of excitatory neurotransmitters (substance P and calcitonin gene-related peptide) at the level of the dorsal horn by binding on the α_2 - δ_1 subunit of presynaptic voltage-gated calcium channels. In veterinary medicine, the use of gabapentin has expanded to treat chronic cancer pain, chronic neuropathic pain and perioperative pain in dogs (Lamont 2008). Because of the potential for substance P to contribute to pain development in AP (Frossard & Pastor 2002), the use of this drug in dogs with severe pain is theoretically sound. The use of gabapentin is preferred to tramadol when managing pain once the animal is discharged (LOE D).

NUTRITION

Traditional management

The role of nutrition in the treatment of AP has gained a lot of attention recently in both human and veterinary medicine, and heralded a change of direction in management (Table 5). 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 (Thomson 2006). Initially in human (and veterinary) gastroenterology, the consensus was to "rest" the pancreas based on the assumption that ongoing pancreatic secretion would perpetuate pancreatic inflammation (Stewart 1994, Williams 1994). It was subsequently demonstrated experimentally in four different rodent models that exocrine pancreatic secretion actually decreased during pancreatitis (Niederer *et al.* 1990). Additionally, the gastrointestinal tract itself is now thought to be a major contributor to the systemic inflammatory state dur-

Table 5. Assessment of the level of evidence for nutritional management of acute pancreatitis, as described in Table 1

Nutritional assumptions	Level of evidence
Total parenteral nutrition confers a poor prognosis in AP	B (humans) C (dogs)
Total parenteral nutrition increases rate of complications in AP	B (humans) B (dogs)
Early enteral nutrition improves survival in AP compared with intestinal rest	B (humans) D (dogs)
Early enteral nutrition improves survival in AP compared with total parenteral nutrition	A (humans) D (dogs)
Early enteral nutrition decreases hospitalisation time in AP	A (humans) D (dogs)
Early enteral nutrition decreases complication rates in AP	A (humans) B (dogs)
Gastric (or oesophageal) feeding is as well tolerated as jejunal feeding in AP	A (humans) C (dogs)
Enteral nutrition may be used in the presence of pancreatic complications such as fistulas, ascites and pseudocysts.	A (humans) D (dogs)
A small peptide-based medium-chain triglyceride (MCT) oil formula may improve tolerance of enteral nutrition	A (humans) C (dogs)
Attainment of full resting energy requirements is not essential to improve outcome	A (humans) C (dogs)
If enteral nutrition is not tolerated, then some form of parenteral nutrition should be instituted after 5 to 7 days of anorexia	A (humans) D (dogs)

AP Acute pancreatitis, MCT Medium-chain triglyceride

ing AP, particularly if it is not supplied with luminal nutrients, with amino acids the major respiratory fuel that is required by the enterocytes (Flint & Windsor 2003). In humans and animal experimental models, it has been shown that fasting leads to intestinal mucosal atrophy (King & Kudsk 1997, Hernandez *et al.* 1999), an increased rate of enterocyte apoptosis in the intestine (Fukuyama *et al.* 2001), changes in mucin composition, and decreased glutamine and arginine transport (Sarac *et al.* 1994). Conversely, nutrition delivered directly to the intestine decreased villus atrophy (Kotani *et al.* 1999), reduced bacterial translocation and decreased pancreatic inflammation in canine models of AP (Kotani *et al.* 1999, Qin *et al.* 2002a,b, 2003, 2007). Survival was not assessed in these studies.

To counteract the negative nitrogen balance in AP, total parenteral nutrition (TPN) was historically recommended in severe cases in both the human and veterinary fields. TPN has been shown to impair humoral and cell-mediated immunity, magnify the pro-inflammatory response, and increase bacterial translocation and infection rate in critically ill humans (Marik & Pinsky 2003). Meta-analysis also shows that TPN worsens the prognosis in humans with AP (Petrov & Zagainov 2007). There have been few reviews on the clinical efficacy of TPN in any specific condition in dogs. One study identified a mortality rate of nearly 50% in over 200 dogs that received TPN, along with a high rate of metabolic (70%), mechanical (25%) and septic (5%) complications (Reuter *et al.* 1998). A more recent study showed that complications of peripheral and centrally administered parenteral nutrition bore no relationship with the outcome (Queau *et al.* 2011) However, this same study also determined that a risk

factor for death was a prolonged period of anorexia prior to the initiation of TPN.

Current management principles in humans

Despite most consensus statements in human gastroenterology supporting the notion of early enteral feeding in severe AP, few clinical studies effectively compare enteral nutrition with full pancreatic rest (Table 5) (Mirtallo *et al.* 2012). One small study suggested that enteral feeding decreased mortality and the rate of septic complications compared with iv fluid therapy alone, albeit with no difference in hospitalisation duration or the rate of non-septic complications (Pupelis *et al.* 2001). Another study comparing intestinal rest with enteral feeding showed an increase in gut permeability in humans fed via a nasojejunal tube, but no difference in inflammatory markers (Powell *et al.* 2000). This was postulated to be because of increased mucosal blood supply. However, mortality, complication rate and hospitalisation duration were not assessed.

Most of the experimental and clinical nutritional studies in humans initially assessed nutrition delivered into the jejunum. This was based on the demonstration that jejunal administration of nutrients did not stimulate exocrine pancreatic production of digestive enzymes, and also stimulated production of polypeptide YY, somatostatin and other substances that inhibit pancreatic secretion (Ioannidis *et al.* 2008). However, multiple studies in humans have shown that nasogastric feeding is safe and well tolerated, and a cheaper and easier alternative to insertion of a nasojejunal feeding tube (Eatock *et al.* 2005, Kumar *et al.* 2006, Petrov *et al.* 2008).

One of the major perceived drawbacks of enteral feeding in humans with AP is the possibility of pain associated with feeding. One study assessed pain associated with feeding in humans with mild AP (Chebli *et al.* 2005). They found that 25% of patients had some pain in the 1st or 2nd day of oral feeding, but this was associated with the presence of pancreatic fluid collection. One study assessed pain in humans with AP when fed orally compared with that via a nasojejunal tube, and found no differences (Pandey *et al.* 2004). A very recent (but small) study showed decreased pain levels and decreased requirements for opiates in humans with AP fed early compared with those given intestinal rest (Petrov *et al.* 2012).

