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 (Booymagoud 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 dextran on crystalloid therapy in AP (Donaldson & Schenck 1979, Knol et al. 1983, Schmidt et al. 1993,

<table>
<thead>
<tr>
<th>Treatment intervention</th>
<th>Treatment recommendations</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous fluid therapy</td>
<td>Lactated Ringers preferable crystalloid</td>
<td>B (humans)</td>
</tr>
<tr>
<td>Anti-emetic therapy</td>
<td>Metoclopramide potentially detrimental</td>
<td>C (dogs)</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Not required unless suspect bacterial translocation</td>
<td>C (dogs)</td>
</tr>
<tr>
<td>Gastric cytoprotection</td>
<td>Nasogastric suctioning contraindicated</td>
<td>A (humans)</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Hydrocortisone could be considered in cases non-responsive to iv fluid resuscitation</td>
<td>B (humans)</td>
</tr>
<tr>
<td>Surgical intervention</td>
<td>No indication for surgical intervention with AP unless infection is documented</td>
<td>A (humans)</td>
</tr>
<tr>
<td>Pancreatic fluid collections</td>
<td>Fluid collections should be aspirated via ultrasound guidance only if associated with pain</td>
<td>A (humans)</td>
</tr>
<tr>
<td>Post-recovery treatment</td>
<td>Exocrine pancreatic supplementation and a low-fat diet should be given for 4 weeks</td>
<td>C (dogs)</td>
</tr>
</tbody>
</table>

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.
Treatment of acute pancreatitis

Antihometics

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 (Benchoumi 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).

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 pathway of pain 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, ʌ, 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%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

<table>
<thead>
<tr>
<th>Factors that may affect pain assessment</th>
<th>Key points to facilitate pain assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altered environment (e.g. in hospital, the presence or not of the owner; the presence of other animal of the same species or not)</td>
<td>Good knowledge of species-specific behaviour</td>
</tr>
<tr>
<td>Species differences (e.g. “Normal” comportment for given species, varied reaction to pain between species)</td>
<td>Knowledge and comparison of the behaviour before with after the trauma or illness</td>
</tr>
<tr>
<td>Within-species variation (e.g. Individual dogs react differently [Labrador versus Greyhound])</td>
<td>Response to analgesic treatment is the best marker for accurate diagnosis of pain</td>
</tr>
<tr>
<td>Drugs might alter behaviour (e.g. sedative agents do not always provide analgesia although case appears comfortable; analgesic drugs might provide sedation)</td>
<td>Behaviour is easily altered by age, illness or drugs</td>
</tr>
</tbody>
</table>

Assess interaction with owner or handler

Assess response to abdominal palpation or manipulation

The assessor must be experienced in pain assessment

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, α₂-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 α₂-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 (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 respiratory 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, adjutively 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

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**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**

<table>
<thead>
<tr>
<th>Anticipated levels of pain associated with acute pancreatitis</th>
<th>Potential analgesic combination</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Quiet but responsive to surroundings; unsettled; looks around when abdomen is palpated</td>
<td>Buprenorphine or methadone (or other full µ-agonist) at high-end of dosage and frequency, reducing down once pain well controlled</td>
</tr>
<tr>
<td>Moderate</td>
<td>Decreased response to surroundings or stimuli; slow or reluctant to move; restless; stretching of abdomen, looking around at abdomen; flinches on abdominal palpation</td>
<td>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 µg/kg/minute then stop, then reduce lidocaine until 25 µg/kg/minute then stop, then reduce dosage and frequency of opioid.</td>
</tr>
<tr>
<td>Severe to excruciating</td>
<td>Non-responsive to stimuli; refuses to move or get up; screams, cries or snaps when tries to get up or abdomen palpated</td>
<td>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 µg/kg/minute, stop and then reduce lidocaine until 25 µg/kg/minute, then stop, and then reduce dosage and frequency of opioid.</td>
</tr>
</tbody>
</table>

**Unanticipated exacerbation of pain**

<table>
<thead>
<tr>
<th>Adjunctive management</th>
<th>Added with any level of pain</th>
<th>Added if opioids associated with decreased gastrointestinal motility</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Assess for pancreatic fluid collection and aspirate via ultrasound guidance</td>
<td>Gabapentin, Methylxanthine</td>
</tr>
</tbody>
</table>

LOE Level of evidence
The LOE is determined as described in Table 1.
study of dogs undergoing forelimb amputation showed no side effects when ketamine was used intra-operatively at 10 µg/kg/minute followed with ketamine postoperatively at a 2 µg/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 α2δ 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 (Niederau et al. 1990). Additionally, the gastrointestinal tract itself is now thought to be a major contributor to the systemic inflammatory state dur-
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 & Zagajnov 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). Another recent study showed that complications of peripheral and centrally administered parenteral nutrition bore no relationship with the outcome (Queue 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, tributyron 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 (Soubra 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).

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

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

*AP: Acute pancreatitis, MCT: Medium-chain triglyceride*
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, intervention 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 × BW (kg) + 70 kcal/day; and if less than 2 kg or greater than 25 kg then 70 × BW0.75. 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.

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

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

*This composition is typical of most human liquid convalescent diets, and therefore, it 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

### 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, debride the sterile fluid collection.
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 splanchic 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 as they are generally useful at ameliorating only one aspect of specific anti-cytokine therapies appear to be highly variable, 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 steatorrhoea 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 & Ammoni 2003). Subclinical exocrine pancreatic insufficiency has been diagnosed in dogs and is not always manifested by overt steatorrhoea (Wiber & 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**


