

# Nutritional management of acute pancreatitis in dogs and cats

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## Abstract

**Objective** – To review current and emerging nutritional approaches in the management of acute pancreatitis (AP) in people, dogs, and cats, and to provide a framework for further investigation in this field.

**Data sources** – Veterinary retrospective studies and reviews, human prospective clinical trials and reviews, and experimental animal studies focusing on nutritional management during AP.

**Summary** – Nutritional management is an important part of the treatment plan for patients with AP. In human medicine, the general approach for providing nutrition in patients with AP has changed in recent years and favors enteral over parenteral nutrition with an emphasis on early enteral nutrition (EN). Although there are limited data available, there is increasing evidence in the veterinary literature that supports the beneficial role of EN in AP and contradicts previous assumptions about poor tolerance to enteral feeding in this patient population. Parenteral nutrition may be appropriate alone or in combination with EN as a temporary measure in malnourished patients that do not tolerate adequate EN; however, enteral feeding should be attempted first in most cases. Immunonutrition is being investigated for its positive role in modulating pancreatic inflammation and improving gut barrier function in cases of human AP.

**Conclusions** – The nutritional management of veterinary patients with AP remains challenging. Based on clinical evidence in people, experimental animal studies, and preliminary studies in dogs and cats, the choice of EN over parenteral nutritional support during AP in dogs and cats appears to be beneficial and well tolerated. Optimization of nutritional therapies in dogs and cats including the use of immunonutrition during AP warrants further investigation.

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## Introduction

Acute pancreatitis (AP) is a common illness in dogs and cats. Although most cases are mild and self-limiting, some cases develop systemic complications that can result in death. Mortality rates of dogs with severe AP have been reported to range from 27 to 42%.<sup>1</sup> In one report, acute pancreatic necrosis was present in 67 of 70 dogs (96%) with fatal AP.<sup>2</sup> Establishing a diagnosis of AP is

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## Abbreviations

AP	acute pancreatitis
cPLI	canine pancreatic lipase immunoreactivity
CRP	C-reactive protein
CT	computed tomography
EN	enteral nutrition
FIP	feline infectious peritonitis
IBD	inflammatory bowel disease
ICGC	International Consensus Guideline Committee
NG	nasogastric
PN	parenteral nutrition
RER	resting energy requirement
TLI	trypsin-like immunoreactivity

difficult, especially in cats, and successful management may depend on a number of factors. Experimental and clinical data strongly support the theory that nutritional management plays an important therapeutic role in both

veterinary and human patients suffering from AP.<sup>3-6</sup> The optimal nutritional management of AP in dogs and cats, however, remains unclear and warrants further research. The aims of this review are to critically evaluate current and emerging nutritional approaches in the management of AP in people, dogs, and cats, and to highlight important clinical implications for managing these cases. An assessment of future developments and research into AP will also be discussed.

### **Etiology and Pathophysiology**

The underlying pathophysiology of AP is incompletely understood, but is thought to center on autophagy, which is the basic catabolic mechanism for degradation and recycling of cellular organelles and proteins by lysosomes.<sup>7</sup> Autophagy is impaired in pancreatitis due to inefficient lysosomal function.<sup>7,8</sup> Impaired autophagy leads to the accumulation of vacuoles in acinar cells and to abnormal intra-acinar activation of digestive enzymes (eg, trypsinogen), representing two key events in the pathophysiology of pancreatitis.<sup>8,9</sup> In dogs, several findings have been implicated as predisposing factors of AP including hyperlipidemia, dietary indiscretion, being overweight, hypercalcemia, ischemia, endocrinopathies, and various drugs (eg, L-asparaginase, potassium bromide, phenobarbital, and organophosphates).<sup>1,10-12</sup> Moreover, certain breeds of dogs are considered to be predisposed to developing pancreatitis, including Miniature Schnauzers, terriers, and miniature Poodles.<sup>1</sup> The majority of cases of AP in cats are thought to be idiopathic in nature, although, as in dogs, pancreatic ischemia, trauma, and organophosphate toxicity have been implicated as risk factors.<sup>13-15</sup> Infectious agents including feline parvovirus, *Toxoplasma gondii*, feline herpes virus, and feline infectious peritonitis (FIP) have also been linked with pancreatitis in cats.<sup>13,14</sup> The association between hepatic lipidosis or cholangitis and pancreatitis has been well documented, and a possible association among feline inflammatory bowel disease (IBD), cholangitis, and pancreatitis, referred to as "triaditis," has been considered.<sup>15-17</sup>

### **Diagnosis of Acute Pancreatitis in Dogs and Cats**

#### **Clinical signs**

A tentative diagnosis of AP can be made on the basis of a compatible history and physical examination findings, although clinical signs can be nonspecific and common to a variety of intra-abdominal disease states. In dogs, vomiting and signs of abdominal pain are the main clinical signs associated with AP.<sup>2</sup> If secondary posthepatic bile duct obstruction is present, jaundice may be present.