According to a consensus review, immunonutrition cannot currently be recommended in humans with AP (Nathens 2004), as no benefit with supplemented glutamine, arginine, tributyrin or omega-3 fatty acids was observed (Pearce *et al.* 2006). This is despite a large body of theoretical data supporting the benefit of glutamine supplementation for enteral health (Souba *et al.* 1990). Additionally, a recent randomised, double-blind, placebo-controlled study conducted in Holland in humans with severe AP assessed probiotic usage (Besselink *et al.* 2008). The mortality rate was significantly greater in the probiotic group, with a relative risk of 2.53. The biggest cause of death was multiple organ dysfunction, although three patients died of bowel ischaemia. Death was not related to aetiological classification or the presence of necrosis. However, the addition of medium-chain triglycerides is recommended in humans (Mirtallo *et al.* 2012).

Veterinary nutritional management

In one randomised, prospective study of enteral nutrition intervention in dogs with parvoviral enteritis, administration of nutrition via a naso-oesophageal tube resulted in an earlier clinical improvement in dogs but no difference in survival (Mohr *et al.* 2003). In a prospective pilot study in dogs with severe AP, oesophageal feeding was well tolerated and safe, albeit with a very small sample size (Mansfield *et al.* 2011). Compared with TPN in that study, there was a more rapid reduction in clinical severity and inflammatory markers; however, no difference in survival was identified. Large scale multicentre randomised prospective studies are required to fully evaluate the benefits of enteral nutrition in dogs.

Based on the medical consensus, it is recommended that dogs with mild AP (no systemic complications) be fasted until they are able to eat voluntarily, unless they have reached 5 days of anorexia (including the pre-hospital period), in which case enteral feeding should be initiated. In dogs with severe AP, interventional 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 studies have shown no difference in dietary fat content on pancreatic secretion in healthy dogs (Manas *et al.* 1996, James *et al.* 2009), avoidance of high-fat diets in dogs with AP is logical as many of the animals are hyperlipidaemic. Given this, veterinary convalescent diets may be too high in fat for dogs with AP and concurrent hyperlipidaemia (Table 6). Alternative products such as human liquid convalescent diets supplemented with protein could be given if naso-oesophageal tubes are being used, which generally have a small lumen and require a very liquid consistency. If an oesophageal tube is inserted, then a low-fat, high-fibre diet that meets the requirements set out in Table 6 could be blended and given through the tube easily. To date, there is no evidence that supplementation of balanced veterinary diets with medium-chain triglycerides or glutamine, or provision of glutamine alone enterally, will result in clinical improvement in dogs with AP.

There is also no evidence that achieving full resting energy requirements (RER) is necessary to confer any positive effect on outcome in humans with AP (Nathens 2004, Petrov *et al.*

2008), which has also been extrapolated to dogs (LOE D). RER is calculated on the lean bodyweight (BW) of the animal using the following formula: BW greater than 2 kg and less than 25 kg: $30 \times \text{BW (kg)} + 70 \text{ kcal/day}$; and if less than 2 kg or greater than 25 kg then $70 \times \text{BW}^{0.75}$. When starting feeding, on the first day a maximum of 25% of the calculated RER should be given, each feed should not be more than 5 to 10 mL/kg BW, and food should be given at approximately 1 minute per 5 mL of food (Saker & Remillard 2010). If this is well tolerated, then the percentage of RER can be increased by up to 25% per day, and the volume of each feed also increased.

In critically ill humans requiring mechanical ventilation, early enteral nutrition lowered mortality rates but increased the risk of pneumonia (Artinian *et al.* 2006). The development of aspiration pneumonia appears to be one of the largest complications of enteral feeding in dogs with AP. Steps to minimise this risk include feeding only when the animal is in sternal position or sitting upright, encouraging the animal to move around (walk) after the feeding (or have the dog held upright for 10 to 15 minutes after feeding) and intermittent bolus feeding rather than continuous infusion. In addition, avoidance of full mu opioids that decrease mentation and gastrointestinal motility aids in the successful introduction of feeding.

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 (Wu & Conwell 2010a). 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 (Wu & Conwell 2010a). The term acute fluid collection is, therefore, the most suitable term for the local pancreatic complications that occur in dogs, although inspissated pancreatic tissue that develops 2 to 3 weeks following AP may be termed a phlegmon (Charles 2007).

Current medical recommendations are to not surgically debride sterile fluid collections, and if infection is documented,

Table 6. Recommendations for assisted (enteral tube) feeding in dogs and common convalescence foods available for use in dogs

Component	Dog requirements (as reported in Saker & Remillard 2010)	Human liquid convalescent diets*	Hills AD convalescent tins	Royal Canin recovery diet
Caloric density	1 kcal/mL	1 kcal/mL	1.15 kcal/g undiluted†	1.18 kcal/g undiluted†
Digestible carbohydrate days 0 to 2	2 to 4 g/100 kcal	13.4 g/100 kcal	3.2 g/100 kcal	1.3 g/100 kcal
Digestible carbohydrate days 3+	6 to 10 g/100 kcal			
Protein	5 to 12 g/100 kcal	3.27 g/100 kcal	9.2 g/100 kcal	10.5 g/100 kcal
Arginine	≥146 mg/ 100 kcal	Unable to determine	495 mg/ 100 kcal	590 mg/100 kcal
Glutamine	≥500 mg/kcal	Unable to determine	1077 mg/ 100 kcal	1270 mg/100 kcal
Fat	5 to 7.5 g/ 100 kcal (except in cases of hyperlipidaemia)	3.27 g/100 kcal	6.3 g/100 kcal	5.5 g/100 kcal
Fat	2.0 to 3.5 g/100 kcal (when hyperlipidaemia)			

*This composition is typical of most human liquid convalescent diets, and therefore, it is recommended that whey protein isolate be added to the formulation after 2-3 days of use
 †For smaller gauge tubes, increased volumes of water will be needed to be able to flush through feeding tubes

then there should be treatment with antimicrobials for as long as possible prior to surgical debridement (Nathens 2004, Johnson 2005, Heinrich *et al.* 2006, Muddana *et al.* 2009) (LOE humans A, dogs B). Surgery to treat pancreatic acute fluid collections in dogs invariably results in a high mortality rate (>50%), regardless of the technique used (Salisbury *et al.* 1988, Bellenger *et al.* 1989, Edwards *et al.* 1990, Johnson & Mann 2006). There have been reported spontaneous resolutions of acute fluid collections in the veterinary literature, and good responses to percutaneous drainage, suggesting that these are preferable methods for managing this particular complication (Smith & Biller 1998, VanEnkevort *et al.* 1999). The authors recommend that the presence of fluid collections be determined whether a dog has persistent or unexpected pain, and to perform percutaneous drainage if the pain is associated with the fluid (LOE humans A, dogs C).

NOVEL THERAPEUTIC DIRECTIONS

There have been many attempts over the past three decades to assess new medical treatments for AP. Initially, there was some promise for protease inhibitors in either reducing mortality or complications in animal experimental models (Mikami *et al.* 2005). Stringent analysis of multiple randomised and well-controlled clinical trials of protease inhibitors such as gabexate mesilate in humans have subsequently shown no benefit in any of these agents to reduce mortality or morbidity of AP (Imrie *et al.* 1978, Uhl *et al.* 1999, Heinrich *et al.* 2006). There was no amelioration of histological inflammation in a study of dogs with induced pancreatitis treated with a somatostatin analogue (Ko *et al.* 1992). Additionally, somatostatin analogues have powerful splanchnic vasoconstrictive properties, which may contribute to and perpetuate pancreatic necrosis (Klar *et al.* 1991). The effects of specific anti-cytokine therapies appear to be highly variable, as they are generally useful at ameliorating only one aspect of the inflammatory cascade and require very early administration (Formela *et al.* 1994, Imamura *et al.* 1998, Buscaglia *et al.* 2008, Pezzilli 2009). The lack of perceived benefit in humans, the lack of widespread availability of veterinary anti-cytokine drugs and prohibitive costs means that these novel therapeutic directions are unlikely to change management of canine AP in the near future.

FOLLOW-UP CARE

Although in most instances, the initiating cause of AP is not known, in a certain percentage of dogs there may be an underlying lipid disorder and therefore it may be prudent to check fasting serum triglyceride and cholesterol concentrations 1 to 2 weeks after recovery (Hess *et al.* 1998). Investigation of underlying causes and long-term management of the hyperlipidaemia is recommended if present (LOE D). If drug administration is implicated in the aetiology, such as azathioprine and potassium bromide, then withdrawal of that drug should be undertaken.

There is no evidence that dogs with dietary indiscretion will be predisposed to recurrent bouts of AP (Lem *et al.* 2008).

A proportion of humans following AP will have exocrine insufficiency that is manifested as steatorrhea and diarrhoea (Wu & Conwell 2010b). One study has shown that the degree of exocrine insufficiency following a bout of AP in humans is directly correlated with the amount of necrosis (Boreham & Ammori 2003). Subclinical exocrine pancreatic insufficiency has been diagnosed in dogs and is not always manifested by overt steatorrhea (Wiberg & Westermarck 2002). On the basis of this, in severely affected dogs, treatment with exocrine pancreatic enzymes for 3 to 4 weeks following a bout of AP may be beneficial in selected instances (LOE D).

CONCLUSION

Large, multicentre studies are required to fully evaluate treatment strategies for AP in dogs. Currently, there exists a reasonable LOE for supportive care such as iv fluid therapy and anti-emetic therapy. The areas that seem to hold the most promise for improving morbidity and/or mortality include evaluating novel analgesic agents, nutritional intervention and the use of low-dose corticosteroids. Currently, recommendations for analgesia are extrapolated from postsurgical studies and are dependent on the level of pain. Extrapolation from humans would suggest that early enteral nutrition in dogs with severe AP may decrease morbidity and pain (Petrov *et al.* 2012, Mirtallo *et al.* 2012), and it has been shown that oesophageal feeding is well tolerated in dogs with AP (Mansfield *et al.* 2011). There is no evidence to support surgical intervention in the management of AP.

Conflict of interest

None of the authors of this article has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

References

- Al Mofleh, I. (2008) Severe acute pancreatitis: pathogenic aspects and prognostic factors. *World Journal of Gastroenterology* **14**, 675-684
- Artinian, V., Krayem, H. & DiGiovine, B. (2006) Effects of early enteral feeding on the outcome of critically ill mechanically ventilated medical patients. *Chest* **129**, 960-996
- Bang, U. C., Semb, S., Nojgaard, C. *et al.* (2008) Pharmacological approach to acute pancreatitis. *World Journal of Gastroenterology* **14**, 2968-2976
- Bellenger, C. R., Ilkiw, J. E. & Malik, R. (1989) Cystogastrostomy in the treatment of pancreatic pseudocyst/abscess in two dogs. *Veterinary Record* **125**, 181-184
- Benchaoui, H. A. (2007) Efficacy of maropitant for preventing vomiting associated with motion sickness in dogs. *Veterinary Record* **161**, 444-447
- Bersenas, A. M., Mathews, K. A., Allen, D. G., *et al.* (2005) Effects of ranitidine, famotidine, pantoprazole, and omeprazole on intragastric pH in dogs. *American Journal of Veterinary Research* **66**, 425-431
- Berti, M., Baciarello, M., Troglia, R., *et al.* (2009) Clinical uses of low-dose ketamine in patients undergoing surgery. *Current Drug Targets* **10**, 707-715
- Besselink, M. G., Van Santvoort, H. C., Buskens, E., *et al.* (2008) Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial. *Lancet* **371**, 651-659
- Bhatia, M., Brady, M., Shokuhi, S., *et al.* (2000) Inflammatory mediators in acute pancreatitis. *Journal of Pathology* **190**, 117-125
- Bhoomagoud, M., Jung, T., Atladottir, J., *et al.* (2009) Reducing extracellular pH sensitizes the acinar cell to secretagogue-induced pancreatitis responses in rats. *Gastroenterology* **137**, 1083-1092
- Boreham, B. & Ammori, B. J. (2003) A prospective evaluation of pancreatic exocrine function in patients with acute pancreatitis: correlation with extent of necrosis and pancreatic endocrine insufficiency. *Pancreatology* **3**, 303-308
- Buscaglia, J. M., Simons, B. W., Prosser, B. J., *et al.* Etanercept: a TNF-alpha binding agent, is ineffective in the prevention of post-ERCP pancreatitis in canines. *Journal of the Pancreas* **9**, 456-467