Cats frequently have more subtle and nonspecific clinical signs such as lethargy and anorexia.<sup>15</sup> In cats, clinical signs associated with intestinal disease (eg, IBD) or liver disease (eg, hepatic lipidosis or cholangitis) may also be reasons for presentation to veterinarians.

### **Clinicopathological Findings**

Hematologic and biochemical abnormalities are nonspecific and can include anemia, leukocytosis or leukopenia, changes consistent with cholestasis (eg, increased liver enzyme activities, hyperbilirubinemia, hypercholesterolemia), prerenal azotemia, and hypoalbuminemia. The most common electrolyte abnormalities are hypokalemia and hypocalcemia.<sup>2</sup> Serum lipase activity had previously been used for the diagnosis of pancreatitis in dogs, but is no longer recommended because of a lack of sensitivity and specificity (lipase can be derived from several other tissues, and does not necessarily reflect pancreatic disease).<sup>18-20</sup>

Canine and feline pancreatic lipase immunoreactivity (cPLI and fPLI, respectively) are enzyme-linked immunoassays developed to measure species specific pancreatic lipase activity. These assays are the most reliable serum markers for AP, and reported sensitivities and specificities for both assays are greater than 80%, but both are affected by the severity of disease, with the accuracy of test improving in patients with moderate to severe pancreatitis.<sup>21-23</sup> As no gold standard test is available for comparison, the presence of histopathologic pancreatic lesions consistent with pancreatitis have been used to assess the diagnostic accuracy of these assays. This approach may be misleading and results can be biased by case selection. In a large multicenter veterinary study the diagnostic utility of two different cPLI assays were assessed and correlated to a clinical diagnosis of pancreatitis made by an expert panel blinded to the results of the cPLI assays.<sup>24</sup> Reported sensitivities and specificities were high, but the assays were less specific when the lower cut-off value (200 µg/L) was used for a positive diagnosis.<sup>24</sup>

Abdominal ultrasonography is currently the most widely used imaging modality for diagnosing AP in dogs and cats.<sup>25</sup> The characteristic changes seen with AP include an enlarged hypoechoic pancreas, which reflects the presence of edema, hemorrhage, and necrosis of the organ.<sup>25,26</sup> In addition, abdominal ultrasonography can identify focal abnormalities such as pancreatic pseudocysts and abscesses, dilation of the pancreatic or biliary ducts, changes to peritoneum suggestive of peritonitis, and the presence of peritoneal fluid.<sup>27-29</sup> Unfortunately, the sensitivity of ultrasonography when used alone to diagnose AP is generally low, with sensitivities ranging from 11 to 67% in cats and 68% in dogs.<sup>4,21</sup> In people, the

sensitivity of computed tomography (CT) is high (75–90%), but to date CT has not been proven to be superior to abdominal ultrasound for the diagnosis of AP in dogs or cats.<sup>22,30</sup> Further research is warranted to ascertain the optimal modalities to diagnose AP in dogs and cats.

### Therapy

Therapy for pancreatitis is largely supportive, and the mainstays of therapy include analgesia, correction of electrolyte and acid–base imbalances, and maintenance of adequate tissue perfusion and oxygen delivery. The traditional approach to AP centered on the premise that withholding food would reduce pancreatic auto-digestion by decreasing pancreatic stimulation and enzyme release.<sup>10,31</sup> However, the pathogenesis of pancreatitis more likely involves premature intracellular activation of proteolytic enzymes rather than pancreatic stimulation. Avoidance of feeding as a means to decrease pancreatic stimulation may be unwarranted and could lead to malnutrition and impaired gastrointestinal barrier function.<sup>32–35</sup> Lack of enteral nutrition results in the loss of normal physiologic intestinal motility, is associated with intestinal villus atrophy, and compromises intestinal mucosal blood flow.<sup>32–37</sup> If sustained, the lack of enteral nutrition could lead to a compromise of local immunoglobulin and biliary salt production with consequent disruption of normal internal bacterial flora and gastrointestinal barrier function.<sup>32–37</sup> It also has been demonstrated in experimental rodent models and in people with naturally occurring disease that exocrine pancreatic secretion actually decreases during pancreatitis and that the decrease is more pronounced with increasing severity of inflammation.<sup>33,35</sup> The practice of withholding food for several days from the time of initiation of therapy may prove detrimental as a period of anorexia often precedes the initial clinical presentation to veterinarians in patients with AP. Implementation of nutritional support may be critical for successful management of patients with AP (Figure 1).