- Cai, J., Zhou, J., Luo, H. S., et al. (2007) Effect of proton pump inhibitor on amylase release from isolated pancreatic acinie. *In Vitro Cellular and Developmental Biology - Animal* **43**, 25-27
- Cassuto, J., Sinclair, R. & Bonderovic, M. (2006) Anti-inflammatory properties of local anesthetics and their present and potential clinical implications. *Acta Anaesthesiologica Scandinavica* **50**, 265-282
- Charles, J. (2007) Pancreas. In: Jubb, Kennedy, and Palmer's Pathology of Domestic Animals. vol. 2. Ed M. G. Maxie. Saunders Elsevier, Edinburgh, Scotland. pp 389-423
- Chebli, J. M. F., Gaburri, P. D., De Souza, A. F. M., et al. (2005) Oral refeeding in patients with mild acute pancreatitis: prevalence and risk factors of relapsing abdominal pain. *Journal of Gastroenterology and Hepatology* **20**, 1385-1389
- Conder, G. A. (2008) Efficacy and safety of maropitant, a selective neurokinin1 receptor antagonist, in two randomized clinical trials for prevention of vomiting due to motion sickness in dogs. *Journal of Veterinary Pharmacology and Therapeutics* **31**, 528-532
- Cook, A. K., Breitschwerdt, E. B., Levine, J. F., et al. (1993) Risk factors associated with acute pancreatitis in dogs: 101 cases (1985-1990). *Journal of the American Veterinary Medical Association* **203**, 673-679
- De la Puente-Redondo, V. A., Siedek, E. M., Benchaoui, H. A. et al. (2007a) The anti-emetic efficacy of maropitant (Cerenia™) in the treatment of ongoing emesis caused by a wide range of underlying clinical aetiologies in canine patients in Europe. *Journal of Small Animal Practice* **48**, 93-98
- De la Puente-Redondo, V. A., Tilt, N., Rowan, T. G., et al. (2007b) Efficacy of maropitant for treatment and prevention of emesis caused by intravenous infusion of cisplatin in dogs. *American Journal of Veterinary Research* **68**, 48-56
- Devor, M., Wall, P. D. & Catalan, N. (1992) Systemic lidocaine silences ectopic neuroma and DRG discharge without blocking nerve conduction. *Pain* **48**, 261-268
- Dobromylskyj, P., Flecknell, P. A., Lascelles, B. D., et al. (2000) Pain assessment. In: Pain Management in Animals. Eds P. Flecknell and A. Waterman-Pearson. Saunders W. B., London, UK. pp 53-79
- Donaldson, L. A. & Schenck, W. G. (1979) Experimental acute pancreatitis: the changes in pancreatic oxygen consumption and the effect of Dextran 40. *Annals of Surgery* **190**, 728-731
- Eatock, F. C., Chong, P., Menezes, N., et al. (2005) A randomized study of early nasogastric versus nasojeunal feeding in severe acute pancreatitis. *American Journal of Gastroenterology* **100**: 432-439
- Edwards, D. F., Bauer, M. S., Walker, M. A., et al. (1990) Pancreatic masses in seven dogs following acute pancreatitis. *Journal of American Animal Hospital Association* **26**, 189-198
- Elwood, C., Devauchelle, P., Elliot, J., et al. (2010) Emesis in dogs: a review. *Journal of Small Animal Practice* **51**(1): 4-22
- Field, B. E., Hepner, G. W., Shabot, M. M., et al. (1979) Nasogastric suction in alcoholic pancreatitis. *Digestive Diseases and Sciences* **24**, 339-344
- Firth, A. M. & Haldane, S. L. (1999) Development of a scale to evaluate postoperative pain in dogs. *Journal of the American Veterinary Medical Association* **214**, 651-659
- Fittschon, C. & Bellamy, J. E. C. (1984) Prednisone treatment alters the serum amylase and lipase activities in normal dogs and cats without causing pancreatitis. *Canadian Journal of Comparative Medicine* **48**, 136-140
- Flint, R. S. & Windsor, J. A. (2003) The role of the intestine in the pathophysiology and management of severe acute pancreatitis. *World Journal of Gastroenterology* **5**, 69-85
- Formela, L. J., Wood, L. M., Whittaker, M., et al. (1994) Amelioration of experimental acute pancreatitis with a potent platelet-activating factor antagonist. *British Journal of Surgery* **81**, 1783-1785
- Fritz, S., Hackert, T., Hartwig, W., et al. (2010) Bacterial translocation and infected pancreatic necrosis in acute necrotizing pancreatitis derives from small bowel rather than from colon. *American Journal of Surgery* **200**, 111-117
- Frossard, J. L. (1999). *Gastroenterology* **116**, 694-701
- Frossard, J.-L. & Pastor, C. M. (2002) Experimental acute pancreatitis: new insights into the pathophysiology. *Frontiers in Bioscience* **7**, d275-d287
- Fukuyama, K., Iwakiri, R., Noda, T., et al. (2001) Apoptosis induced by ischemia-reperfusion and fasting in gastric mucosa compared to small intestinal mucosa in rats. *Digestive Diseases and Sciences* **46**, 545-549
- Fuller, R. K., Loveland, J. P. & Frankel, M. H. (1981) An evaluation of the efficacy of nasogastric suction treatment in alcoholic pancreatitis. *American Journal of Gastroenterology* **75**, 349-353
- Gardner, T. B., Vege, S. S., Pearson, R.K., et al. (2008) Fluid resuscitation in acute pancreatitis. *Clinical Gastroenterology and Hepatology* **6**, 1070-1076
- Gaynor, J. S. (2008) Control of cancer pain in veterinary patients. *Veterinary Clinics of North America: Small Animal Practice* **38**, 1429-1448, viii
- Hackert, T., Tudor, S., Felix, K., et al. (2010) Effects of pantoprazole in experimental acute pancreatitis. *Life Sciences* **87**, 551-557
- Heinrich, S., Schafer, M., Roussan, V., et al. (2006) Evidence-based treatment of acute pancreatitis: a look at established paradigms. *Annals of Surgery* **243**, 154-168
- Heller, A. (1999) Pancreatitis-associated protein protects the lung from leukocyte-induced injury. *Anesthesiology* **91**, 1408-1414
- Hernandez, G., Velasco, N., Wainstein, C., et al. (1999) Gut mucosal atrophy after a short enteral fasting period in critically ill patients. *Journal of Critical Care* **14**, 73-77
- Hess, R. S., Saunders, H. M., Van Winkle, T. J., et al. (1998) Clinical, clinicopathologic, radiographic, and ultrasonographic abnormalities in dogs with fatal acute pancreatitis: 70 cases (1986-1995). *Journal of the American Veterinary Medical Association* **213**, 665-670
- Hollmann, M. W., Gross, A., Jelacin, N., et al. (2001) Local anesthetic effects on priming and activation of human neutrophils. *Anesthesiology* **95**, 113-122
- Holm, J. L., Chan, D. L. & Rozanski, E. A. (2003) Acute pancreatitis in dogs. *Journal of Veterinary Emergency and Critical Care* **13**, 201-213
- Holton, L., Pawson, P., Nolan, A., et al. (2001) Development of a behaviour-based scale to measure acute pain in dogs. *Veterinary Record* **148**, 525-531
- Imamura, M., Mikami, Y., Takahashi, H., et al. (1998) Effect of a specific synthetic inhibitor of neutrophil elastase (ONO-5046) on the course of acute hemorrhagic pancreatitis in dogs. *Journal of Hepatobiliary Pancreatic Surgery* **5**, 422-428
- Imrie, C. W., Benjamin, I. S., Ferguson, J. C., et al. (1978) A single-centre, double blind trial of trasyolol therapy in primary acute pancreatitis. *British Journal of Surgery* **65**, 337-340
- Ioannidis, O., Lavrentieva, A. & Botsios, D. (2008) Nutrition support in acute pancreatitis. *Journal of the Pancreas* **9**, 375-390
- Iovanna, J., Orelle, B., Keim, V., et al. (1991) Messenger RNA sequence and expression of rat pancreatitis-associated protein, a lectin-related protein overexpressed during acute experimental pancreatitis. *Journal of Biological Chemistry* **266**, 24664-24669
- Jaffe, R. A. & Rowe, M. A. (1995) Subanesthetic concentrations of lidocaine selectively inhibit a nociceptive response in the isolated rat spinal cord. *Pain* **60**, 167-174
- James, F. E., Mansfield, C. S., Stiener, J. M., et al. (2009) Pancreatic response in healthy dogs fed diets of various fat compositions. *American Journal of Veterinary Research* **70**, 614-618
- Johnson, C. D. (2005) UK Working Party on Acute Pancreatitis: UK guidelines for the management of acute pancreatitis. *Gut* **54**(Suppl III), iii1-iii9
- Johnson, M. D. & Mann, F. A. (2006) Treatment for pancreatic abscesses via omentalization with abdominal closure versus open peritoneal drainage in dogs: 15 cases (1994-2004). *Journal of the American Veterinary Medical Association* **228**, 397-402
- Kalli, I., Adamama-Moraitou, K. K. & Rallis, T. S. (2009) Acute pancreatitis in dogs: a review article. *European J of Companion Animal Practice* **19**, 147-155
- Kandil, E., Lin, Y.-Y., Bluth, M. H., et al. (2006) Dexamethasone mediates protection against acute pancreatitis via upregulation of pancreatitis-associated proteins. *World Journal of Gastroenterology* **12**, 6806-6811
- Karanjia, N. D., Lutrin, F. J., Chang, Y. B., et al. (1990) Low dose dopamine protects against hemorrhagic pancreatitis in cats. *The Journal of Surgical Research* **48**, 440-443
- Kazantsev, G. B., Hecht, D. W., Rao, R., et al. (1994) Plasmid labeling confirms bacterial translocation in pancreatitis. *The American Journal of Surgery* **167**, 201-207
- Keck, T., Friebe, V., Warshaw, A. L., et al. (2005) Pancreatic proteases in serum induce leukocyte-endothelial adhesion and pancreatic microcirculatory failure. *Pancreatology* **5**, 241-250
- Kellum, J. A. (2002) Fluid resuscitation and hyperchloremic acidosis in experimental sepsis: improved short-term survival and acid-base balance with Hextend compared with saline. *Critical Care Medicine* **30**, 300-305
- Kerr, C. (2007). Pain Management 1: systemic analgesics. In: BSAVA Manual of Canine and Feline Anaesthesia and Analgesia. Eds C. Seymour and T. Duke-Novakosvski. BSAVA, Quedgeley, UK. pp 89-103
- King, B. K. & Kudsk, K. A. (1997) A temporal study of TPN-induced changes in gut-associated lymphoid tissue and mucosal immunity. *Archives of Surgery* **132**: 1303-1309
- Klar, E., Rattner, D. W., Compton, C., et al. (1991) Adverse effect of therapeutic vasoconstrictors in experimental acute pancreatitis. *Annals of Surgery* **214**, 168-174
- Knol, J. A., Edgcomb, L. P., Inman, M.G., et al. (1983) Low molecular weight dextran in experimental pancreatitis: effects on pancreatic microcirculation. *The Journal of Surgical Research* **35**, 73-82
- Ko, T. C., Bertram, M. F., Prinz, R. A., et al. (1992) Effect of somatostatin analogue and cholecystokinin receptor antagonist on bile-induced acute canine pancreatitis. *American Journal of Surgery* **58**, 213-219
- Kotani, J., Usami, M., Nomura, H., et al. (1999) Enteral nutrition prevents bacterial translocation but does not improve survival during acute pancreatitis. *Archives of Surgery* **134**, 287-292
- KuKanich, B. & Papich, M. G. (2004) Pharmacokinetics of tramadol and the metabolite O-desmethyltramadol in dogs. *J Vet Pharmacol Ther* **27**(4): 239-246
- Kumar, A., Singh, N., Prakash, S., et al. (2006) Early enteral nutrition in severe acute pancreatitis: a prospective randomized controlled trial comparing nasojeunal and nasogastric routes. *J Clin Gastroenterol* **40**(5): 431-434
- Lamont, L. A. (2008) Adjunctive analgesic therapy in veterinary medicine. *Veterinary Clinics of North America: Small Animal Practice* **38**(6): 1187-1203
- Lascelles, B. D., Cripps, P. J., Jones, A., Waterman, A. E., et al. (1997) Post-operative central hypersensitivity and pain: the pre-emptive value of pethidine for ovariohysterectomy. *Pain* **73**(3): 461-471
- Lasson, A. & Ohlsson, K. (1984) Protease inhibitors in acute human pancreatitis. *Scandinavian Journal of Gastroenterology* **19**, 779-786
- Leese, T., Holliday, M., Heath, D., et al. (1987) Multicentre clinical trial of low volume fresh frozen plasma therapy in acute pancreatitis. *British Journal of Surgery* **74**, 907-911