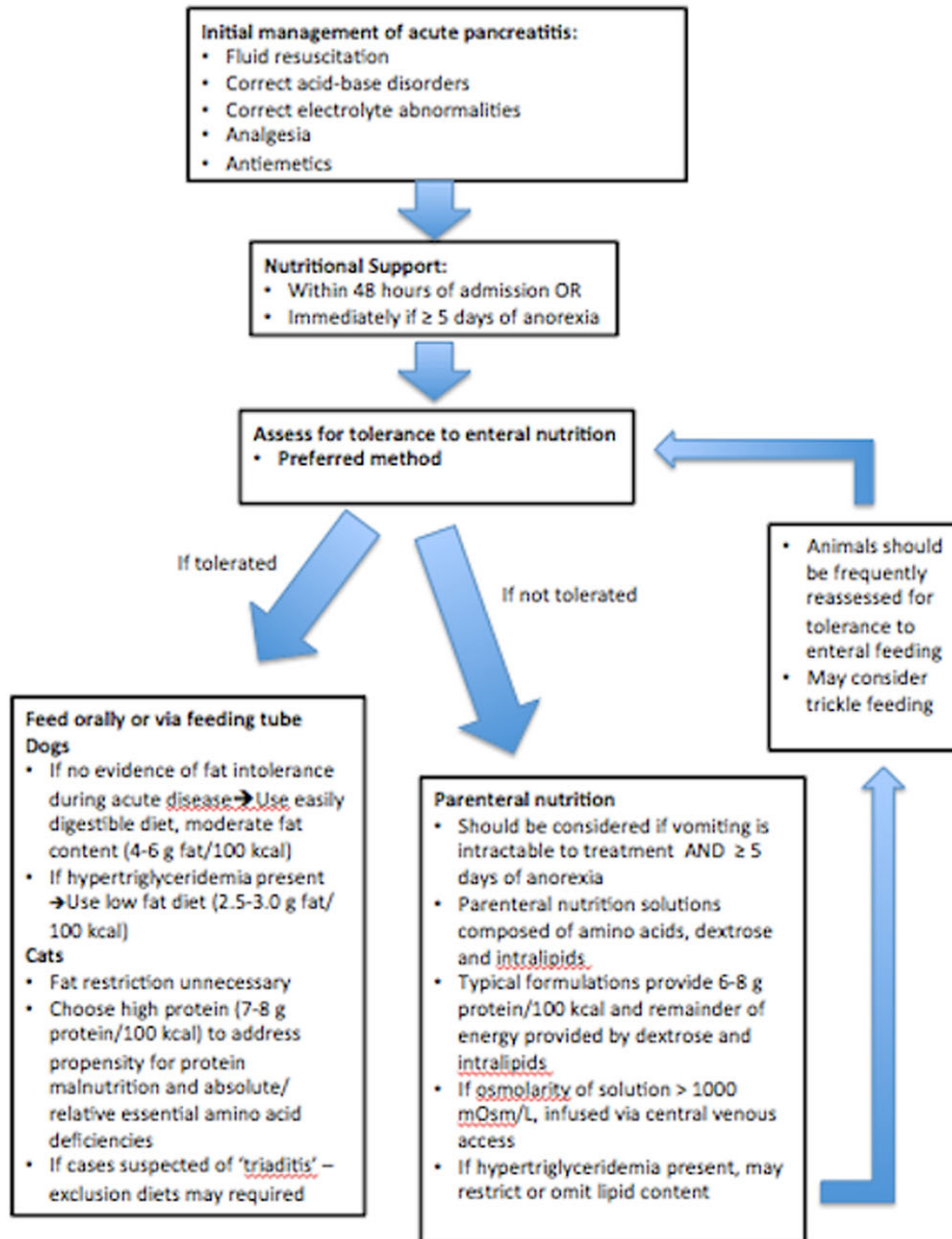
### Enteral nutrition in people with AP

Nutritional support during AP plays a central role in the management of AP in people. Parenteral nutrition (PN) had been the standard therapy for many years based on the theory that enteral nutrition (EN) stimulated pancreatic secretion, potentially exacerbating the inflammatory response and delaying recovery.<sup>32,34,36–38</sup> However, recent data suggest that EN in people is not only well tolerated, but safer and associated with fewer complications than with PN and is even associated with improved survival in some studies.<sup>6,39,40</sup> In recent years EN has become the new gold standard of nutritional therapy in managing AP in people.<sup>6,39–42</sup>

Several studies have shown that EN can be safely administered via nasojejunal feeding tubes and that intrajejunal feeding has no stimulatory effects on pancreatic secretion.<sup>6,40,43</sup> Data from experimental animal models suggest that enteral feeding has the advantage of preventing mucosal atrophy and thereby perhaps reducing the risk of bacterial translocation and septic complications.<sup>5,44</sup> Additional proposed advantages include improved immune function and a more rapid reduction of concentrations of C-reactive protein (CRP) and other acute phase reactants and markers of inflammation.<sup>45</sup>