- Leese, T., West, K., Morton, D., et al. (1988) Fresh frozen plasma therapy in acute pancreatitis: an experimental study. *International J Gastrointestinal Cancer* **3**, 437-447
- Leese, T., Thomas, W. M., Holliday, M., et al. (1991) A multicentre controlled clinical trial of high-volume fresh frozen plasma therapy in prognostically severe acute pancreatitis. *Annals of the Royal College of Surgeons of England* **73**, 207-214
- Leffler, A. (2009) Characterization of species-related differences in the pharmacology of tachykinin NK receptors 1, 2 and 3. *Biochemical Pharmacology* **77**, 1522
- Lem, K. Y., Fosgate, G.T., Norby, B., et al. (2008) Associations between dietary factors and pancreatitis in dogs. *Journal of the American Veterinary Medical Association* **233**, 1425-1431
- Lemke, K. A. & Creighton, C. M. (2010) Analgesia for anesthetized patients. *Topics in Companion Animal Medicine* **25**, 70-82
- Levant, J. A., Secrist, D. M., Resin, H., et al. (1974) Nasogastric suction in the treatment of alcoholic pancreatitis: a randomised study. *Journal of the American Medical Association* **229**, 51-52
- Louidice, T. A., Lang, J., Mehta, H., et al. (1984) Treatment of acute alcoholic pancreatitis: the roles of cimetidine and nasogastric suction. *American Journal of Gastroenterology* **79**, 553-558
- Manas, M., Yago, M. D., Quiles, J. L., et al. (1996) Absence of rapid adaptation of the exocrine pancreas of conscious dogs to diets enriched in fat or carbohydrates. *Archives of Physiology Biochemistry* **104**, 819-825
- Mansfield, C. S. (2012) Pathophysiology of acute pancreatitis: potential application from experimental models and human medicine to dogs. *Journal of Veterinary Internal Medicine* **26**, 875-887
- Mansfield, C. S., James, F. E. & Robertson, I. D. (2008) Development of a clinical severity index for dogs with acute pancreatitis. *Journal of the American Veterinary Medical Association* **233**, 936-944
- Mansfield, C. S., James, F. E., Steiner, J., et al. (2011) A pilot study to assess tolerability of early enteral nutrition via esophagostomy tube feeding in dogs with severe acute pancreatitis. *Journal of Veterinary Internal Medicine* **25**, 419-425
- Marik, P. E. (2008) Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the American College of Critical Care Medicine. *Critical Care Medicine* **36**, 1937-1949
- Marik, P. & Pinsky, M. (2003) Death by total parenteral nutrition. *Intensive Care Medicine* **29**, 867-869
- Mastrocinque, S. & Fantoni, D. T. (2003) A comparison of preoperative tramadol and morphine for the control of early postoperative pain in canine ovariohysterectomy. *Veterinary Anaesthesia and Analgesia* **30**, 220-228
- Mathews, K. A. (2000) Pain assessment and general approach to management. *Veterinary Clinics of North America: Small Animal Practice* **30**(4): 729-755, v.
- Mehler, S. J., Mayhew, P. D., Drobatz, K. J., et al. (2004) Variables associated with outcome in dogs undergoing extrahepatic biliary surgery: 60 cases (1988-2002). *Veterinary Surgery* **33**, 644-649
- Mikami, Y., Takeda, K., Matsuda, K., et al. (2005) Rat experimental model of continuous regional arterial infusion of protease inhibitor and its effects on severe acute pancreatitis. *Pancreas* **30**, 248-253
- Mirtallo, J. M. (2012) International consensus guidelines for nutrition therapy in pancreatitis. *Journal of Parenteral and Enteral Nutrition* **36**, 284-291
- Mithofer, K., Warshaw, A. L., Frick, T. W., et al. (1995) Calcium administration augments pancreatic injury and ectopic trypsinogen activation after temporary systemic hypotension in rats. *Anesthesiology* **83**, 1266-1273
- Mohr, A. J., Leisewitz, A. L., Jacobson, L. S., et al. (2003) Effect of early enteral nutrition on intestinal permeability, intestinal protein loss, and outcome in dogs with severe parvoviral enteritis. *Journal of Veterinary Internal Medicine* **17**, 791-798
- Morton, C. M., Reid, J., Scott, E. M., et al. (2005) Application of a scaling model to establish and validate an interval level pain scale for assessment of acute pain in dogs. *American Journal of Veterinary Research* **66**, 2154-2166
- Muddana, V., Whitcomb, D. C. & Papachristou, G. I. (2009) Current Management and novel insights in acute pancreatitis. *Expert Review of Gastroenterology and Hepatology* **3**, 435-444
- Muller, C. A., Vogeser, M., Belyaev, O., et al. (2006) Role of endogenous glucocorticoid metabolism in human acute pancreatitis. *Critical Care Medicine* **34**, 1060-1066
- Murrell, J. C., Psatha, E. P., Scott, E. M., et al. (2008) Application of a modified form of the Glasgow pain scale in a veterinary teaching centre in the Netherlands. *Veterinary Record* **162**, 403-408
- Naeije, R., Salingret, E., Clumeck, N., et al. (1978) Is nasogastric suction necessary in acute pancreatitis? *British Journal of Medicine* **2**, 659-660
- Nathens, A. B. (2004) Management of the critically ill patient with severe acute pancreatitis. *Critical Care Medicine* **32**, 2524-2536
- Navarro, S., Roe, E., Aused, R., et al. (1984) Comparison of fasting, nasogastric suction and cimetidine in the treatment of acute pancreatitis. *Digestion* **30**, 224-230
- Newman, S. J., Steiner, J. M., Woosley, K., et al. (2006) Histologic assessment and grading of the exocrine pancreas in the dog. *Journal of Veterinary Diagnostic Investigation* **18**, 115-118
- Niederer, C., Niederer, M., Luthen, R., et al. (1990) Pancreatic exocrine secretion in acute experimental pancreatitis. *Gastroenterology* **99**, 1120-1127
- Noble, M. D., Romac, J., Vigna, S. R., et al. (2008) A pH-sensitive, neurogenic pathway mediates disease severity in a model of post-ERCP pancreatitis. *Gut* **57**, 1566-1571
- Ortiz, E. M., Dusetti, N. J., Vasseur, S., et al. (1998) The pancreatitis-associated protein is induced by free radicals in AR4-2J cells and confers cell resistance to apoptosis. *Gastroenterology* **114**, 808-816
- Pandey, S. K., Ahuja, V., Joshi, Y. K., et al. (2004) A randomized trial of oral refeeding compared with jejunal tube refeeding in acute pancreatitis. *Indian Journal of Gastroenterology* **23**, 53-55
- Parent, J. (1982) Effects of dexamethasone on pancreatic tissue and on serum amylase and lipase activities in dogs. *Journal of the American Veterinary Medical Association* **180**, 743-746
- Pastor, C. M. & Frossard, J.-L. (2001) Are genetically modified mice useful for the understanding of acute pancreatitis. *FASEB Journal* **15**, 893-897
- Pearce, C. B., Sadek, S. A., Walters, A. M., et al. (2006) A double-blind, randomised, controlled trial to study the effects of an enteral feed supplemented with glutamine, arginine, and omega-3 fatty acid in predicted acute severe pancreatitis. *Journal of the Pancreas* **7**, 361-371
- Peng, Y.-S., Wu, C.-S., Chen, Y.-C., et al. (2009) Critical illness-related corticosteroid insufficiency in patients with severe acute biliary pancreatitis: a prospective cohort study. *Critical Care* **13**, R123.
- Petrov, M. S. & Zagainov, V. E. (2007) Influence of enteral versus parenteral nutrition on blood glucose control in acute pancreatitis: a systematic review. *Clinical Nutrition* **26**, 514-523
- Petrov, M. S., Correia, M. I. T. D. & Windsor, J. A. (2008) Nasogastric tube feeding in predicted severe acute pancreatitis. A systematic review of the literature to determine safety and tolerance. *Journal of the Pancreas* **9**, 440-448
- Petrov, M. S., Mclroy, K., Grayson, L., et al. (2012) Early nasogastric tube feeding versus nil per os in mild to moderate acute pancreatitis: a randomized controlled trial. *Clinical Nutrition* **32**, 697-703
- Pezzilli, R. (2009) Pharmacotherapy for acute pancreatitis. *Expert Opinion on Pharmacotherapy* **10**, 2999-3014
- Powell, J. J., Murchison, J. T., Fearon, K. C., et al. (2000) Randomized controlled trial of the effect of early enteral nutrition on markers of the inflammatory response in predicted severe acute pancreatitis. *British Journal of Surgery* **87**(10): 1375-1381
- Price, J. & Nolan, A. M. (2007) The physiology and pathophysiology of pain. *BSAVA Manual of Canine and Feline Anaesthesia and Analgesia*. Eds C. Seymour and T. Duke-Novakoski. BSAVA, Quedgeley, UK. 79-88.
- Pupelis, G., Selga, G., Austrums, E., et al. (2001) Jejunal feeding, even when instituted late, improves outcomes in patients with severe pancreatitis and peritonitis. *Nutrition* **17**, 91-94
- Qin, H. L., Su, Z. D., Gao, Q., et al. (2002a) Early intrajejunal nutrition: bacterial translocation and gut barrier function of severe acute pancreatitis in dogs. *Hepatobiliary Pancreatic Diseases International* **1**, 150-154
- Qin, H. L., Su, Z. D., Hu, L.G., et al. (2002b) Effect of early intrajejunal nutrition on pancreatic pathological features and gut barrier function in dogs with acute pancreatitis. *Clinical Nutrition* **21**, 469-473
- Qin, H. L., Su, Z. D., Hu, L. G., et al. (2003) Parenteral versus early intrajejunal nutrition: effect on pancreatic natural course, entero-hormones release and its efficacy on dogs with acute pancreatitis. *World Journal of Gastroenterology* **9**, 2270-2273
- Qin, H. L., Su, Z. D., Hu, L. G., et al. (2007) Effect of parenteral and early intrajejunal nutrition on pancreatic digestive enzyme synthesis, storage and discharge in dog models of acute pancreatitis. *World Journal of Gastroenterology* **13**, 1123-1128
- Queau, Y., Larsen, J. A., Kass, P. H., et al. (2011) Factors associated with adverse outcomes during parenteral nutrition administration in dogs and cats. *Journal of Veterinary Internal Medicine* **25**, 446-452
- Rau, S. E., Barber, L. G. & Burgess, K. E. (2010) Efficacy of maropitant in the prevention of delayed vomiting associated with administration of doxorubicin to dogs. *Journal of Veterinary Internal Medicine* **24**, 1452-1457
- Reuter, J. D., Marks, S.L., Rogers, Q. R., et al. (1998) Use of total parenteral nutrition in dogs: 209 cases (1988-1995). *Journal of Veterinary Emergency and Critical Care* **8**, 201-213
- Rinderknecht, H. (1986) Activation of pancreatic zymogens: normal activation, premature intrapancreatic activation, protective mechanisms against inappropriate activation. *Digestive diseases and Sciences* **31**, 314-321
- Saker, K. E. & Remillard, R. L. (2010) Critical care nutrition and enteral-assisted feeding. In: *Small Animal Clinical Nutrition*. Eds M. S. Hand, M. S. Thatcher and R. L. Remillard. 5th ed. Mark Morris Institute, Topeka, KS, USA. pp 439-476
- Salisbury, S. K., Lantz, G. C., Nelson, R.W., et al. (1988) Pancreatic abscess in dogs: six cases (1978-1986). *Journal of American Veterinary Medical Association* **193**, 1104-1108
- Sarac, T. P., Souba, W. W., Miller, J. H., et al. (1994) Starvation induces differential small bowel luminal amino acid transport. *Surgery* **116**, 679-685
- Sarr, M. G., Sanfey, H. & Cameron, J. L. (1986) Prospective, randomized trial of nasogastric suction in patients with acute pancreatitis. *Surgery* **100**, 500-504
- Schmidt, J., Fernandez-del-Castillo, C., Rattner, D. W., et al. (1993) Hyperoncotic ultrahigh molecular weight dextran solutions reduce trypsinogen activation, prevent acinar necrosis, and lower mortality in rodent pancreatitis. *The American Journal of Surgery* **165**, 40-45