Human meta-analyses support the fact that the use of EN in comparison to PN is associated with significant reductions in duration of hospital stay, infectious morbidity, and total cost of therapy. Some studies have shown a significantly reduced mortality in patients receiving EN in comparison to PN.<sup>46–48</sup> However, enrollment of small patient groups have precluded assessment of mortality in some studies, and larger randomized controlled clinical trials are required to support the conclusions. Despite the fact that studies to date are heterogeneous with respect to inclusion criteria, feeding regimes and other supportive treatment provided, the beneficial effects of EN are retained. The International Consensus Guideline Committee (ICGC) has recently developed a clinical consensus guideline for nutritional management of pancreatitis in people based on existing clinical guidelines graded according to the level of evidence. Of particular importance is the agreement that there should be a preference of EN over PN and that the use of PN should be reserved in situations when EN is contraindicated or not well tolerated, and both of these recommendations are supported by the highest level of evidence.<sup>49</sup>

Most human studies have assessed nasojejunal feeding only and the evidence supporting nasogastric (NG) feeding is currently limited.<sup>34,36,50–52</sup> In veterinary medicine, the main disadvantage of nasojejunal feeding tubes is the need for endoscopic or fluoroscopic assistance for tube placement and the risk of tube dislodgement following placement.<sup>53–55</sup> In comparison, placement of NG feeding tubes is simple and is a more feasible option in clinical practice. Several randomized controlled trials comparing NG feeding to nasojejunal feeding in human patients with AP did not show any significant difference in mortality rate, duration of hospital stay or infectious complications rates.<sup>50,51,56</sup> These results suggest that postpyloric feeding is not necessary and that nasogastric feeding is equally tolerated. The ICGC's guidelines on nutrition therapy for AP, state that postpyloric feeding is not required and support the use of NG feeding, although consensus agreement was not reached.<sup>49</sup>



**Figure 1:** Nutritional management algorithm for dogs and cats with acute pancreatitis.

### Enteral nutrition in dogs and cats with AP

In veterinary medicine, the premise that the gut plays an important role during critical illness and that EN is preferable to PN whenever possible is well established.<sup>3,25,57–60</sup> Although studies prospectively evaluating tolerance of enteral feeding in dogs and cats with AP are limited, there is growing evidence supporting the benefits of EN in dogs and cats with AP.

Dogs with experimentally induced AP have compared the effects of early intrajejunal feeding to PN, and demonstrated no difference in serum concentrations

of amylase and lysosomal enzyme activities.<sup>61</sup> In addition, circulating plasma endotoxin activity and bacterial translocation was reduced significantly in the intrajejunal fed group versus the PN group.<sup>4,5</sup> The intrajejunal fed group also displayed improved gut barrier health when assessed histopathologically (evaluating enteral villus height, thickness of mucosa, and bowel wall in the ileum and transverse colon). Additional studies by the same group of investigators assessed pancreatic activation in response to a number of enterohormones. They found that increased concentrations of cholecystokinin,

secretin, and gastrin did not induce increased release of pancreatic enzymes, which previously have been assumed to be the reason for induction of pancreatic autodigestion in AP.<sup>61</sup>

A recent small pilot study that evaluated the tolerability of prepyloric EN in dogs with AP showed promising results, with no exacerbation of signs of pain or vomiting in the enterally fed group when compared to the parenterally fed group.<sup>3</sup> The frequency of vomiting or regurgitation episodes was higher in the group of dogs receiving PN, and it was hypothesized that EN may improve gut health and thereby reduce ileus and vomiting. No exacerbation of signs of abdominal pain was found in the enterally fed group. However, because of the study's very small sample size (5 dogs in each group) further studies are warranted to confirm these findings.

Nasogastric tube feeding has been assessed retrospectively in 55 cats with AP.<sup>62</sup> Administration of bolus or continuous rate infusion feedings were compared, in addition to whether or not the cats had received an intravenous amino acid-dextrose solution. NG feeding was well-tolerated and there were no significant differences between groups or before and after feeding within the same group with respect to the clinical variables assessed (including frequency of vomiting, incidence of diarrhea, and hypersalivation). Complications were considered mild and the overall rate of complications was considered low. Based on the broad evidence in human studies and the preliminary results of experimental and clinical studies in animals, EN, when possible, is considered superior to PN for managing patients with AP.

In addition to providing adequate EN, adjunctive multimodality antiemetic therapy should be administered to improve tolerance to enteral feeding. Chemoreceptor trigger zone D2-dopamine receptors are less important in mediating humoral emesis in the cat, and D2-dopamine receptor antagonists (eg, metoclopramide) may be less effective when compared to other antiemetics in this species.<sup>63</sup> Despite these facts, and in light of the limited number of prokinetic drugs available, metoclopramide may still play an important role in the management of ileus, which is a commonly encountered complication of AP.<sup>2,28</sup> Central antiemetic drugs such as NK1-antagonists (eg, maropitant) are widely used in dogs with AP. In view of the potential role of substance P in the pain, vascular permeability, and systemic inflammation associated with AP, use of NK1-receptor antagonists as antiemetic drugs may also provide analgesia for patients with AP.<sup>9</sup>

### Feeding tubes and routes

Recognizing the importance of EN in the management of patients with AP, and the fact that voluntary intake is often insufficient to meet daily caloric intake goals, more

effective methods of nutritional support are required. Feeding tubes provide an efficient means of facilitating nutritional support and several options are available. A brief overview of their use in the management of AP in dogs and cats are discussed below.

Nasoesophageal or NG feeding tubes are easily placed with a local anesthetic and do not require general anesthesia. They are therefore an appropriate choice for short-term nutritional support of the severely debilitated patient, where a general anesthetic is contraindicated. The major disadvantage is their small diameter which increases the risk of clogging and limits the type of diet that can be used to liquid enteral diets. Currently available liquid veterinary diets have a high fat content (eg, 45% of total caloric content<sup>4</sup>) to increase caloric density, which may not be ideal for dogs with hyperlipidemia-associated pancreatitis. Although liquid diets with lower fat contents are available for people, they are not complete with respect to amino acid composition and are therefore inappropriate for use in veterinary patients, especially cats, unless they are supplemented with various amino acids (eg, arginine).

Nasoesophageal tubes have been advocated by some authors over NG tubes because of concerns about increased risk of regurgitation and gastroesophageal reflux caused by the presence of the tube across the lower esophageal sphincter. However, a recent study comparing the complication rates of nasoesophageal versus NG feeding tubes did not find a significant difference in complication rates between the 2 methods in dogs, and so the choice of feeding tube may not be as important as once thought.<sup>64</sup> Radiographic confirmation of nasoesophageal tube placement is recommended prior to feeding to assess for incorrect placement (ie, intratracheal positioning). An alternative method to rule out intratracheal placement is to measure end-tidal CO<sub>2</sub> (via a side-stream capnograph) produced from the tube; a properly placed tube should not generate any end-tidal CO<sub>2</sub>, whereas a tracheally placed tube will show changes in end-tidal CO<sub>2</sub> with respiration.<sup>65</sup>

Esophagostomy tubes require a short general anesthetic for placement, but are an excellent option for cats and dogs of most sizes and have the advantage that a liquidized complete diet can be fed, which permits individualized diet selection (eg, low fat content). Feeding of a commercial low-fat diet via esophagostomy tube was well-tolerated in dogs with AP in one pilot study.<sup>3</sup> Potential complications include hemorrhage, which is rare but can be life-threatening if major vessels are involved, tube migration, and vomiting with resultant displacement of the aboral end of the tube.

Gastrostomy tubes may be placed surgically or endoscopically (ie, percutaneous endoscopically guided gastrostomy or PEG tube). If the patient is managed

surgically (eg, correction of biliary obstruction, biopsied), a gastrostomy tube can be placed during surgery. However, if this is not the case, less invasive methods are recommended. The advantages of these large diameter tubes include the ability to use blenderized complete diets and long-term management (eg, months), if required. Potential complications include peristomal food leakage and abscess formation, aggravation of nausea and vomiting, premature tube removal and rarely, septic peritonitis.<sup>66,67</sup>

Jejunal feeding bypasses the upper gastrointestinal tract, which may be the last resort in cases with intractable vomiting. Their use has been well described in dogs, including in cases of canine AP.<sup>68–70</sup> Given that traditional jejunostomy feeding tube placement is only indicated in patients who require surgical laparotomy, which is likely to be a more severely affected population, it precludes comparisons with medically managed AP with respect to outcome. Two retrospective veterinary studies described the application of jejunostomy tubes in dogs and cats with AP undergoing surgical management for pancreatitis.<sup>71,72</sup> In one study, 30 of 37 dogs (81%) had a jejunostomy tube placed and 1 of 11 (9%) of the reported major complications was directly related to the tube.<sup>71</sup> The risk of dislodgement and peritonitis is theoretically higher with jejunostomy tubes in comparison to gastrostomy tubes, although severe complications associated with breakdown of the surgical site were reported in a very low number of patients (3/47 [6%]) in 2 veterinary studies.<sup>69,70</sup>

Minimally invasive techniques for placement of nasojejunal tubes using fluoroscopy or endoscopy in dogs have been described but have not yet been widely adopted.<sup>53,54</sup> Feeding tubes were successfully placed in the jejunum in 74–78% of cases, and one study documented an increasing success rate (100%) as technical proficiency improved over time.<sup>54</sup> The major complication was oral tube migration (3 of 11 patients [27%]). Acute pancreatitis was the primary diagnosis of dogs undergoing fluoroscopic wire-guided placement of nasojejunal tubes in one study.<sup>54</sup> Slow constant rate infusion of a liquid diet (“trickle feeding”) is recommended and jejunostomy tubes are therefore only suitable for hospitalized patients.