- Schmidt, J., Huch, K., Mithofer, K., *et al.* (1996) Benefits of various dextrans after delayed therapy in necrotizing pancreatitis of the rat. *Intensive Care Medicine* **22**, 1207-1213
- Sedlacek, H. S., Ramsey, D. S., Boucher, J. F., *et al.* (2008) Comparative efficacy of maropitant and selected drugs in preventing emesis induced by centrally or peripherally acting emetogens in dogs. *Journal of Veterinary Pharmacology and Therapeutics* **31**, 533-537
- Smith, S. A. & Biller, D. S. (1998) Resolution of a pancreatic pseudocyst in a dog following percutaneous ultrasonographic-guided drainage. *Journal of the American Animal Hospital Association* **34**, 515-522
- Souba, W. W., Klimberg, V. S., Plumley, D. A., *et al.* (1990) The role of glutamine in maintaining a healthy gut and supporting the metabolic response to injury and infection. *Journal of Surgical Research* **48**, 383-391
- Stevens, T., Conwell, D. L. & Zuccaro, G. (2004) Pathogenesis of chronic pancreatitis: an evidence-based review of past theories and recent developments. *American Journal of Gastroenterology* **99**, 2256-2270
- Stewart, A. F. (1994) Pancreatitis in dogs and cats: cause, pathogenesis, diagnosis, and treatment. *Compendium on Continuing Education for the Practising Veterinarian* **16**, 1423-1430
- Strombeck, D. R. (1990) The exocrine pancreas. In: Small Animal Gastroenterology. D. R. Strombeck and W. G. Guilford. Stonegate Publishing, Davis, CA, USA. p 429
- Sun, W., Watanabe, Y., Toki, A., *et al.* (2007) Beneficial effects of hydrocortisone in induced acute pancreatitis of rats. *Chinese Medical Journal (England)* **120**, 1757-1761
- Thomson, A. (2006) Nutrition therapy in acute pancreatitis. *Journal of Parenteral and Enteral Nutrition* **30**, 536-537; author reply 537-538
- Tolbert, K., Bissett, S., King, A., *et al.* (2011) Efficacy of oral famotidine and 2 omeprazole formulations for the control of intragastric pH in dogs. *Journal of Veterinary Internal Medicine* **25**, 47-54
- Uhl, W., Buchler, M., Malfertheiner, P., *et al.* (1999) A randomised, double blind, multicentre trial of octreotide in moderate to severe acute pancreatitis. *Gut* **45**, 97-104
- VanEnkevort, B. A., O'Brien, R. T., Young, K. M. (1999) Pancreatic pseudocysts in 4 dogs and 2 cats: ultrasonographic and clinicopathologic findings. *Journal of Veterinary Internal Medicine* **13**, 309-313
- Vigneault, L., Turgeon, A. F., Cote, D., *et al.* (2011) Perioperative intravenous lidocaine infusion for postoperative pain control: a meta-analysis of randomized controlled trials. *Canadian Journal of Anesthesia* **58**, 22-37
- Wagner, A. E., Walton, J. A. & Hellyer, P. W., *et al.* (2002) Use of low doses of ketamine administered by constant rate infusion as an adjunct for postoperative analgesia in dogs. *Journal of the American Veterinary Medical Association* **221**, 72-75
- Watson, P. (2004) Pancreatitis in the dog: dealing with a spectrum of disease. *In Practice* **26**, 64-77
- Watson, P. J., Roulois, A. J., Scase, T., *et al.* (2007) Prevalence and breed distribution of chronic pancreatitis at post-mortem examination in first-opinion dogs. *Journal of Small Animal Practice* **48**, 609-618
- Weatherston, L. K. & Streeter, E. M. (2009) Evaluation of fresh frozen plasma administration in dogs with pancreatitis: 77 cases (1995-2005). *Journal of Veterinary Emergency and Critical Care (San Antonio)* **19**, 617-622
- Williams, D. A. (1994) Diagnosis and management of pancreatitis. *Journal of Small Animal Practice* **35**, 445-454
- Windsor, J. A. & Hammodat, H. (2000) Metabolic management of severe acute pancreatitis. *World Journal of Surgery* **24**, 644-672
- Wu, B. U. & Conwell, D. L. (2010a) Acute pancreatitis. Part I: Approach to early management. *Clinical Gastroenterology and Hepatology* **8**, 410-416
- Wu, B. U. & Conwell, D. L. (2010b) Acute pancreatitis. Part II: approach to follow-up. *Clinical Gastroenterology and Hepatology* **8**, 417-422
- Wu, B. U., Hwang, J. Q., Gardner, T. H., *et al.* (2011) Lactated Ringer's solution reduces systemic inflammation compared with saline in patients with acute pancreatitis. *Clinical Gastroenterology and Hepatology* **9**, 710-717, e711.
- Zenilman, M. E., Magnuson, T. H., Swinson, K., *et al.* (1996) Pancreatic thread protein is mitogenic to pancreatic-derived cells in culture. *Gastroenterology* **110**, 1208-1214
- Zhang, L., Zhang, X. & Westlund, K. N. (2004) Restoration of spontaneous exploratory behaviors with an intrathecal NMDA receptor antagonist or a PKC inhibitor in rats with acute pancreatitis. *Pharmacology Biochemistry & Behavior* **77**, 145-153