### Parenteral nutrition

In patients with severe AP and intractable vomiting who do not tolerate EN, PN is a valuable treatment modality to prevent malnutrition. Although compounding PN solutions requires specialized expertise and is limited to referral centers, ready-made amino acid and glucose solutions for PN can be used in general practice as interim solutions until the animal can tolerate either place-

ment of a feeding tube or is voluntarily eating.<sup>73</sup> The use of PN in experimental animal models has been associated with a high risk of infection and gut atrophy, with subsequent risk of bacterial translocation and sepsis.<sup>74</sup> However, there are no studies on PN in dogs or cats that indicate a high risk for infection or sepsis and the single veterinary study that specifically evaluated PN nutritional support in dogs with AP did not identify any septic complications.<sup>38</sup> Although not exclusively evaluating patients with pancreatitis, one study documented that dogs and cats receiving supplemental EN in addition to PN survived more often than animals who received PN alone.<sup>57</sup> It is possible that this could represent a true benefit of EN or to be a reflection of decreased illness severity in the group that tolerated some EN. Although most patients receiving PN did not tolerate EN initially, many may tolerate provision of enteral “trickle feeding” and gradual weaning onto EN, which may help to maintain intestinal integrity and function. In addition, early (<24 h from presentation) enteral feeding has been associated with earlier return of gastrointestinal motility and cessation of vomiting. As the goal of trickle feeding is to test whether patients can tolerate enteral feedings rather than meet daily energy requirements, the precise amounts of energy provided that confer this benefit have not been evaluated. The practice of trickle feeding, although potentially beneficial, remains nonstandardized, empirical, and anecdotal.

Selection or formulation of an appropriate nutritional solution is critical when using PN and it necessitates consideration of the patient’s caloric requirements and comorbidities. Commercially available PN solutions for people are not designed to meet the needs of animals and may not provide adequate nutritional support.<sup>75</sup> Although a great proportion of energy in 3-in-1 PN solutions is derived from fat, there is currently no evidence to suggest that the lipid content in PN solutions is detrimental in the management of canine or feline pancreatitis. High lipid formulations appear to be well-tolerated in nonhyperlipidemic acute pancreatitis.<sup>75</sup> The optimal parenteral solution for dogs with pancreatitis and hypertriglyceridemia is not known.

The most frequently cited complications of PN include metabolic disturbances such as hyperglycemia, hyperlipidemia, azotemia, and hypophosphatemia, and mechanical issues related to technical aspects of PN administration.<sup>57,76</sup> Administering the same PN solution centrally or peripherally did not result in different rates of metabolic, mechanical or septic complications in one study.<sup>57</sup> Most metabolic complications associated with PN administration are described as mild and transient and adjustment of the rate of the infusion appears to be sufficient to correct the complications in most cases.

Hyperglycemia has been a topic of interest in human and veterinary critical care patients in recent years, and development of hyperglycemia during PN administration has been associated with higher risks of mortality in some, but not all, studies.<sup>57,73,76–79</sup> It is possible that the differences in the impact of hyperglycemia on patient outcome may have been confounded by the nonstandardized manner by which hyperglycemia was managed in these studies (eg, varying protocols used for initiating insulin therapy), differences in the PN dextrose content, differences in the definition of hyperglycemia used in each study, and differences in how the presence of hyperglycemia was statistically related to outcome. It is also possible that hyperglycemia may serve as a surrogate marker of disease severity and that the relationship to outcome may be independent of PN administration. Nevertheless, as there are no known advantages for hyperglycemia, it may be prudent to devise protocols to address the development of hyperglycemia including reduction of the PN administration rate, reduction of the dextrose content in PN solution and administration of insulin to reduce blood glucose.<sup>60</sup> Intensive insulin therapy in hyperglycemic human patients receiving PN has been associated with a reduction in morbidity,<sup>77</sup> however, this approach has not been applied to veterinary patients.

In view of the potential for metabolic complications, monitoring of clinical vital parameters, body weight, serum biochemical parameters, and catheter site for evidence of complications should be performed regularly during administration of PN.<sup>57,75</sup> PN can be a beneficial mode of therapy, either alone or in conjunction with EN, for carefully selected patients, such as those in whom protracted vomiting precludes sufficient enteral caloric intake.

In people with AP, the current consensus is that EN should be initiated as early as possible (ideally within the first 48 h of diagnosis) usually via a nasojejunal or a nasogastric feeding tube.<sup>32,42</sup> The time for initiation of PN is controversial in light of recent findings that initiation of PN in critically ill human patients within the first 7 days of ICU hospitalization could be harmful.<sup>80</sup> The effect of time to PN initiation or combination of PN with EN in veterinary patients has not been assessed, but the use of PN to complement EN may be useful in some cases.<sup>57</sup>

### Dietary considerations

When implementing enteral feeding, an appropriate diet should be selected. Although, there is a paucity of veterinary studies evaluating the influence of diet type on disease course, a highly digestible diet designed for patients with gastrointestinal disease is generally recommended. Avoidance of a diet high in fat has been the

general recommendation for years, although in naturally occurring disease, the link between a high dietary fat content and pancreatitis is not clear. An investigation on the influence of dietary fat content on pancreatic function in normal dogs did not result in significant differences in pancreatic response assessed by quantification of trypsin-like immunoreactivity (TLI) and cPLI. However, these findings may not be applicable to dogs with pancreatitis.<sup>81</sup> The presence of hypertriglyceridemia in certain dog breeds has been shown to act as a predisposing factor and fat-restricted diets (<15% fat on dry matter basis) will, therefore, serve a benefit in management of pancreatitis in these cases.<sup>82,83</sup> Although fat restriction is considered an important component of the management of chronic pancreatitis in dogs, the role of diet in nonhypertriglyceridemic acute pancreatitis is not well understood. Obesity is a risk factor for pancreatitis in dogs and considered a negative prognostic factor in people with AP.<sup>84,85</sup>

Cats have specialized dietary requirements that differ considerably from dogs with respect to dietary fat and protein requirements. Cats are also more prone to carbohydrate intolerance.<sup>86</sup> Cats have a higher dietary fat requirement and appear to have a high tolerance for dietary fat.<sup>87</sup> The high dietary protein requirement makes cats more susceptible to protein-energy malnutrition and lean muscle loss during stressed starvation. In addition, decreased dietary arginine and methionine may limit the synthesis of liver lipoproteins and phospholipids, possibly contributing to the development of hepatic lipidosis.<sup>87</sup> Cats also have the ability to digest and use high levels of dietary fat and there is no current evidence supporting fat restriction in the diet of cats with AP. In a retrospective study evaluating NG tube feeding in cats with AP, feeding of a liquid enteral high-lipid diet (45% of total calories fed) was well tolerated.<sup>62</sup> The recommendations for using low-fat diets (ie, <25% fat on dry matter basis or <3 g fat/100 kcal) does not therefore apply to cats, although a highly digestible fat-restricted diet with a novel or hydrolyzed protein source may be of benefit if concurrent IBD is present.

### Energy requirements

The resting energy requirement (RER), also referred to as resting energy expenditure, “represents the energy requirement of a normal but fed animal at rest in a thermoneutral environment.”<sup>88</sup> Although the precise amount of energy expenditure of animals with various diseases is unknown, the current convention is to use RER, as calculated by the Kleiber equation ( $RER = [\text{body weight in kg}]^{0.75} \times 70$ ) as the initial starting point for initiating nutritional support in hospitalized animals.<sup>59,60,89</sup> If patients have been anorexic for more than 3–5 days,

it is recommended to feed only one third of the RER on day 1, and then gradually increase calories if tolerated, and reach full RER usually by day 3.<sup>38,59</sup> This is to ensure tolerability to the volume fed and decrease risk of metabolic complications, for example, vomiting, regurgitation, signs of abdominal pain, hyperglycemia, hypertriglyceridemia, and hypophosphatemia.

Traditionally, illness factors had been applied to the RER of critically ill patients to address a presumed marked increases in energy expenditure. The validity of multiplying RER by an illness factor has been questioned, as it has been shown that during states of illness or injury, an increase in total energy expenditure is not necessarily encountered and the body may transition to a state of insulin resistance.<sup>90,91</sup> In this state, excessive nutritional supplementation can exacerbate hyperglycemia and other metabolic complications. Given that the consequences of overfeeding may be detrimental to the patient, the current consensus in human and veterinary medicine is to provide the RER to patients with critical illness including AP, and to only increase calories fed based on positive clinical response (eg, tolerance to feeding).<sup>58,92,93</sup>

### Emerging role of immunonutrition

In human medicine, there is increasing evidence that certain nutrients such as glutamine, arginine, and fatty acids play an important role in modulating metabolic, inflammatory, and immune processes in AP. The use of these specific nutrients in the care of critically ill human patients, including those with AP, is becoming commonplace, with increasing evidence of their benefits and low risk of complications.<sup>94,95</sup>

Glutamine is the most abundant amino acid in the plasma and is essential for a wide variety of physiologic processes. The pancreas has high protein turnover, and glutamine supplementation in animals has prevented atrophy of pancreatic acinar cells, improved pancreatic exocrine function, and improved outcomes following critical illness.<sup>96–98</sup> Human patients with AP treated with glutamine-enriched PN solutions demonstrated significant decreases in CRP concentrations as well as decreased dependence on PN, reduced infectious complications, and reduced duration of hospitalization.<sup>95</sup> Formulation of glutamine-supplemented PN is complicated by the fact that glutamine is unstable in solution and generally has to be provided as a di-peptide to maintain stability.<sup>99</sup> Glutamine is currently not supplemented routinely in PN formulations in veterinary medicine.

Arginine is an essential amino acid in cats and dogs, although cats develop clinical signs of deficiency more rapidly than dogs. Arginine is an intermediary in the urea cycle, and its absence leads

to hyperammonemia and development of hepatic encephalopathy.<sup>100</sup> Arginine also has immunomodulatory functions, affecting lymphocyte proliferation and macrophage activation.<sup>101,102</sup> Arginine levels are reduced in people and dogs with critical illness, and subnormal concentrations have been negatively related to survival.<sup>102,103</sup>

Meta-analyses of the use of immune-enhancing diets in critically ill people have shown a reduction of hospital stay and infection rate, but no effect on mortality rate.<sup>95</sup> Most recently, a large prospective multicenter placebo-controlled trial unexpectedly demonstrated a statistical trend for higher mortality risk in critically ill patients treated with glutamine and antioxidants administered enterally and parenterally.<sup>104</sup> This finding, especially given the high quality of the study design in this latest trial, raises questions over the appropriateness of this approach in this patient population. The exact causal relationship for these findings were not determined; however, there are substantial differences between this trial and previous trials. One major difference was the dose and mode of glutamine administration. This trial used the highest dose of glutamine to date (over 30 g glutamine more than previous studies), glutamine was administered both enterally and parenterally, and—perhaps most notably—it targeted critically ill patients in shock, which differs from all previous studies. This last distinction may be important, as initiation of nutritional support prior to cardiovascular stability is not recommended.<sup>105,106</sup> Given these confounding factors, further investigations into potential benefits and harmful effects of nutritional supplements in both human and veterinary medicine are warranted. It is unknown if these latest results preclude use of glutamine in patients with AP without shock.

The use of probiotics has also been suggested as a means of immune modulation and to reduce infectious complications in people with AP.<sup>108,109</sup> Unfortunately, the major trial in human patients performed to date (PROPATRIA) failed to show any improvement in any of the primary endpoints of the study including the development of infected pancreatic necrosis, bacteremia, pneumonia, and actually demonstrated an increase in mortality in patients treated with probiotics compared with controls (16% vs. 6%).<sup>108</sup> Results of trials that used rodent models of AP to justify the evaluation of probiotics in people with AP have since been criticized and therefore, there is little evidence supporting the use of probiotics in the management of AP.<sup>109</sup> Current guidelines for management of AP in people do not recommend the use of probiotics.<sup>106</sup> Although the use of probiotics has not been evaluated in dogs or cats, there is little rationale for supporting their use or for further evaluation in veterinary patients with AP.



## Summary and Recommendations

There is increasing evidence supporting the important role of early EN (within 48 h of diagnosis of pancreatitis) in positively impacting outcome in patients with AP. Nutritional support is an integral and key aspect of the successful management of AP. The use of enteral feeding in veterinary medicine is now considered to be safe, effective, and well-tolerated in severe AP. Enteral nutrition is less expensive than parenteral feeding and helps to maintain gastrointestinal mucosal function, and therefore is likely to have a beneficial influence on the disease course. Use of NG, nasoesophageal, jejunal, and esophagostomy feeding tubes is effective and safe in dogs and cats and should be used unless specific contraindications are identified. The optimal enteral diet for patients with AP has not been identified, but diets commonly used for convalescing dogs and cats can be used. Avoidance of enteral diets with high fat content does not appear to be necessary in the majority of patients. Despite the growing evidence that EN can be used effectively in the management of patients with AP, there may still be patients that require some form of PN until sufficient EN can be tolerated.

Given that several human and experimental animal studies in AP have reported promising results associated with immunonutrition, evaluation in clinical veterinary patients may be warranted. However, recent findings regarding glutamine supplementation in critically ill people demand a careful and cautious approach. Future veterinary studies investigating feeding routes, dietary composition, and optimal timing of nutritional support in AP are warranted.

## Footnote

<sup>a</sup> CliniCare Canine/Feline Liquid Diet, Abbott Animal Health, Abbott Laboratories, Abbott Park, IL.

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